Field research

MEDICI CON L'AFRICA CUAMM
Doctors with Africa

Scientific papers, abstracts and posters from cooperation activities in Africa – 2023

photo © Nicola Berti

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MEDICI CON L'AFRICA
CUAMM
Doctors with Africa

Doctors with Africa CUAMM
via San Francesco, 126 - 35121
Padua - tel +39 049 8751279
www.mediciconlafrica.org
cuamm@cuamm.org
c/c postale 17101353

Design
Heads Collective

Layout
Publistampa Arti Grafiche

Photography
Nicola Berti

Editorial staff
Chiara Di Benedetto
Giovanni Putoto
Francesca Tognon

Translated in part by
Sara Copeland Benjamin

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Fondazione
Cassa di Risparmio
di Padova e Rovigo

"Their compulsion to do research was fueled by a singular curiosity, a readiness to reflect critically on their own work, to reject dogmas and cultural stereotypes, to delve deep into the phenomena they encountered, and to engage in reasoned discussion and debate. For these pioneers of development cooperation, curiosity was a gateway to further questions and hypotheses – in short, to research."

"C'era, infatti, una curiosità straordinaria che alimentava la passione per la ricerca. La curiosità intesa come disposizione alla riflessione critica, senza sconti, del proprio operato; rifiuto dei dogmi e degli stereotipi culturali del tempo; approfondimento puntuale dei fenomeni e desiderio di confronto e discussione. Per questi medici la curiosità è stata l'anticamera delle domande, degli interrogativi, dei quesiti, delle ipotesi. Della ricerca, appunto."

Giovanni Putoto,
Medici con l'Africa Cuamm

"WHAT IF...?": PAST, PRESENT AND FUTURE

Scarce resources, boundless curiosity and intellectual humility: these were prime traits of CUAMM's doctors when they first embarked on research in Africa decades ago. With barely enough resources to get by, and despite the absence of programs, logical frameworks, theories of change, budgets, indicators and donor reports, our predecessors worked in anything but a haphazard manner. Their compulsion to do research was fueled by a singular curiosity, a readiness to reflect critically on their own work, to reject dogmas and cultural stereotypes, to delve deep into the phenomena they encountered, and to engage in reasoned discussion and debate. For these pioneers of development cooperation, curiosity was a gateway to further questions and hypotheses – in short, to *research*.

They were also intellectually humble, which kept them mindful of both the complexity of phenomena and the limits of their knowledge, drove them to continually reconsider their perspective with others, and spurred their desire to pursue a common good, rather than private interests, through research. This humility was the mark of a particular intellectual path – a path "in reverse" from Africa to Europe and on to America – that would become their permanent way of being in the world. Their curiosity and humility led to the first clinical studies, primary health care analyses, and medical anthropology research – the start of a crescendo of topics and methodologies that would see valuable contributions from generations of doctors and practitioners in the decades to follow.

Among the many issues we face today, both old and new, are health inequalities. Indeed, despite undeniable progress, Tudor Hart's inverse care law still applies: those who most need health care are least likely to receive it. Universal health coverage, however essential, and charitable attitudes, however understandable, are not enough; we need to address the *causes* of inequality (as our *Mothers and Children First* program seeks to do) by making services available in places where there are none. But we need to do even more. How?

Our planet is on fire, disasters and epidemics are proliferating, violence and conflicts are intensifying, and people's health is at risk. One of the most pressing necessities today is the need to set a research agenda focused on how the climate crisis is impacting the physical and mental health of those living in primary care settings in Africa. There are also major gaps with regard to our ability to help patients, communities, and non-health-related sectors cope with the phenomenon. Research is essential to help identify these gaps and related barriers. Against this backdrop, what is the role of Africa's deeply heterogeneous health systems and communities? As to the latter, there is much talk of engagement, active participation, and – last but not least – information, education and communication, the famous IEC approach to community development projects. Yet we sometimes forget that communities, having tackled and overcome inconceivable challenges, are often much more than this; they are guardians of knowledge, holders of ancient wisdom, the very foundation of participatory action research. So it's vital that we alter our research "arsenals" to work hand in hand, through multipronged, mutually respectful research partnerships, with the communities whose concerns and health issues we are seeking to address. Are we truly ready to do so? The resources are there if we look for them; so are the research agendas. There are plenty of helpful tools and technologies. But those simple but precious ingredients – curiosity and humility – are also still necessary today. That *"What if...?"* that was so essential in the past remains just as important in the present, and will continue to do so in the future.

Giovanni Putoto

E SE? IERI, OGGI E DOMANI

Risorse magre, curiosità sconfinata, umiltà intellettuale. Sono stati questi gli ingredienti utilizzati dai primi medici del Cuamm quando hanno affrontato la ricerca in Africa. Le risorse erano risicatissime, quanto bastava per vivere. Non esistevano i progetti, il piano logico o la teoria del cambiamento, il budget, gli indicatori e la reportistica per i donatori. Eppure, anche senza questi strumenti, non si lavorava a casaccio. Anzi! C'era, infatti, una curiosità straordinaria che alimentava la passione per la ricerca. La curiosità intesa come disposizione alla riflessione critica, senza sconti, del proprio operato; rifiuto dei dogmi e degli stereotipi culturali del tempo; approfondimento puntuale dei fenomeni e desiderio di confronto e discussione. Per questi medici la curiosità è stata l'anticamera delle domande, degli interrogativi, dei quesiti, delle ipotesi. Della ricerca, appunto. Questi medici erano anche molto umili. Umiltà intellettuale che li rendeva consapevoli della complessità dei fenomeni; coscienti del limite delle proprie conoscenze e certezze; predisposti a rivedere costantemente la propria visione insieme ad altri; desiderosi di perseguire, attraverso la ricerca, un bene comune e non un interesse privato. Per questi primi professionisti della cooperazione, l'umiltà intellettuale ha contrassegnato un peculiare percorso accademico – un percorso al contrario, dall'Africa all'Europa fino all'America – tanto da diventare un tratto umano indistinguibile del loro modo di stare in mezzo agli altri. Dalla curiosità e dall'umiltà nacquero i primi studi clinici, le prime analisi sulla Primary Health Care*, le prime ricerche di antropologia medica in un crescendo di temi, metodi e approcci a cui hanno dato il loro prezioso contributo, nei decenni a seguire, generazioni di medici e cooperanti.*

Oggi ci ritroviamo di fronte a temi antichi e nuovi. Ne accenniamo alcuni.

Le diseguaglianze in ambito di salute. Un problema antico e, nonostante grandi miglioramenti, tutt'ora permane valida la legge dell'assistenza inversa di Tudor Hart: chi ha maggiore bisogno di cure ne riceve di meno. I sistemi universalistici (UHC), per quanto indispensabili, e gli atteggiamenti benevoli, per quanto comprensibili, non bastano. Bisogna agire sulle cause delle disuguaglianze.

Ci proviamo con il nostro programma Prima le mamme e i bambini*, che porta i servizi dove non ci sono. Ma dobbiamo fare di più: come?*

I cambiamenti climatici. La terra scotta, le catastrofi e le epidemie si moltiplicano, i conflitti rialzano la cresta, la salute è a rischio. Una delle aree di grande bisogno è stabilire un'agenda di ricerca focalizzata sui cambiamenti climatici e i loro effetti sulla salute fisica e mentale nei contesti di assistenza primaria in Africa. Sono presenti però dei vuoti nel coinvolgimento dei pazienti, delle comunità e dei settori non sanitari, e la ricerca può aiutarci a identificare questi vuoti e le barriere esistenti. In tutto questo, qual è il ruolo del sistema sanitario e delle comunità africane tenuto conto della eterogeneità dei contesti? Le comunità locali. Se ne parla tanto, sempre in termini di coinvolgimento, partecipazione attiva, e non ultimo, di informazione, comunicazione ed educazione: la mitica "ICE" dei progetti di cooperazione comunitaria. Eppure, si dimentica che la comunità è spesso molto di più. È maestra di conoscenze, è sopravvissuta a sfide impensabili, ha una saggezza antica nell'affrontare i problemi. È la base della cosiddetta ricerca azione partecipata. Bisogna però cambiare il nostro armamentario di ricerca e lavorare in collaborazione in partenariati di ricerca multidirezionali e reciprocamente rispettosi con le comunità le cui preoccupazioni o questioni di salute si propone di affrontare.

Ma siamo davvero pronti?

Non mancano le risorse se le cerchiamo, neppure le agende di ricerca, se lo vogliamo. Gli strumenti abbondano, la tecnologia aiuta. Tutto vero. Dobbiamo metterci però gli ingredienti di base: curiosità e umiltà. E SE? Ieri, oggi e domani.

Giovanni Putoto

OPERATIONAL RESEARCH IN AFRICA: A CRUCIAL CHALLENGE

In 2023, thanks to partnerships with 132 research centers and institutions around the world, almost 50 of which in Africa, CUAMM published 31 studies in international journals and conducted research in each of the countries we collaborate with. This achievement was the result of a synergy that has developed over time based on our commitment to integrating quality research into health programs for developing countries.

All of CUAMM's programs and research activities are guided by this approach, one in which our organization firmly believes. This was evidenced frequently in 2023 during public meetings where specialized practitioners and partners came together for discussion and debate. One of the most significant such occasions – *"Operational research and civil society contributions to enhance universal health coverage"* – was an official side event coordinated by CUAMM at the 3rd International Conference on Public Health in Africa (CPHIA 2023), organized by the African Union and Africa CDC in Lusaka, Zambia.

Our published research in 2023 covered a broad range of topics. Several papers addressed the topic of infectious diseases, including COVID-19, tuberculosis and HIV, while others examined the use of antibiotics, particularly in neonatal intensive care (the latter is the focus of ongoing CUAMM studies, reflecting our special interest in this area).

Our research also explored the future of vaccines in Africa and the effective management of non-communicable (chronic) diseases, a topic of increasing concern in both developed and developing countries. Nutrition remained a key focus as well, with investigations into the little-explored topic of paternal nutrition, along with studies on poor dietary practices and determinants of dietary diversity. Furthermore, we conducted analyses on the roles of community engagement and perceptions of development and health-building processes.
The journals hosting CUAMM's work, including *BioMed Central* (BMC) and *Frontiers in Public Health*, serve as a testament to our increasing authority and position as a recognized research contributor.

Furthermore, in 2023 we continued to disseminate our research findings to practitioners and experts through oral presentations and poster sessions at conferences in Italy and abroad, including the most recent edition of the European Congress on Global Health in Utrecht, the Netherlands (ECTMIH 2023).

Our research activity has continued to expand over the years, both quantitatively and qualitatively. This growth reflects CUAMM's recognition of the essential role operational research plays as both a strategic and planning tool and a complement to program interventions on the ground – and, consequently, our determination to continue to invest in it.

LA RICERCA OPERATIVA IN AFRICA: UNA SFIDA NECESSARIA

31 ricerche pubblicate nel 2023 su riviste internazionali e un'attività di ricerca che ha coperto tutti i Paesi in cui CUAMM opera ed è il risultato di collaborazioni con 132 centri di ricerca e istituzioni internazionali, di cui quasi 50 sono partner africani. Una sinergia costruita nel tempo da Cuamm, con l'obiettivo di integrare la ricerca scientifica di qualità nella programmazione sanitaria anche dei Paesi in via di sviluppo.

Un approccio 'sul campo' in cui Cuamm crede fortemente e che orienta tutte le progettualità e le linee di ricerca, come è spesso emerso anche in diverse occasioni pubbliche di confronto tra esperti e partner nel 2023: tra le più significative quella dal titolo eloquente Operational research and civil society contributions to enhance Universal Health Coverage *promossa da Cuamm come evento satellite dell'ultima* International Conference on Public Health in Africa*, organizzata da Africa CDC e African Union a Lusaka (Zambia).*

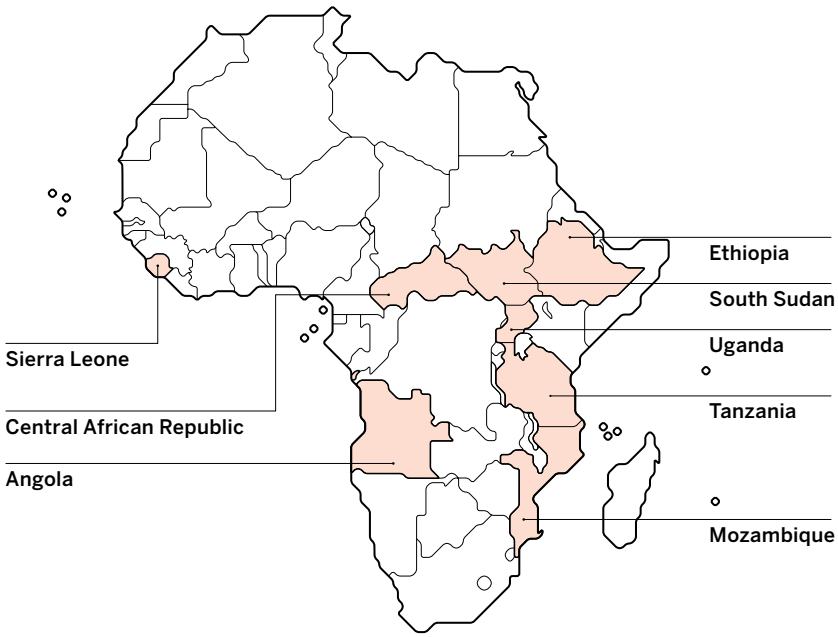
Nel 2023 sono stati molteplici i focus delle ricerche pubblicate: numerosi gli articoli dedicati alle malattie infettive, in particolare Covid-19, TB e HIV, e quelli sull'utilizzo degli antibiotici, in particolare nelle terapie intensive neonatali. Quest'ultimo, tra l'altro, è un argomento di forte interesse e oggetto di approfondimento nelle progettualità in corso.

Lo sguardo delle ricerche pubblicate nel 2023 si è allargato però anche all'analisi prospettica sui vaccini in Africa e sul tema delle malattie croniche non trasmissibili e di processi efficaci per la loro gestione, sempre più rilevante a livello mondiale e anche nei Paesi in via di sviluppo. Non mancano approfondimenti in ambito nutrizione, in particolare sul tema poco esplorato della nutrizione paterna e delle pratiche alimentari scorrette e determinanti della diversità alimentare. Interessanti sono anche le analisi che approfondiscono il ruolo delle comunità, del loro engagement e della loro percezione nei processi di sviluppo e costruzione di salute.

Le riviste che hanno ospitato i lavori del Cuamm – tra cui BMC e Frontiers in Public Health *– confermano una crescita di autorevolezza e posizionano l'organizzazione come autore di ricerca accreditato. Inoltre, i progetti di ricerca di cui Cuamm è stato promotore e autore sono stati presentati a esperti e addetti ai lavori anche durante presentazioni orali e poster session di convegni in Italia e all'estero, tra cui l'European Congress on Tropical Medicine and International Health ad Utrecht (Paesi Bassi).*

Un'attività di ricerca che è cresciuta costantemente negli anni, in termini quantitativi e qualitativi, e testimonia la determinazione del Cuamm nel continuare a investire in questa direzione, nella convinzione che la ricerca operativa sia uno strumento strategico e di programmazione imprescindibile da affiancare alle azioni sul campo.

Doctors with Africa CUAMM
Medici con l'Africa Cuamm



Doctors with Africa CUAMM is the largest Italian NGO working to **improve the health of vulnerable communities in Sub-Saharan Africa**. CUAMM carries out **long-term projects in 8 countries** in the region and partners with **universities and research centers** in Italy and abroad to raise awareness about people's right to health care. CUAMM also organizes **courses on global health** for medical students and health professionals and conducts **research** with international partners, convinced that such endeavors are vital to developing **quality international healthcare programs**.

*Medici con l'Africa Cuamm è la più grande organizzazione italiana per la **promozione e la tutela della salute delle popolazioni africane**. Medici con l'Africa Cuamm realizza **progetti a lungo termine in 8 Paesi** dell'Africa Sub-sahariana e collabora con **università e centri di ricerca in Italia e in Europa**. Organizza inoltre **corsi di Salute Globale** per studenti di Medicina e professionisti sanitari e lavora con partner internazionali a **progetti di ricerca**, nella convinzione che questi sforzi siano necessari per lo sviluppo di **programmi sanitari internazionali di qualità**.*

Doctors with Africa CUAMM currently operates in Angola, Central African Republic, Ethiopia, Mozambique, Sierra Leone, South Sudan, Tanzania and Uganda.
Medici con l'Africa Cuamm attualmente lavora in Angola, Etiopia, Mozambico, Repubblica Centrafricana, Sierra Leone, Sud Sudan, Tanzania e Uganda attraverso:

16
hospitals /
ospedali

128
districts (for public health activities, mother-child care, the fight against HIV/AIDS, tuberculosis and malaria, training) /
distretti (iniziative per la salute pubblica, assistenza e cure per la salute materna e infantile, lotta contro l'HIV/AID, la tubercolosi e la malaria)

4
nursing schools /
scuole per infermieri e ostetriche

1
university (Mozambique) /
università (Mozambico)

3,465
health workers, including /
collaboratori sanitari, che includono:

282
from Europe and abroad /
europei e internazionali

802
health facilities /
strutture sanitarie supportate

Operational research in 2023
Ricerca operativa nel 2023

In 2023, **31** studies in international journals presented our research on a range of topics, from infectious diseases to the use of antibiotics and vaccines, as well as in-depth explorations of maternal and child health issues such as neonatal intensive care and the little-explored topic of paternal nutrition. CUAMM's operational research focused on the challenges we encounter daily in the field – our preferred methodological approach, which entails conducting research and interventions in parallel to continue to improve the quality of our programs. By partnering with **132** research centers across Italy, Africa and other countries, and thanks to the hard work of **313** researchers, we were able to generate fresh insights and develop new projects in limited-resource countries.

31 *ricerche pubblicate su riviste internazionali: dalla ricerca sulle malattie infettive a quella sull'utilizzo degli antibiotici e sui vaccini fino all'approfondimento di alcuni temi più specifici, legati in particolare alla salute materna e infantile come la terapia intensiva neonatale o la nutrizione paterna, ancora poco esplorato. Nel 2023 la ricerca operativa Cuamm è entrata nei temi di lavoro sul campo, dimostrando l'approccio metodologico che intendiamo perseguire: una ricerca che si integra all'intervento per garantire qualità. Abbiamo lavorato a fianco di* ***132*** *centri di ricerca italiani, africani e internazionali, coinvolgendo* ***313*** *ricercatori e ricercatrici che hanno collaborato per costruire nuova conoscenza e sviluppare progetti in Paesi con risorse limitate.*

- Maternal and child health
  Salute materna e infantile
- Infectious and tropical diseases
  Malattie infettive e tropicali
- Public health and universal coverage
  Copertura sanitaria universale ed equità
- Nutrition
  Nutrizione
- Chronic diseases
  Malattie croniche

OUR RESEARCH PARTNERS

Below is a list of the 132 research centers, universities and other organizations – in Africa, Europe (including Italy), and other countries around the world – with which Doctors with Africa CUAMM partnered on research in 2023.
I 132 centri di ricerca, università e organizzazioni con cui Medici con l'Africa Cuamm ha collaborato per produrre la ricerca nel 2023.

AFRICA

1. Aber Hospital, Aber, Uganda
2. Alliance for Africa Health Research, Nairobi, Kenya
3. Armauer Hansen Research Institute, Addis Ababa, Ethiopia
4. Bugisi Health Centre, Shinyanga, Tanzania
5. Catholic University of Mozambique, Beira, Mozambique
6. Department of Anaesthesia and Intensive Care Medicine, Makerere University, Kampala, Uganda
7. Department of Anaesthesia and Perioperative Medicine, University of Cape Town, Cape Town, South Africa
8. Department of Anaesthesia, The Aga Khan University, Nairobi, Kenya
9. Department of Anaesthesiology and Intensive care, Komfo Anokye Teaching Hospital, Kumasi, Ghana
10. Department of Anesthesia and Intensive Care, Connaught Hospital, University of Sierra Leone, Freetown, Sierra Leone
11. Department of Global Health, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana
12. Department of Paediatry, Central Hospital of Maputo, Maputo 1113, Mozambique
13. Department of Pneumology, Central Hospital of Maputo, Maputo 1113, Mozambique
14. Department of Research, Faculty of Health Sciences, Universidade Catolica de Mocambique, Beira, Mozambique
15. Department of Surgery, Central Hospital of Beira, Beira, Mozambique
16. Faculdade de Ciências de Saúde, Universidade Católica de Moçambique, Beira, Mozambique
17. Faculty of Medicine, Eduardo Mondlane University, Maputo, Mozambique
18. Health Office, Oyam District Local Government, Loro, Uganda
19. Health Research Team, Oromia Regional Health Bureau, Addis Ababa, Ethiopia
20. Institut Supérieur des Techniques Médicales (ISTM) Marie-Reine-de-la-Paix de Kenge, Kenge, Democratic Republic of Congo
21. Jinka General Hospital, Jinka, South Omo, Ethiopia
22. Matany Saint Kizito Hospital, Moroto, Uganda
23. Ministry of Health and Sanitation, Freetown, Sierra Leone
24. Missionary Catholic Hospital of Chiulo, Ombadja 23030, Angola
25. Mycobacterial Diseases Research, Armauer Hansen Research Institute, Addis Ababa, Ethiopia
26. National Aids Control Program (NACP), Dodoma, Tanzania
27. National Institute for Medical Research(NIMR)-Muhimbili centre, Dar es Salaam, Tanzania
28. Neonatal Intensive Care Unit, St Luke Catholic Hospital, Wolisso, Ethiopia
29. Ngokolo Health Centre, Shinyanga, Tanzania
30. Non-Communicable Diseases Department, Ministry of Health, Maputo, Mozambique
31. Nucleo de Investigacao Operacional de Pemba, Pemba, Mozambique
32. Nursing, Arua Regional Referral Hospital, Arua, West Nile, Uganda
33. Operational Research Unit, African Network for Change, Kampala, Uganda
34. Operational Research Unit, St. John's XXIII Hospital Aber, Jaber, Uganda
35. Princess Christian Maternity Hospital, Freetown, Sierra Leone
36. Programs, UNICEF Uganda
37. Saint Kizito Hospital, Matany, Uganda
38. Saint Luke Hospital, Wolisso, Ethiopia
39. School of Public Health, Department of Epidemiology and Statistics, Muhimbili University of Health and Allied Science, Dar es Salaam, Tanzania
40. Shinyanga and Simiyu Test & Treat Project, Shinyanga, Tanzania
41. Shinyanga Regional Referal Hospital, Shinyanga, Tanzania
42. St. John's XXIII Hospital Aber, Jaber 21310, Uganda
43. The Ethics Lab, Neuroscience Institute, Department of Medicine, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa
44. Tosamaganga Hospital, Iringa, United Republic of Tanzania
45. Uganda Heart Institute, University of Makerere, Makerere, Uganda
46. UNICEF Mozambique, Maputo, Mozambique
47. UNICEF, Peer Support Volunteers MCO, Mozambique

ITALY

1. Accademia Nazionale dei Lincei, Rome
2. Alma Mater Studiorum University of Bologna, Bologna, Italy
3. Alma Mater Studiorum University of Bologna, Department of Medical and Surgical Sciences DIMEC
4. Anesthesia and Intensive Care Medicine, University of Bari, Bari, Italy
5. ANLAIDS Sezione Lombardia, 20124 Milan, Italy
6. ARCO (Action Research for CO-development), PIN Educational and Scientific Services for the University of Florence, Prato, Italy
7. Azienda Ospedaliero - Universitaria di Sassari
8. Azienda Ospedaliero - Universitaria Pisana, Pisa, Italy
9. Center for Health Emergencies, Bruno Kessler Foundation, Trento
10. Clinic of Infectious Diseases, Department of Biomedical Sciences and Human Oncology, University of Bari, Bari, Italy
11. Clinical Infectious Diseases, Department of System Medicine, Tor Vergata University, Rome, Italy
12. Clinical Psychology Unit, San Gerardo Hospital, Monza
13. CRIMEDIM - Center for Research and Training in Disaster Medicine, Humanitarian Aid and Global Health, Università del Piemonte Orientale, Novara
14. Department of Anesthesia and Intensive Care, University of Piemonte Orientale, Novara, Italy

15. Department of Clinical Sciences and Community Health (DISCCO), University of Milan, Milan, Italy
16. Department of Economics and Management, University of Florence, Florence, Italy
17. Department of Infectious Diseases, Istituto Superiore di Sanità, Rome, Italy
18. Department of Infectious-Tropical Diseases and Microbiology, IRCCS Sacro Cuore Don Calabria Hospital, Verona, Italy
19. Department of Medicine, University of Padua, 35128 Padova, Italy
20. Department of Precision and Regenerative Medicine and Ionian Area, Clinic of Infectious Diseases, University of Bari
21. Department of Statistical Sciences, University of Padua
22. Department of Statistics, Computer Science, Applications "G. Parenti", University of Florence, Florence, Italy
23. Department of Surgical, Oncological and Gastroenterological Sciences, University of Padova
24. Department of Translational Research and of New Surgical and Medical Technologies, University of Pisa, Pisa, Italy
25. Department of Woman's and Child's Health, University Hospital of Padua
26. Dipartimento di Chirurgia DIDAS, Unità Operativa Complessa (UOC) Istituto Anestesia e Rianimazione, Azienda Ospedale University of Padua
27. Direzione sanitaria aziendale, Asl Bari
28. Division of Paediatric Emergency Medicine, Department of Women's and Children's Health, University of Padua
29 Division of Pediatric Infectious Diseases, Department of Women's and Children's Health, University of Padua, Padua, Italy
30. Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Pediatric Area, Milan, Italy
31. Geriatric Unit, Department of Internal Medicine and Geriatrics, University of Palermo
32. Hepatobiliary Surgery Unit, Foundation "Policlinico Universitario A. Gemelli", IRCCS, Catholic University, Rome
33. Hygiene and Public Health Unit, DCTVSP, University of Padua
34. Independent Statistician, Solagna
35. Infectious Diseases Unit, AUSL Romagna, Morgagni Pierantoni Hospital Forlí, Doctors with Africa CUAMM IT, Forlí, Italy
36. IRCCS Azienda Ospedaliero-Universitaria di Bologna, Division of Endocrinology and Diabetes Prevention and Care, Bologna, Italy
37. IRCCS Azienda Ospedaliero-Universitaria di Bologna, Nephrology- Dialysis and Renal Transplant Unit, Bologna, Italy
38. IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano, Milan, Italy
39. IRCCS Humanitas Research Hospital,Milan
40. Missionary Sisters of the Sacred Heart, Rome, Italy
41. National Institute for Infectious Diseases, Lazzaro Spallanzani, IRCCS, Rome, Italy
42. Neonatal Intensive Care Unit, AUSL-IRCCS of Reggio Emilia, Reggio Emilia, Italy
43. Ospedale San Giuseppe Multimedica, Milano
44. Policlinico Umberto I, Rome, Italy
45. Scuola di specializzazione in Igiene e medicina preventiva, Dipartimento di Scienze mediche e chirurgiche, Università di Foggia
46. Transfusion Medicine Department of Azienda Sanitaria Universitaria Giuliano Isontina (ASU GI), Trieste, Italy
47. Unit of Infectious and Tropical Diseases, Department of Medicine, Surgery and Pharmacy, University of Sassari, Sassari, Italy
48. Unità Operativa Complessa di Epidemiologia Clinica con Registro Tumori, Azienda Ospedaliera Universitaria Policlinico "Paolo Giaccone", Palermo, Italy
49. Università degli Studi di Milano - Bicocca
50. University of Pavia, Italy
51. University of Pisa, Italy
52. Zerouno Procreazione, Centro di Medicina, Venezia, Italy

EUROPE

1. Amsterdam Institute for Global Health and Development, Amsterdam, The Netherlands
2. Amsterdam UMC, Department University of Amsterdam, Department of Global Health, Amsterdam Institute for Global Health and Development
3. Intensive Care Medicine, University of Amsterdam, Amsterdam, The Netherlands
4. Medical Preparedness and Crisis Management Unit (MPCMU), Directorate-General for Personnel, European Parliament, Brussels, Belgium
5. UNICEF communication for development

OTHER COUNTRIES

1. All India Institute of Medical Sciences, New Delhi, India
2. Centre for Health, Performance and Wellbeing, Anglia Ruskin University, Cambridge CB1 1PT, UK
3. Centre for Inflammation Research, University of Edinburgh, Edinburgh, UK
4. Centre for Preoperative Medicine, University College London, London, UK
5. Chelsea and Westminster Hospital NHS Foundation Trust and LSHTM, London, UK
6. Chennai Critical Care Consultants Private Limited, Chennai, India
7. Department of Biostatistics, Yale School of Public Health, New Haven, CT, USA
8. Department of Community and Family Medicine, University of Jaffna, Jaffna, Sri Lanka
9. Department of Critical Care Medicine, Apollo Hospitals Educational and Research Foundation, Chennai, India
10. Department of Critical Care Medicine, Ziauddin University, Karachi, Pakistan
11. Department of Critical Care, Nepal Intensive Care Research Foundation, Kathmandu, Nepal
12. Department of Critical Care, University College London Hospitals NHS Foundation Trust, London, UK
13. Department of Intensive Care Anaesthesiology, International Islamic University Malaysia, Kuala Lumpur, Malaysia
14. Department of Medicine, Chittagong Medical College Hospital, Chattogram, Bangladesh

15. Department of Pediatrics, Faculty of Medicine, University of British Columbia, Vancouver, Canada
16. Department of Targeted Intervention, University College London, London, UK
17. D'Or Institute for Research and Education, Sao Paulo, Brazil
18. General Surgery, Wazir Akbar Khan Hospital, Kabul, Afghanistan
19. Institute of Applied Health Research, University of Birmingham, Birmingham, UK
20. Institute of Health Informatics, University College London, London, UK
21. Laboratory for Computational Epidemiology and Public Health, Department of Epidemiology and Biostatistics, Indiana University School of Public Health, Bloomington, USA
22. Mahidol Oxford Tropical Medicine Research Unit, Bangkok, Thailand
23. Nat-Intensive Care Surveillance, Mahidol Oxford Tropical Medicine Research Unit, Colombo, Sri Lanka
24. National Institute of Infectious Diseases, Oswaldo Cruz Foundation, Rio de Janeiro, Brazil
25. Nuffield Department of Medicine, University of Oxford, Oxford, UK
26. Oxford University Clinical Research Unit, University of Oxford, Ho Chi Minh City, Vietnam
27. School of Education and Social Care, Anglia Ruskin University, Chelmsford, UK
28. Teaching Hospital Jaffna, Jaffna, Sri Lanka

132 Research partners
partner di ricerca

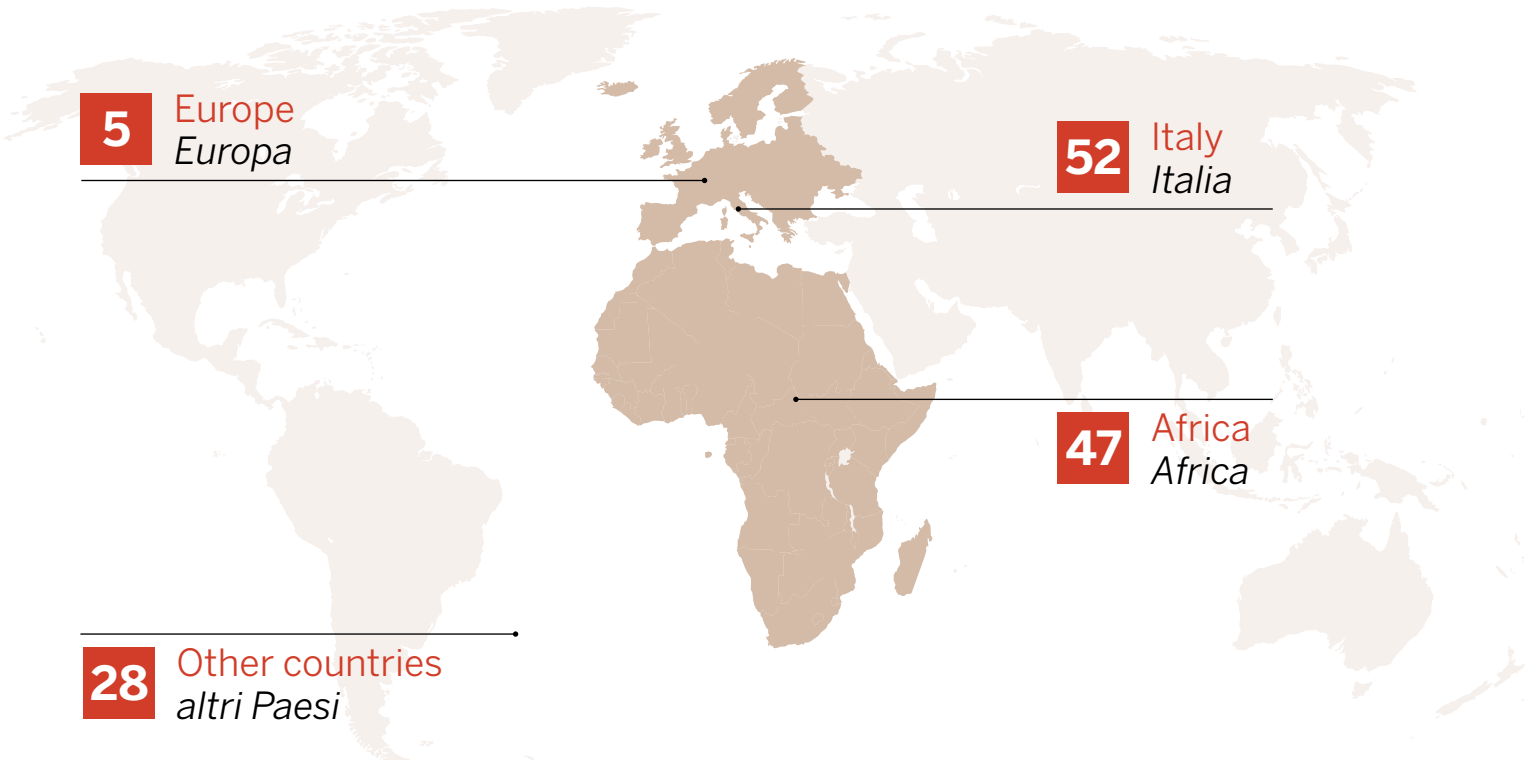


TABLE OF CONTENTS

21 Maternal and child health

PAPERS

22 01 → Ethiopia
Fonzo M. et al., **The HIV paradox: Perinatal mortality is lower in HIV-positive mothers-A field case-control study in Ethiopia**, in *Int J Gynaecol Obstet.*, February 2023

29 02 → Tanzania
Rossi E. et al., **Rewarming rate of hypothermic neonates in a low-resource setting: a retrospective single-center study**, in *Frontiers in Pediatrics*, May 2023

37 03 → Ethiopia
La Vecchia A. et al., **Adherence to WHO guidelines on severe pneumonia management in children and its impact on outcome: an observational study at Jinka General Hospital in Ethiopia**, in *Front Public Health*, July 2023

45 04 → Sierra Leone
Orsi M. et al., **A Clinical and Ethical Dilemma: Expectant Management for Ectopic Pregnancy with a Vital Fetus in a Low-Resource Setting**, in *Journal of clinical medicine*, August 2023

54 05 → Sierra Leone
Mortara M. et al., **Impact and burden of sickle cell disease in critically ill obstetric patients in a high dependency unit in Sierra Leone-a registry based evaluation**, in *BMC Pregnancy Childbirth*, August 2023

65 06 → Uganda
Farina U. et al., **Indagine conoscitiva sulla violenza di genere tra i giovani residenti nel distretto di Oyam, Uganda**, in *Il Pensiero Scientifico Editore*, September 2023

Maternal and child health

POSTERS AND ORAL PRESENTATIONS

68

01 → Mozambique
17th INTEREST Congress
Maputo, Mozambique, 9 - 12 May 2023
- Occa E. et al., A *Good Start in Life: An Investigation on Basic ECD Knowledge and Practices in Two Districts of Zambezia Province*

69

02 → Sierra Leone
FIGO World Congress of Gynecology and Obstetrics
Paris, France, 9 - 12 October 2023
- Orsi M. et al., *What if one of the biggest killers was even bigger? Hypertensive disorders of pregnancy underlying maternal death secondary to other direct and indirect causes*

70

03 → Uganda
3rd National Safe Motherhood Conference
Kampala, Uganda, 23 - 25 October 2023
- Boxtel A. L. et al., *Utilizing surgical Camps for clinical skills transfer: An experience of doctors with Africa CUAMM in Karamoja*

71

04 → Uganda
3rd National Safe Motherhood Conference
Kampala, Uganda, 23 - 25 October 2023
- Christine M. et al., *Kangaroo Mother Care: Experience from Matany Hospital in Napak District Karamoja*

72

05 → Uganda
3rd National Safe Motherhood Conference
Kampala, Uganda, 23 - 25 October 2023
- Pande S. et al., *Group ANC improves maternal and newborn outcomes. A case of Moroto RRH, Moroto District*

73

06 → Tanzania
2nd Reproductive, Maternal, Newborn, Child, Adolescent health and Nutrition Scientific Conference
Dar Es Salaam, Tanzania, 15 - 17 November 2023
- Didonè M. et. al., *Barriers to Care Mental Health Status and Impact of COVID-19 Pandemic on Adolescents and Young Adults Living with HIV in Shinyanga Region, Tanzania*

74

07 → Tanzania
2nd Reproductive, Maternal, Newborn, Child, Adolescent health and Nutrition Scientific Conference
Dar Es Salaam, Tanzania, 15 - 17 November 2023
- Mancini V. et al., *Pediatric Outpatient Services In Rural Tanzania: Retrospective Cohort Study On Predictive Factors For Hospitalization*

75

08 → Tanzania
2nd Reproductive, Maternal, Newborn, Child, Adolescent health and Nutrition Scientific Conference
Dar Es Salaam, Tanzania, 15 - 17 November 2023
- Dalla Porta F. et al., *Special Needs Population Of Malnourished Paediatric Patients In Tosamaganga Hospital, Rural District Of Iringa, Tanzania*

77

Public health and universal coverage

PAPERS

78 01 → Angola
Quaglio G. et al., **International medical electives in Sub-Saharan Africa: experiences from a 19-year NGO-driven initiative**, in *BMC Medical Education*, March 2023

91 02 → Multi-country
La Raja M. et al., **Knowledge, attitudes and practices for blood safety in a worldwide perspective**, in *Blood transfusion*, November 2023

94 03 → Multi-country
Rashan A. et al., **Mixed methods study protocol for combining stakeholder-led rapid evaluation with near real-time continuous registry data to facilitate evaluations of quality of care in intensive care units**, in *Wellcome Open Res*, November 2023

108 04 → Multi-country
Nannini M. et al., **Comparative Insights to Advance Political Economy Analysis: A Response to Recent Commentaries**, in *Int J Health Policy Manag*, December 2023

POSTERS AND ORAL PRESENTATIONS

112 01 → Mozambique
Association of Social Anthropologist (ASA) of the UK Conference
London, UK, 11 - 14 April 2023
- Occa E., *From "reproductive" to "generative" health. Anthropology as a tool for an epistemological review of health development strategies in Africa*

113 02 → Mozambique
17th INTEREST Congress
Maputo, Mozambique, 9 - 12 May 2023
- Occa E., *Perception of Services and Barrier to Retention in Care for Girls and Young Women in Beira, Mozambique. Doctors with Africa CUAMM INGO*

114 03 → Mozambique
European Association of Social Anthropology - AHN Anthropology of Humanitarian NetworkWorkshop
Manchester, UK, 13 - 14 July 2023
- Occa E., *Taxonomic Criteria and Creation of Imaginaries; Field Experience on the Definition of "Beneficiary" in Humanitarian Interventions in Mozambique*

115 04 → Mozambique
Congresso della Società Italiana di Antropologia Applicata
Perugia, Italy, 14 - 16 December 2023
- Occa E., *"Gli squali non stanno nei fiumi". L'esperienza di risposta umanitaria al ciclone Freddy in Mozambico come paradigma di una nuova ecologia del pensiero antropologico e della cooperazione sanitaria*

Public health and universal coverage

OTHER RELEVANT PUBLICATIONS

116 01 → Mozambique
Saide C. M. et al., **A percepção da qualidade do atendimento das gestantes nos centros de saúde apoiados pela Médicos com África CUAMM**, in *Revista Científíca*, September 2023

121 02 → Mozambique
Chambisse E. et al., **Implementação da Linha de Base de Pré-intervenção do Programa Governamental Família Modelo para Adoção de Comportamentos Preventivos da Cólera e outras Doenças Transmissíveis, em seis Distritos da Província de Cabo Delgado**, in *Revista Científica – RMCS (Instituto Nacional de Saude)*, September 2023

126 03 → Multi-country
Nieman N. R. et al., **Community Engagement: Non-Governmental and Faith-based Organizations**, in *Global Health Essentials. Sustainable Development Goals Series*, September 2023

127

Infectious and tropical diseases

PAPERS

128 **01 → Multi-country**
Mantovani A. et al., **COVID-19 vaccines and a perspective on Africa**, in *Trends Immunol.*, January 2023

145 **02 → Italy**
Parotto E. et al., **Exploring Italian healthcare facilities response to COVID-19 pandemic: Lessons learned from the Italian Response to COVID-19 initiative**, in *Frontiers in Public Health*, January 2023

158 **03 → Italy**
Totaro V. et al., **HIV-HCV Incidence in Low-Wage Agricultural Migrant Workers Living in Ghettos in Apulia Region, Italy: A Multicenter Cross Sectional Study**, in *Viruses*, January 2023

171 **04 → Tanzania**
Trifirò S. et al., **Hypertension in people living with HIV on combined antiretroviral therapy in rural Tanzania**, in *African Health Science*, March 2023

180 **05 → Ethiopia**
Galli M. et al., **Priority age targets for COVID-19 vaccination in Ethiopia under limited vaccine supply**, in *Sci Rep*, April 2023

193 **06 → Tanzania**
Abdul R. et al., **Effectiveness of provider-initiated versus client-initiated HIV testing by different health facility departments in Northern Tanzania**, in *AIDS Res Therapy*, May 2023

202 **07 → Multi-country**
Papagni R. et al., **Human African Trypanosomiasis (sleeping sickness): Current knowledge and future challenges**, in *Sec Neglected Tropical Disease*, May 2023

219 **08 → Multi-country**
Segala F. V. et al., **Stool Xpert MTB/RIF as a possible diagnostic alternative to sputum in Africa: a systematic review and meta-analysis**, in *Frontiers in Public Health*, May 2023

229 **09 → Mozambique**
Chilundo J. et al., **Successful Management, in a Low-Resource Setting, of Disseminated Tuberculosis in a 3-Year Old Boy: A Case Report**, in *Pathogens*, September 2023

236 **10 → Ethiopia**
Benoni R. et al., **Exploring the use of cluster analysis to assess antibiotic stewardship in critically-ill neonates in a low resource setting**, in *Antimicrob Resist Infect Control*, October 2023

248 **11 → Uganda**
Segala F. V. et al., **Impact of the COVID-19 pandemic on malaria in pregnancy indicators in Northern Uganda: a joinpoint regression analysis**, in *Pathog Glob Health*, October 2023

249 **12 → Uganda**
Segala F. V. et al., **COVID Perceptions among Pregnant Women Living in a Malaria Hyperendemic Rural Region in Uganda: A Cross-Sectional Study**, in *The American Journal of Tropical Medicine Hygiene*, November 2023

Infectious and tropical diseases

255 **13 → Mozambique**
Benoni R. et al., **SARS-CoV-2 seroprevalence and associated factors, based on HIV serostatus, in young people in Sofala province, Mozambique**, in *BMC Infect Dis*, November 2023

265 **14 → Ethiopia**
Segala F. V. et al., **Active close contact investigation of tuberculosis through computer-aided detection and stool Xpert MTB/RIF among people living in Oromia Region, Ethiopia (CADOOL Study): protocol for a prospective, cross-sectional study**, in *BMJ Open*, December 2023

274 **15 → Multi-country**
Frallonardo L. et al., **Incidence and burden of long COVID in Africa: a systematic review and meta-analysis**, in *Sci Rep*, December 2023

POSTERS AND ORAL PRESENTATIONS

283 **01 → Uganda**
30th Conference on Retroviruses and Opportunistic Infections (CROI)
Seattle, USA, 19 - 22 February 2023
- Di Gennaro F. et al., *Impact of the COVID-19 pandemic on malaria in pregnancy indicators in Northern Uganda: a joinpoint regression analysis*

284 **02 → Uganda**
European Congress of Clinical Microbiology and Infectious Diseases
Copenhagen, Denmark, 15 - 18 April 2023
- Segala F. et al., *Impact of the COVID-19 pandemic on maternal and malaria services in thirty health facilities in northern Uganda: an interrupted time series analysis*

285 **03 → Ethiopia**
Emerging issues in Infectious Diseases Congress
Bari, Italy, 13 - 14 November 2023
- Cotugno S. et al., *Active close contact investigation of tuberculosis through computer-aided detection and stool Xpert MTB/RIF among people living in Oromia Region, Ethiopia (CADOOL Study): preliminary data*

286 **04 → Mozambique**
3rd International Conference on Public Health in Africa (CPHIA 2023)
Lusaka, Zambia, 27 - 30 November 2023
- Occa E. et al., *Measuring preparedness to infectious diseases among 2124 households exposed to climate disasters in Mozambique: a cross-sectional study*

287 **05 → Mozambique**
13th European Congress on Tropical Medicine and International Health (ECTMIH)
Utrecht, Netherlands, 20 - 23 November 2023
- Segala F. et al., *Measuring preparedness to infectious diseases among 2124 households exposed to climate disasters in Mozambique: a cross-sectional study*

Infectious and tropical diseases

288

06 → Uganda

13th European Congress on Tropical Medicine and International Health (ECTMIH)
Utrecht, Netherlands, 20 - 23 November 2023

- Segala F. et al., *COVID Perceptions among Pregnant Women Living in a Malaria Hyperendemic Rural Region in Uganda: A Cross-Sectional Study*

289

07 → Tanzania

13th European Congress on Tropical Medicine and International Health (ECTMIH)
Utrecht, Netherlands, 20 - 23 November 2023

- Ntanguligwa C. A. et al., *Barriers to Care, Mental Health Status and Impact of COVID-19 Pandemic on Adolescents and Young Adults Living with HIV in Shinyanga Region, Tanzania*

290

08 → Mozambique

XXII Congress SIMIT (Italian Society Infectious and Tropical Diseases)
Florence, Italy, 4 - 6 December 2023

- Di Gennaro F. et al., *Measuring preparedness to infectious diseases among 2124 households exposed to climate disasters in Mozambique: a cross-sectional study*

291

Chronic diseases

PAPERS

292 01 → Uganda
Salvador L. et al., **Wandering spleen: An unsuspected presentation at a general hospital in Uganda**, in *Int J Surg Case Rep*, January 2023

297 02 → Tanzania
Mattiotti M. et al., **Diabetic Kidney Disease: a comparison of selected cohorts of patients from low and middle-income countries**, in *Diabetic Kidney Disease, Drugs and Treatments*, March 2023

300 03 → Multi-country
Taliente F. et al., **Enhancing surgical oncology in Sub-Saharan Africa through international cooperation**, in *European Journal of Surgical Oncology*, May 2023

301 04 → Mozambique
Massaro P. et al., **The hypertension corner - a new concept to increase hypertension awareness and diagnosis in a poor setting**, in *Eur J Prev Cardiol*, August 2023

POSTERS AND ORAL PRESENTATIONS

302 01 → South Sudan
17th World Congress on Public Health
Rome, Italy, 2 - 6 May 2023
- Sgorbissa B. et al., *Epilepsy care in resources-constrained settings: the nodding syndrome alliance experience in three clinics in Western Equatoria, South Sudan*

303 02 → Tanzania
5th Regional Non-Communicable Disease Scientific Conference
Dar Es Salaam, Tanzania, 1 - 3 November 2023
- Ndile E. et al., *Influence of socioeconomic factors on Blood Pressure Control among Hypertensive Patients in an NCDs Clinic in rural Tanzania*

304 03 → Tanzania
5th Regional Non-Communicable Disease Scientific Conference
Dar Es Salaam, Tanzania, 1 - 3 November 2023
- Mutalemwa K. et al., *Paper based integrated management system of Diabetes and Hypertension and on the job training in the HCs could be the key in the management of NCDs*

305

Nutrition

PAPERS

306

01 → Angola
Pietravalle A. et al., **Incorrect Feeding Practices, Dietary Diversity Determinants and Nutritional Status in Children Aged 6–23 Months: An Observational Study in Rural Angola**, in *Children, MDPI*, August 2023

315

02 → Multi-country
Pizzol D. et al., **Paternal nutrition: a neglected periconceptual influence on offspring health**, in *Nutrire*, August 2023

317

Publications in which CUAMM is mentioned

PAPERS

318

01 → Uganda
Mokori A. et al., **Use of collaborative learning approach for increased cure rate among children aged 6-59 months with severe wasting in Karamoja, Uganda**,in *BMJ Open Quality*, February 2023

319

02 → Multi-country
WHO Health and Migration Programme et al., **Promoting the health of refugees and migrants: experiences from around the world**, in *World Health Organization*, March 2023

320

03 → Uganda
Noirjean S. et al., **Estimating causal effects of community health financing via principal stratification**, in *Stat Methods Appl*, June 2023

321

04 → Tanzania
Reynolds L. et al., **Mediating immediacy in the era of 'treat all': The (chrono) logics of HIV treatment initiation in Shinyanga, Tanzania**, in *Social Science & Medicine*, December 2023

Maternal and child health

The HIV paradox: Perinatal mortality is lower in HIV-positive mothers-A field case-control study in Ethiopia

PAPER

Authors
Fonzo M., Dalla Zuanna T., Amoruso I., Resti C., Tsegaye A., Azzimonti G., Sgorbissa B., Centomo M., Ferretti S., Manenti F., Putoto G., Baldovin T., Bertoncello C.

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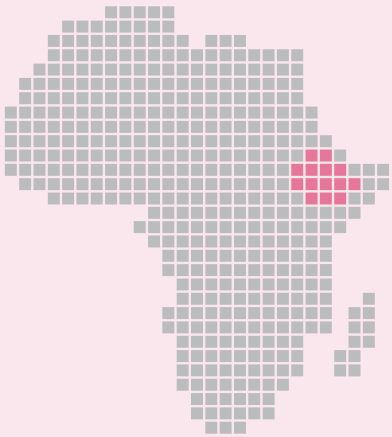

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CLINICAL ARTICLE

Obstetrics

The HIV paradox: Perinatal mortality is lower in HIV-positive mothers—A field case–control study in Ethiopia

M. Fonzo[1] | T. D. Zuanna[1] | I. Amoruso[1] | C. Resti[2] | A. Tsegaye[2] | G. Azzimonti[3] | B. Sgorbissa[1] | M. Centomo[1] | S. Ferretti[1] | F. Manenti[3] | G. Putoto[3] | T. Baldovin[1] | C. Bertoncello[1]

[1]Hygiene and Public Health Unit, DCTVSP, University of Padova, Padova, Italy

[2]Doctors with Africa CUAMM, Addis Ababa, Ethiopia

[3]Doctors with Africa CUAMM, Padova, Italy

Correspondence
Marco Fonzo, Hygiene and Public Health Unit, DCTVSP, University of Padova, Via Loredan, 18, 35121 Padova, Italy.
Email: marco.fonzo@unipd.it

Abstract

Objective: Sub-Saharan African countries have the highest perinatal mortality rates. Although HIV is a risk factor for perinatal death, antioretroviral therapy (ART) programs have been associated with better outcomes. We aimed to investigate how maternal HIV affects perinatal mortality.

Methods: The authors performed a nested case–control study at Saint Luke Hospital, Wolisso, Ethiopia. Data on sociodemographic characteristics, current maternal conditions, obstetric history, and antenatal care (ANC) services utilization were collected. The association between perinatal mortality and HIV was assessed with logistic regression adjusting for potential confounders.

Results: A total of 3525 birthing women were enrolled, including 1175 cases and 2350 controls. Perinatal mortality was lower among HIV-positive women (18.3% vs. 33.6%, $P = 0.007$). Crude analysis showed a protective effect of HIV (odds ratio, 0.442 [95% confidence interval, 0.241–0.810]), which remained after adjustment (adjusted odds ratio, 0.483 [95% confidence interval, 0.246–0.947]). Among HIV-negative women, access to ANC for women from rural areas was almost half (18.8% vs. 36.2%; $P < 0.001$), whereas in HIV-positive women, no differences were noted ($P = 0.795$).

Conclusion: Among HIV-positive mothers, perinatal mortality was halved and differences in access to ANC services by area were eliminated. These data highlight the benefits of integrating ANC and HIV services in promoting access to the health care system, reducing inequalities and improving neonatal mortality.

KEYWORDS
AIDS, community care, HIV, maternal and child health, millennium development goals, primary health care

1 | INTRODUCTION

Sub-Saharan Africa has the highest perinatal mortality rate worldwide, with 34.7 deaths per 1000 live births, and Ethiopia is substantially in line with the rate in the region, with 33 deaths per 1000 live births.[1] Perinatal mortality is defined as the combination of stillbirths occurring in the third trimester of pregnancy and neonatal deaths within 7 days of birth.

Risk factors for perinatal mortality are diverse, but overall they can be gathered into three main groups: conditions related to the mother (e.g. maternal education, alcohol abuse during pregnancy, marital status, overweight or obesity, previous preterm delivery, previous spontaneous or induced miscarriage, prepregnancy hypertensive disorder, or severe anemia); conditions related to the fetus and the pregnancy (e.g. occurrence of antepartum hemorrhage, fetal growth retardation, infection, or sepsis); and conditions related to the delivery.[2]

HIV infection is in the ranks of causes of perinatal death.[3,4] The prevalence of HIV is particularly relevant in all sub-Saharan African countries: in 2020 there were 37.7 million people with HIV infection worldwide, of which 25.4 million were living in sub-Saharan Africa. In this region, approximately 3.6% of the adult population were HIV-positive. In Ethiopia, the estimated prevalence of HIV infection in the general population in 2016 was 0.9% (1.2% in females and 0.6% in males), substantially lower than the rest of the region.[5] On the other hand, the presence of ART programs, as well as, for example, private ownership of health care facilities and the number of qualified personnel per bed, were found to be associated with higher quality of care and thus better health outcomes.[6]

Since the beginning of the global pandemic of HIV/AIDS, the fight against the disease has always been at the center of global health agendas and has triggered a series of large vertical programs on an international scale. Programs are usually driven by goals that have evolved over time, such as the Millennium Development Goals, the so-called 90-90-90 Fast Track, and the Sustainable Development Goals (SDGs), until the most recent 2025 Targets based on the 10s - 95s - integration strategy.

Globally, efforts to combat the disease have focused on prevention, treatment, and especially reducing mother-to-child transmission (vertical transmission), which is a major cause of new incident cases in sub-Saharan Africa. In fact, the number of pregnant women living with HIV globally is estimated at 1 400 000 and, of these, 90% live in sub-Saharan Africa. HIV prevalence among pregnant women in Ethiopia reaches 5.74%, distributed unevenly in the different areas of the country. In the Oromia region, 4% (95% confidence interval [CI], 2.56–6.41) of pregnant women have HIV.[7]

Considerable resources have therefore been invested in trying to prevent vertical transmission and thus reduce the number of new cases. The Prevention of Mother to Child Transmission (PMTCT) program has been a priority in many projects and has highlighted the importance of an integrated system of maternal and child care with dedicated HIV services, which would contribute to better identification of cases, faster initiation of antiretroviral therapy, and continuity of care for both mother and child.[8,9]

Recently, with the introduction of the Option B+ strategy, the need to strengthen integrated systems proved to be of paramount importance, recognizing above all in prenatal care a crucial moment to start a process of prevention and care of pregnant women at risk or already infected with HIV. Large vertical programs dedicated to PMTCT have led to improved access to testing and treatment in sub-Saharan Africa, especially in East Africa.[10]

Given the complexity of the picture described so far, the aim of our study was to investigate in the field how and to what extent perinatal mortality is concretely influenced by the HIV-positive status of birthing mothers and its implications.

2 | METHODS

We performed a monocentric, nested case–control study at Saint Luke Hospital in Wolisso, South West Shoa Zone, Ethiopia. The hospital is private not-for-profit and accredited by the Oromiya public health system. It serves as the referral hospital for the three primary hospitals of Ameya, Bantu, and Tullu Bolo in the South West Shoa Zone, a catchment area of approximately 1 250 000 inhabitants. The hospital is provided with a maternity waiting home, a facility where pregnant women living far from the hospital are usually referred in case of potentially high-risk pregnancy. In 2017, 4300 deliveries were performed.

For the purposes of our case–control study, we considered as 'cases' all mothers giving birth at the hospital, whose childbirth resulted in stillbirth or early neonatal death. In line with the definition proposed at the World Health Organization (WHO) audit and review of stillbirths and neonatal deaths *Making every baby count*, stillbirth was defined as a baby born with no signs of life after 28 weeks of gestation or weighing more than 1000 g. In more detail, both macerated stillbirth (dead before the onset of labor and presenting degenerative changes) and fresh stillbirth (dead during labor or delivery) were considered. Early neonatal mortality was defined as a baby born alive but dead within 7 days.[11,12]

On the other hand, we considered as 'controls' mothers giving birth in the same hospital, whose childbirth resulted in a baby alive at 7 days (or until hospital discharge). For each case, we included two controls, more specifically the two mothers who followed each case on the delivery registry. In case of twin birth, both mothers who gave birth to both dead twins and mothers with a dead and an alive newborn were considered as cases. Conversely, mothers who gave birth to both twins alive were selected as controls. The exposure of interest was the maternal HIV status.

Diagnosis and treatment for HIV are supported by the Oromia Health Bureau. These services are financed by the Global Fund and supervised for the scientific-technical aspects by the Centers for Disease Control and Prevention and the ICAP (Columbia University's Mailman School of Public Health). Saint Luke Hospital is a beneficiary of this support as any other Government Hospital. Tests are offered to all pregnant women and their partner. The test is offered once as routine, but it can be repeated more than once if specific risk factors are recognized. In case of an HIV-positive result, women are followed up to 18 months after delivery. During pregnancy, HIV-positive women are followed up by the antenatal care (ANC) service and are invited up to four times if they fail to show up. In addition, at the hospital, the HIV test is offered to all women presenting in labor. All prevention and treatment services for HIV-positive women are free of charge.

We collected data on sociodemographic characteristics (age, area of residence of the mother—either urban or rural area); current maternal conditions (HIV status, hypertension, occurrence of other chronic or infectious diseases); obstetric history (parity, previous cesarean sections, previous complicated pregnancies); and ANC services utilization for the current pregnancy (number of ANC visits, access to maternity waiting home before the delivery).

We reviewed the delivery register, the hospital electronic inpatient database, the neonatal admission charts and the maternity waiting home register considering a 4-year period between January 2014 and December 2017. All information sources were linkable to each other. Data collection followed the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement for observational studies (see online supplemental appendix for the checklist of items included). The study complied with the Declaration of Helsinki. Ethical approval was obtained from the ethical committee of the Saint Luke Hospital and, because of the retrospective nature of the study, no informed consent was collected. Personal data were processed in an anonymous and aggregate form.

Contingency tables of frequencies and proportions were used to show findings. We conducted a preliminary bivariate analysis to identify eventual differences between HIV-positive and HIV-negative mothers. Fisher exact test was used to assess the association with potential confounding factors. We performed a crude analysis to establish the association between perinatal mortality (entered as a dependent variable) and HIV positivity of the mother (as an independent variable) for the total sample using logistic regression. All of the other investigated variables were included in the multivariable logistic regression to assess this association after adjusting for potential confounders. Unadjusted and adjusted ORs (AORs), 95% CIs, and *P* values are reported. The level of significance was set at a *P* value of <0.05. Statistical analyses were performed using IBM SPSS Statistics version 28.0.0.0.

3 | RESULTS

A total of 3525 birthing women were enrolled in the study between January 2014 and December 2017, including 1175 cases and 2350 controls, as shown in Table 1. Among these 71 (2.0%) women were HIV-positive of which there were 13 cases (18.3%) and 58 controls (81.7%). Among HIV-negative women, there were 1162 cases (33.6%) and 2292 controls (66.4%). Perinatal mortality was significantly lower among HIV-positive women compared with HIV-negative women (18.3% vs. 33.6%, $P = 0.007$). In fact, crude analysis showed a protective effect of the diagnosis of HIV seropositivity towards perinatal mortality (unadjusted odds ratio [OR], 0.442 [95% CI, 0.241–0.810]).

In Table 2, HIV-positive and HIV-negative women are compared on the basis of sociodemographic characteristics, current maternal conditions, and obstetric history. In addition, the rate of utilization of ANC services and maternity waiting home is described. The main differences between the two groups involve maternal age, area of residence, and access to ANC. HIV-positive mothers were in general significantly older than HIV-negative mothers, with only 13.0% being younger than 25 years, compared with 36.8% of HIV-negative mothers ($P < 0.001$). While 59.2% of HIV-positive mothers were from rural areas, this proportion was higher in HIV-negative mothers (69.4%), although the statistical significance of this difference is just below the set threshold ($P = 0.069$). The protective effect of HIV infection on perinatal mortality remained also after adjusting for all potential confounders investigated (adjusted OR, 0.483 [95% CI, 0.246–0.947]).

TABLE 1 Rate of perinatal death by HIV status in the study population: Ethiopia, 2014–2017.

	Perinatal death		
	Yes (cases)	No (controls)	
	n (%)	*n* (%)	*P* value
HIV-positive	13 (18.3)	58 (81.7)	0.007
HIV-negative	1162 (33.6)	2292 (66.4)	
Total	1175 (100)	2350 (100)	

Given the dramatic difference in access to antenatal services, particularly ANC visits, between HIV-positive and HIV-negative mothers, we conducted a subanalysis to investigate access to antenatal services in relation to the area of residence (either urban or rural), as the latter is known to be associated with perinatal mortality and may act as a distal determinant for access to antenatal services itself.[12] Results of this subanalysis are shown in Table 3. Among HIV-negative women, access to ANC for women from rural areas was almost half as high as for women from urban areas (18.8% vs. 36.2%, $P < 0.001$), whereas in HIV-positive women no differences attributable to the area of residence of the women were noted ($P = 0.795$).

4 | DISCUSSION

In our sample, approximately 2% of birthing women tested positive for HIV, apparently in line with the prevalence in the general population in the Oromia region, as reported in a recent systematic review and meta-analysis.[7] Our results show that exposure to HIV infection is associated with a halved risk of perinatal mortality. This suggests what we might call a paradox, namely that HIV may be a protective factor for perinatal mortality since HIV is recognized as a risk factor for perinatal mortality in low- and middle-income countries.[13,14]

To explain this result, we analyzed in the study population the maternal variables capable of influencing pregnancy outcome. No maternal pathological history was found to differ between the two groups (hypertension or other chronic or infectious diseases other than HIV). No statistically significant differences were found with regard to obstetrical-gynecological history either (multiparity, previous cesarean section, or previous complicated pregnancies). On the contrary, significant differences emerged when considering maternal age: in our sample, HIV-positive birthing women were on average

TABLE 2 Conditions related to maternal health and current pregnancy in HIV-positive and HIV-negative women in the study population: Ethiopia, 2014–2017.

	HIV-positive ($n = 71$)	HIV-negative ($n = 3454$)	
	n (%)	*n* (%)	*P* Value
Sociodemographic characteristics			
Age (years)			
≤24	9 (13.0)	1262 (36.8)	<0.001
25–34	48 (69.6)	1720 (50.2)	
≥35	12 (17.4)	443 (12.9)	
Area of residence			
Urban	29 (40.8)	1057 (30.6)	0.069
Rural	42 (59.2)	2397 (69.4)	
Current maternal conditions			
Hypertension	1 (1.4)	81 (2.3)	1.000
Chronic diseases	2 (2.8)	43 (1.2)	0.229
Infectious diseases (except HIV)	1 (1.4)	8 (0.2)	0.168
Obstetric history			
Parity			
≤4 born	67 (94.4)	3092 (89.5)	0.238
≥5 born	4 (5.6)	362 (10.5)	
Previous cesarean sections			
None	68 (95.8)	3189 (92.3)	0.368
At least once	3 (4.2)	265 (7.7)	
Previous complicated pregnancies			
Negative anamnesis	71 (100.0)	3436 (99.5)	1.000
Positive anamnesis	0 (0.0)	18 (0.5)	
ANC services utilization			
Access to ANC			
None	22 (31.0)	2597 (75.8)	<0.001
At least once	49 (69.0)	828 (24.2)	
Access to MWH	3 (4.2)	191 (5.5)	1.000

Abbreviations: ANC, antenatal care; MWH, maternity waiting home.

TABLE 3 Subanalysis––access rate to ANC services by mother's area of origin and HIV maternal status: Ethiopia, 2014–2017.

	Access to ANC		
	At least once	None	
	n (%)	*n* (%)	*P* value
HIV-positive			
Urban	21 (72.4)	8 (27.6)	0.795
Rural	28 (66.7)	14 (33.3)	
HIV-negative			
Urban	381 (36.2)	672 (63.8)	<0.001
Rural	447 (18.8)	1925 (81.2)	

Abbreviation: ANC, antenatal care.

older than HIV-negative women, as already reported in previous literature.[15] Most important, we observed a statistically significant difference in access to antenatal visits: among the HIV-positive population, a higher proportion of women had access to at least one antenatal visit. Only a quarter of HIV-negative women received at least one visit during pregnancy, whereas, among HIV-positive women, almost 70% had access to ANC at least once.

Access to ANC plays a major role in preventing adverse pregnancy outcomes, and access to at least one antenatal visit is an important protective factor against perinatal mortality in low- and middle-income countries.[16–20] Moreover, in recent years, ANC visits have become a crucial service for intercepting HIV-infected women, through programs that foster a high level of integration between the two services with the aim of improving maternal and child outcomes and reducing the spread of HIV. This is done through PMTCT projects aimed at increasing identification of HIV-positive women, tracing, rapid initiation of ART, and taking care of the mother and newborn after delivery. Women who access ANC are included in integrated pathways of obstetrical-gynecological and infectious care.[21–26]

These care pathways are organized on the basis of international and national guidelines, which are aligned with major global health goals such as the SDGs, also applied in Ethiopia. The use of ART by HIV-positive mothers is the cornerstone of PMTCT strategies during the antepartum and peripartum periods and for the duration of breastfeeding. In 2013, WHO revised HIV treatment and prevention guidelines and recommended that all pregnant and lactating women with HIV infection, regardless of CD4 cell count, should continue ART throughout the life course, in view of the Option B+ regimen. As of October 2015, Option B+ has been implemented nationwide in 14 of 21 countries in sub-Saharan Africa, including Ethiopia. Option B+ is now the rule across sub-Saharan Africa.[27]

In 2014, 2495 health facilities in Ethiopia were providing PMTCT service and the percentage of pregnant women counseled and tested for HIV was 57.0%. In subsequent years, the number of facilities offering this service has increased markedly. Moreover, of the women who received antenatal counseling at these centers, a proportion ranging between 90% and 100% chose to be tested for HIV, with a very high posttest return rate (90%–100%). This means that raising women's awareness of HIV during ANC visits is highly successful and leads to an important increase in women's awareness of their own health and the health of their baby.[28]

HIV-positive women are therefore included in programs with regular follow-ups; these contribute to an increase in the number of ANC visits. According to the guidelines, follow-ups should take place once per trimester until pregnancy. In Ethiopia, four antenatal visits are scheduled, and, to ensure adherence to treatment, the guideline recommends that women lost to care should be contacted within 7 days of their missed appointment.[29]

Effective PMTCT programs require that women and their babies receive a *cascade of interventions*, including antenatal services and HIV testing during pregnancy, use of ART by pregnant women living with HIV, safe birthing practices, and appropriate infant feeding, with infant prophylaxis, HIV testing, and other postnatal health services. Mother and child are placed on pathways that allow for comprehensive health monitoring, providing an important advantage on perinatal survival.[27]

In our study, we also observed that the urban/rural gap in access to ANC nullifies among HIV-positive women. In the general population, coming from urban areas is associated with better neonatal outcomes and greater access to antenatal visits than in rural areas. The urban/rural difference is one of the most important indicators of equity of access to health services, especially in low- and middle-income countries, acting as a proxy for the socioeconomic status of the family. Women living in cities are on average better educated, belong to wealthier families, and have easier access to medical and social care services than women living in rural areas.[11,30] Interestingly, in our sample, the difference in access to ANC between HIV-positive and HIV-negative women changes when stratifying the two populations on the basis of the area of origin. In the HIV-negative population, women who live in cities and have attended at least one ANC visit are twice as likely as women from rural areas (36.2% vs. 18.8%, $P < 0.001$). In contrast, among HIV-positive women, we did not find a statistically significant difference in access to ANC between women living in urban and women living in rural areas.

This success is probably attributable to the fact that Eastern and Southern African countries have in recent years expanded access to prenatal HIV testing for most women, regardless of their level of education, wealth status, and place of residence. The high awareness of PMTCT and the high rate of HIV testing among pregnant women could also be linked to the high diffusion of ANC services.[10] This leads us to believe that programs aimed at intercepting and treating HIV-positive mothers give an advantage with respect to perinatal mortality, but, not only that, these entrenched and widespread programs effectively nullify socioeconomic differences in access to ANC, supporting the fact that highly integrated ANC-HIV services promote not only better outcomes but also greater equity in access to care.

This study has several strengths. The number of variables examined is large, allowing adjustment for a number of potential confounders. It should also be noted that all cases occurring during the study period were included, resulting in a relatively large sample. However, this study has some limitations that need to be taken into account. Maternal socioeconomic status was not specifically assessed, although this may play a role in determining, at least in part, the risk of perinatal mortality. Our work is based on a single-center study, which limits the generalizability of our results and comparison with other contexts. Further multicenter studies would be welcome in this regard.

Our study shows that in HIV-positive birthing mothers, perinatal mortality is halved compared with HIV-negative women, and the difference in access to maternal and child services by area of origin (either urban or rural) is eliminated. A higher proportion of HIV-positive women had at least one ANC visit. These data highlight the benefits of integrated ANC and HIV services in promoting access to the health care system, reducing inequalities and improving neonatal mortality. All of this suggests that resource allocation aimed at strengthening integrated health systems and breaking down barriers to accessing services may be key to improving pregnancy outcomes. Further studies are required to assess which of the strategies implemented, starting with active call and catch-up, are effective in promoting accessibility to services and adherence to follow-up. Such levers could then be used in maternal and child services, targeting all pregnant women, regardless of HIV-positive status, with a net reduction in perinatal mortality rates.

AUTHOR CONTRIBUTIONS

Conception or design of the work: M. Fonzo, T. D. Zuanna, G. Putoto, C. Bertoncello; Data collection: T. D. Zuanna, C. Resti, A. Tsegaye, G. Azzimonti, F. Manenti; Data analysis and interpretation: M. Fonzo, B. Sgorbissa, M. Centomo, C. Bertoncello; Drafting the article: M. Fonzo, T. D. Zuanna, S. Ferretti, I. Amoruso; Critical revision of the article: G. Putoto, T. Baldovin, C. Bertoncello; Final approval of the version to be submitted: M. Fonzo, T. D. Zuanna, C. Resti, A. Tsegaye, G. Azzimonti, B. Sgorbissa, M. Centomo, S. Ferretti, F. Manenti, G. Putoto, C. Bertoncello.

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None.

DATA AVAILABILITY STATEMENT

Research data are not shared.

ORCID

M. Fonzo https://orcid.org/0000-0002-9561-0711

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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Rewarming rate of hypothermic neonates in a low-resource setting: a retrospective single-center study

PAPER

Authors
Rossi E., Maziku D.M., Leluko D.E., Guadagno C., Brasili L., Azzimonti G., Putoto G., Pietravalle A., Cavallin F., Trevisanuto D.

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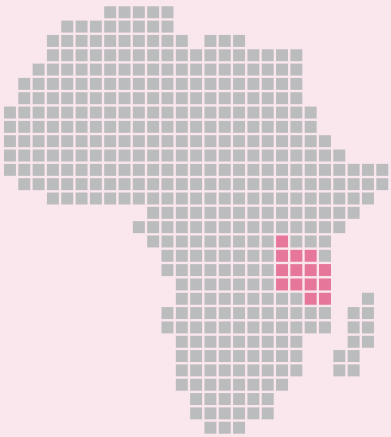

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EDITED BY
Jeroen J. van Vonderen,
Leiden University Medical Center (LUMC), Netherlands

REVIEWED BY
Christopher McKinlay,
The University of Auckland, New Zealand
Joaquim Pinheiro,
Albany Medical College, United States
Susan Niermeyer,
University of Colorado Denver, United States

*CORRESPONDENCE
Daniele Trevisanuto
daniele.trevisanuto@unipd.it

†These authors have contributed equally to this work

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Rewarming rate of hypothermic neonates in a low-resource setting: a retrospective single-center study

Elisa Rossi[1], Donald Micah Maziku[2], Dionis Erasto Leluko[2], Chiara Guadagno[1], Luca Brasili[1], Gaetano Azzimonti[1], Giovanni Putoto[3], Andrea Pietravalle[3], Francesco Cavallin[4†] and Daniele Trevisanuto[5*†]

[1]Doctors with Africa CUAMM, Dar es Salaam, Tanzania, [2]Maternal and Child Department, Tosamaganga Council Designated Hospital, Ipamba, Tanzania, [3]Department of Research, Doctors with Africa CUAMM, Padova, Italy, [4]Independent Statistician, Solagna, Italy, [5]Department of Woman's and Child's Health, University Hospital of Padova, Padova, Italy

Background: Hypothermic neonates need to be promptly rewarmed but there is no strong evidence to support a rapid or a slow pace of rewarming. This study aimed to investigate the rewarming rate and its associations with clinical outcomes in hypothermic neonates born in a low-resource setting.
Methods: This retrospective study evaluated the rewarming rate of hypothermic inborn neonates admitted to the Special Care Unit of Tosamaganga Hospital (Tanzania) in 2019–2020. The rewarming rate was calculated as the difference between the first normothermic value (36.5–37.5°C) and the admission temperature, divided by the time elapsed. Neurodevelopmental status at 1 month of age was assessed using the Hammersmith Neonatal Neurological Examination.
Results: Median rewarming rate was 0.22°C/h (IQR: 0.11–0.41) in 344/382 (90%) hypothermic inborn infants, and was inversely correlated to admission temperature (correlation coefficient −0.36, $p < 0.001$). Rewarming rate was not associated with hypoglycemia ($p = 0.16$), late onset sepsis ($p = 0.10$), jaundice ($p = 0.85$), respiratory distress ($p = 0.83$), seizures ($p = 0.34$), length of hospital stay ($p = 0.22$) or mortality ($p = 0.17$). In 102/307 survivors who returned at follow-up visit at 1 month of age, rewarming rate was not associated with a potential correlate of cerebral palsy risk.
Conclusions: Our findings did not show any significant association between rewarming rate and mortality, selected complications or abnormal neurologic exam suggestive of cerebral palsy. However, further prospective studies with strong methodological approach are required to provide conclusive evidence on this topic.

KEYWORDS

rewarming, newborns, hypotermia, cerebral palsy, low-resource setting

Introduction

Worldwide, over 2 million neonates die every year, with the highest risk during the first 24 h of life (1). Postnatal temperature plays a crucial role in this context, and hypothermia has been recognized as an important risk factor for adverse neonatal outcomes in both high- and low-resource settings (2). In fact, hypothermia is strongly associated with neonatal mortality, with a dose-response effect which rapidly increases the risk of mortality when departing from normothermia (3).

In addition, hypothermic neonates may experience several complications such as bradycardia, tachypnea, apnea, distress, poor feeding, hypoglycemia, sepsis, and metabolic acidosis (2). The World Health Organization (WHO) has been stressing the importance of preventing thermal loss since 1993 (4), nevertheless the incidence of neonatal hypothermia remains unacceptable especially in low-resource settings (2, 5, 6). Hence, hypothermic neonates need to be promptly rewarmed and different options may be available for achieving normothermia (2).

Previous studies assessed the rewarming pace in the treatment of hypothermic neonates (7–13), but this aspect remains a matter of debate and official recommendations are still lacking (14). Slow rewarming may be preferred if considering its claimed protective role on cerebral flow and rapid cardiovascular changes (15–17). On the other hand, some reports advise that rapid rewarming may reduce the hazard associated with prolonged hypothermia (12, 18–20). In addition, anecdotal cases of complications such as hyperthermia, convulsions, and apnea were ascribed as reasons for avoiding rapid rewarming (15, 16, 21).

Hence, to date, there is no clear indication whether to prefer a rapid or a slow pace when rewarming hypothermic neonates. This study aimed to investigate the rewarming rate and its associations with clinical outcomes in hypothermic neonates born in a low-resource setting.

Materials and Methods

Study design and setting

This is a retrospective study on rewarming rate of hypothermic neonates admitted to the special care unit in a low-resource setting. The study was conducted at the Special Care Unit (SCU) of Tosamaganga District Hospital (Tanzania), where about 3,000 deliveries and 500 admissions occur every year. The hospital is a referral facility for a geographical area covering around 260,000 people for major obstetric emergencies. The SCU offers basic intensive care including intravenous therapies, phototherapy and oxygen therapy. Non-invasive positive-pressure support and mechanical ventilation are not available. At admission to the SCU, all neonates are screened for hypothermia, while hypoglycemia and hyperbilirubinemia are investigated based on clinical suspicion of abnormality.

Since 2019, the hospital provides follow-up for all discharged babies during their first year of life.

The study was part of a project approved by the Institutional Review Board of Tosamaganga Hospital (protocol number DOIRA/TCDH/VOL.016/5), which waived the need for written informed consent given the retrospective nature of the study and the use of anonymized data from hospital records. The research was performed in accordance with relevant guidelines and regulations.

Patients

All neonates admitted with hypothermia to the SCU of Tosamaganga Hospital between January 1, 2019, and December 31, 2020 were evaluated for inclusion in the study. Exclusion criteria were (i) outborn neonates, (ii) being admitted to the SCU after the first day of life, and iii) missing data about body temperature at admission.

Thermal management

At admission to SCU, neonatal axillary temperature was measured by the attending nurse using a digital thermometer (C202; Terumo, Tokyo, Japan). Severe/moderate hypothermia was defined as temperature <36°C, mild hypothermia as 36–36.4°C, normal temperature as 36.5–37.5°C and hyperthermia as >37.5°C (22). Hypothermic neonates were rewarmed in the SCU using three infant warmers and two incubators, which were used in manual mode due to the lack of temperature probes. The radiant warmer was set at 40% heater power and increased/decreased by 5% every 30 min according to measured temperature, until normothermia was reached. The incubator was manually set at 37°C (without humidity) until normothermia was reached. The rewarming rate was calculated as the difference between the first normothermic value (36.5–37.5°C) and the admission temperature, divided by the time elapsed.

Neurological examination

The description of the neurological follow-up was reported elsewhere (23). Briefly, the neurological examination was carried out using the Hammersmith method because of the lack of expensive diagnostic equipment and personnel trained in neurological examination in the setting. We used the Hammersmith Neonatal Neurological Examination (HNNE) by Spittle et al. (24, 25), who used the percentiles of the score to define low risk (10th–90th centiles), medium risk (5th–10th or 90th–95th centiles), and high risk (<5th or >95th centiles) of neurodevelopmental impairment. Healthcare providers with 6 months of on-the-job training (CG and LB) examined the infants with the HNNE and classified them as low risk, medium risk, or high risk of neurodevelopmental impairment. At Tosamaganga Hospital, the neonatal follow-up program is scheduled at 1–3–6–9–12 months of age, but we focused on the 1-month assessment because of the high rate of loss to follow-up at later ages (22).

Data collection

All data were retrieved from hospital records by hospital staff and were collected in an anonymized dataset. Diagnosis at admission was based on clinical examination because availability of laboratory and instrumental exams was limited. The definitions of diagnoses at admission were described elsewhere (23). Briefly, birth asphyxia was defined as 5-min Apgar Score below 7. Respiratory distress was defined as presence of signs of increased work of breathing (assessed by the Silverman Anderson Score) and/or hypoxemia with need for supplemental oxygen. Kramer's rule was used to classify the jaundice (26). Skin infection included abscess and

Rossi et al. 10.3389/fped.2023.1113897

omphalitis. Sepsis was defined as presence of clinical signs (i.e., fever, hypotonia, irritability) within (early onset) or after (late onset) the first 7 days of life. The threshold of 2.6 mmol/L blood glucose was used to define hypoglycemia.

Statistical analysis

Continuous data were summarized as median and interquartile range (IQR), and categorical data as number and percentage. Rewarming rate was compared among subgroups of patients using Mann-Whitney test or Kruskal–Wallis test. Correlation between continuous variable was evaluated using Spearman correlation coefficient). Logistic regressions were used to evaluate the effect of rewarming rate on jaundice and respiratory distress, adjusting for clinically relevant confounders (birth weight, admission temperature, Apgar score at 5 min, meconium-stained fluid, caesarean section and birth asphyxia). Linear regression was used to evaluate the effect of rewarming rate on length of hospital stay, adjusting for clinically relevant confounders (birth weight, admission temperature, Apgar score at 5 min, meconium-stained fluid, caesarean section and birth asphyxia). Logistic regression was used to evaluate the effect of rewarming rate on mortality in neonates without possibly lethal congenital anomalies (cardiac heart disease, conjoined sibling, cranial malformation), adjusting for clinically relevant confounders (birth weight and Apgar score at 5 min). Multivariable analyses of hypoglycemia, late onset sepsis and seizures could not be performed due to the small occurrence of such events. Gestational age could not be included because it was largely missing. All tests were two-sided and a *p*-value less than 0.05 was considered statistically significant. Statistical analysis was performed using R 4.1 (R Foundation for Statistical Computing, Vienna, Austria) (27).

Results

Among 906 newborn infants who were admitted to the SCU of Tosamaganga Hospital during the study period, 456 were inborn neonates admitted at the day of birth. Of them, three with unknown admission temperature and 71 normothermic infants were excluded. Among the 382 hypothermic (<36.5°C) inborn infants who were admitted at their day of birth (382/453, 84.3%), the rewarming rate could be retrieved in 344 infants (90%) who were included in the analysis (**Figure 1**).

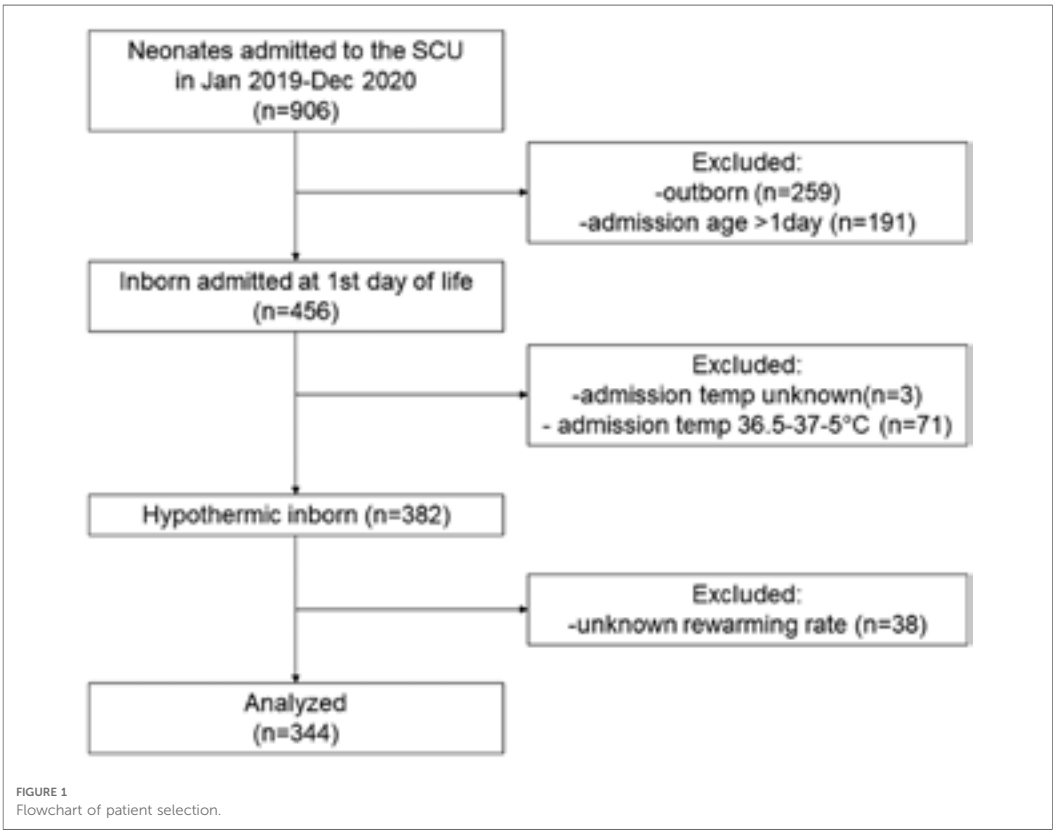

FIGURE 1
Flowchart of patient selection.

Patient characteristics are reported in Table 1. Information on gestational age was largely missing (312/344, 90.7%).

Median temperature at admission was 35.2°C (IQR: 34.5–35.8°C; min 30.6°C, max 36.4°C) (Figure 2A). Severe/moderate hypothermia was recorded in 289 neonates (84.0%) and mild hypothermia in 55 (14.0%). Median rewarming rate was 0.22°C/h (IQR: 0.11–0.41; 0.03–2.70) (Figure 2B) and was inversely correlated to admission temperature (Spearman correlation coefficient −0.36, $p < 0.001$) (Figure 2C). Median rewarming rate was 0.24°C/h (IQR: 0.13–0.43) in neonates admitted with severe/moderate hypothermia and 0.10°C/h (IQR: 0.06–0.23) in those admitted with mild hypothermia ($p < 0.0001$ (Figure 2D). Of note, 43 neonates (12.5%) reached the hyperthermic range (>37.5°C) during the rewarming process, and they had a higher rewarming rate with respect to neonates ending up in the normothermic range (36.5–37.5°C) ($p = 0.007$, Table 2).

TABLE 1 Patient characteristics.

N of neonates	344
Males	176 (51.2)
Birth weight, grams[a]	2,675 (1,880–3,100)
Birth weight:	
Normal BW (≥2,500 grams)	190 (55.2)
LBW (1,500–2,499 grams)	110 (32.0)
VLBW (1,000–1,499 grams)	38 (11.1)
ELBW (<1,000 grams)	6 (1.7)
Temperature at admission, °C[a]	35.2 (34.6–35.8)
Temperature at admission:	
36–36.5°C	55 (16.0)
<36°C	289 (84.0)
HIV-positive mother	30/339 (7.5)
Maternal VDRL[b]	5/331 (1.5)
Apgar score at 1 min[a]	5 (3–7)
Apgar score at 5 min[a]	7 (5–10)
PROM[c]	66 (19.2)
Meconium:	
Clear	243 (70.6)
Stained	101 (29.4)
Maternal fever	6 (1.7)
Dexamethasone:	
None	310 (90.1)
Complete cycle	22 (6.4)
Incomplete cycle	12 (3.5)
Mode of delivery	
Spontaneous vaginal delivery	161 (46.8)
Assisted vaginal delivery	28 (8.1)
Caesarean section	155 (45.1)
Twin pregnancy	51 (14.8)
Birth asphyxia	132 (38.4)
Respiratory distress	235 (68.3)
Early onset sepsis	18 (5.2)
Late onset sepsis	15 (4.4)
Hypoglycemia	17 (4.9)
Jaundice	77 (22.4)
Skin infection	10 (2.9)
Major malformations or chromosomopathies[d]	15 (4.4)
Seizures	37 (10.8)
Hyperthermia after rewarming	43 (12.5)

Data were summarized as *n* (%) or.
[a]median (IQR).
[b]VDRL was treated in 5/5 mothers.
[c]PROM prophylaxis in 21/66 mothers.
[d]Major malformations included cardiac heart disease ($n = 6$), club feet ($n = 3$), conjoined sibling ($n = 2$), cranial malformation ($n = 1$), Down syndrome ($n = 1$), imperforate anus ($n = 1$) and hypospadias ($n = 1$).

Treatments included antibiotics (233 neonates, 67.7%), anticonvulsant (37 neonates, 10.8%) and aminophylline or caffeine (62 neonates, 18.0%). Oxygen therapy was administered to 308 neonates (89.5%) for a median of 2 days (IQR: 1–6). IV fluids were administered to 257 neonates (74.7%) for a median of 6 days (IQR: 4–9). Phototherapy was offered to 64 neonates (18.6%).

Rewarming rate was not associated with hypoglycemia ($p = 0.16$), late onset sepsis ($p = 0.10$), jaundice ($p = 0.85$), respiratory distress ($p = 0.83$), seizures ($p = 0.34$) or length of hospital stay ($p = 0.22$) (Table 2). Multivariable analyses confirmed that rewarming rate was not associated with jaundice (odds ratio 0.72, 95% confidence interval 0.36–1.90; $p = 0.72$), respiratory distress (odds ratio 0.74, 95% confidence interval 0.37–1.56; $p = 0.41$) or length of hospital stay (mean difference −2.4 days, 95% confidence interval −5.4–0.6 days; $p = 0.11$), adjusting for clinically relevant confounders. Unfortunately, multivariable analyses of hypoglycemia, late onset sepsis and seizures could not be performed due to the small occurrence of such events.

After a median length of stay of 7 days (IQR: 5–12), 37 neonates died (10.8%) while 302 were discharged (87.8%) and five were transferred to other health facilities (1.4%). Median rewarming rate was 0.26 °C/h (IQR: 0.14–0.57) in neonates who died and 0.21°C/h (IQR: 0.11–0.40) in those who did not ($p = 0.17$). At multivariable analysis, rewarming rate was not an independent predictor of mortality (odds ratio 1.27, 95% confidence interval 0.48–3.09; $p = 0.61$) in neonates without possibly lethal congenital anomalies (cardiac heart disease, conjoined sibling, cranial malformation), adjusting for clinically relevant confounders.

Later, 102 out of 307 survivors (33.2%) returned at follow-up visit at 1 month of age. The neurodevelopmental assessment suggested low potential correlate of cerebral palsy risk in 68 neonates (66.7%), moderate risk in 26 (25.5%) and high risk in 8 (7.8%). Median rewarming rate was 0.20°C/h (IQR: 0.10–0.29) in neonates with lower potential correlate of cerebral palsy risk, 0.20°C/h (IQR: 0.15–0.47) in those with moderate risk and 0.22°C/h (IQR: 0.07–0.47) in those with high risk ($p = 0.63$).

Discussion

Our findings revealed a median rewarming rate of 0.22°C/h in hypothermic neonates, with a large variability ranging from 0.03–2.70°C/h. The rewarming rate was inversely correlated to admission temperature but was not associated with any clinical outcomes apart from the occurrence of hyperthermia with rapid rewarming.

Although avoiding heat losses immediately after birth is acknowledged as a crucial aspect in neonatal management, a substantial proportion of neonates is hypothermic at admission to intensive care unit and requires thermal intervention (2). Our

Rossi et al. 10.3389/fped.2023.1113897

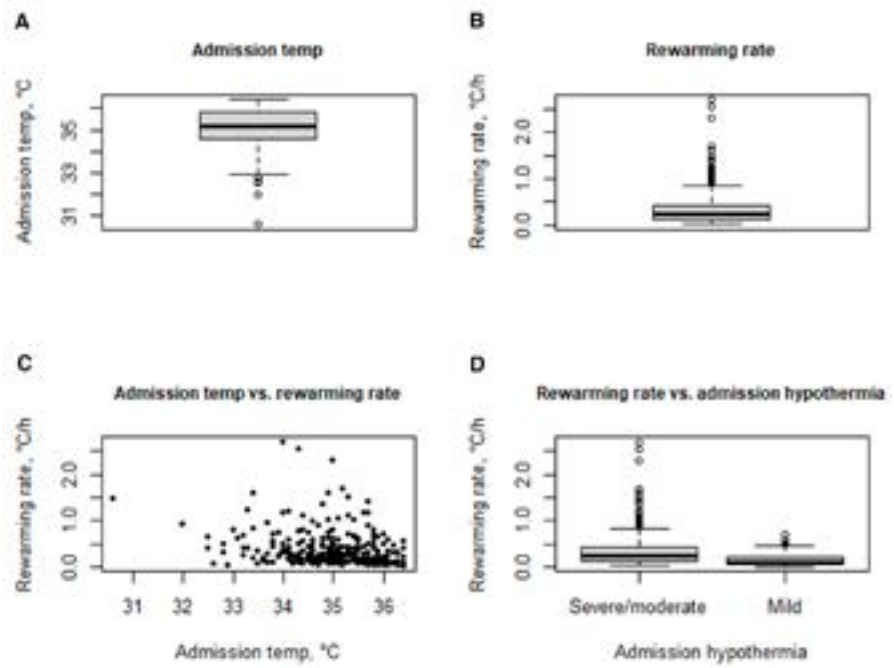

FIGURE 2
Temperature at admission (A); rewarming rate (B); correlation between admission temperature and rewarming rate (C); rewarming rate according to severe/moderate vs. mild hypothermia at admission.

TABLE 2 Association between rewarming rate and clinical outcome measures.

Outcome measure	Rewarming rate was (°C/h)	*p*-value
Hypoglycemia:		0.16
No	0.22 (0.11–0.41)	
Yes	0.16 (0.07–0.22)	
Late onset sepsis:		0.10
No	0.22 (0.11–0.42)	
Yes	0.16 (0.08–0.23)	
Jaundice:		0.85
No	0.22 (0.10–0.42)	
Yes	0.20 (0.12–0.35)	
Respiratory distress:		0.83
No	0.21 (0.11–0.42)	
Yes	0.22 (0.11–0.41)	
Seizures:		0.34
No	0.22 (0.11–0.42)	
Yes	0.19 (0.08–0.30)	
Hyperthermia after rewarming:		0.007
No	0.20 (0.11–0.37)	
Yes	0.33 (0.18–0.55)	
Length of hospital stay	−0.06 [a]	0.22

Data were summarized as median (IQR) or.
[a]Spearman correlation coefficient.

data confirmed a high proportion (84.3%) of hypothermia among inborn neonates admitted to the SCU.

When dealing with cold infants, health caregivers face difficult choices as different options may be considered (using manual or automatic rewarming, setting a target temperature or a rewarming rate, using the maximum output of the warmer or adjusting the output during the process) but the optimal rewarming rate is still unknown (14). Literature offers different reasons for choosing between slow and rapid rewarming of hypothermic neonates. Some authors supported the rapid rewarming as it may lower the hazard associated with prolonged hypothermia (12, 18–20). Others argued that slow rewarming may have a protective role on cerebral flow and rapid cardiovascular changes (15–17). Of note, some authors recommended avoiding rapid rewarming on the basis of anecdotal cases of hyperthermia, convulsions or apnea (15, 16, 21). On the other hand, rapid rewarming may allow to treat a larger number of hypothermic neonates in settings with high burden of neonatal hypothermia and limited numbers of warmers machines (13). However, literature does not provide any conclusive indications whether to prefer a rapid or a slow pace when rewarming hypothermic neonates, since previous studies reported comparable clinical outcomes between the two

approaches (7, 12, 13). Our data confirmed those findings, as rewarming rate was not associated with any clinical outcomes including hypoglycemia, late onset sepsis, jaundice, respiratory distress, seizures, length of hospital stay, or mortality. On the other hand, faster rewarming rate was associated with increased likelihood of reaching hyperthermia during the rewarming process, and this may exacerbate hypoxic-ischemic brain injury in asphyxiated newborns.

Of note, we did not find any association between rewarming rate and potential correlate of cerebral palsy risk at 1 month of age, but caution is suggested as only one third of the survivors attended the follow-up visit. While the HNNE has being considered a reliable assessment of neurobehaviour in the neonatal period (28), the reader should be aware that its score intervals were used as proxy for risk of cerebral palsy in our study.

Beyond the uncertainty around rewarming rate, important aspects to consider when dealing with cold infants in low-resource settings include the lack of protocol for rewarming, the lack of temperature probes to provide continuous monitoring, and the lack of skin-to-skin contact as a method for rewarming. Implementation of these approaches may contribute to reduce the burden on hypothermia but requires efforts involving organizational, cultural and economic assets.

Literature shows high heterogeneity in the rewarming rate of hypothermic neonates, with a wide range from 0.71 to 5.5°C/h (10, 13, 18, 29). Our data revealed a slower median rewarming rate (0.22°C/h), but a large range which might be due to the lack of a standardized protocol, the limited availability of warmer machines and the severity of the hypothermia. The inverse correlation between admission temperature and rewarming rate suggests that the severity of the hypothermia might have influenced the health care providers, who decided about the speed of the rewarming in absence of a standardized protocol. In our series, most hypothermic neonates were rewarmed at <0.5°C/h, which was the threshold considered in previous studies (12, 13) as it is the rewarming rate used in asphyxiated infants treated with therapeutic hypothermia (30).

The study has some limitations that should be considered when reading the results. First, the retrospective design limits the quality of the data and does not allow drawing any causal relationships, despite our results were in broad agreement with the literature. Second, the partial compliance and the short duration of the follow-up suggest caution when speculating about the long-term neurological status of the hypothermic neonates.

Conclusions

Our findings did not show any significant association between rewarming rate and mortality, selected complications or abnormal neurologic exam suggestive of cerebral palsy. However, available information resulted from studies suffering from several limitations including the retrospective design or the small sample size, hence further prospective studies with strong methodological approach are required to provide conclusive evidence on the rewarming rate of hypothermic neonates.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Institutional Review Board of Tosamaganga Hospital (protocol number DOIRA/TCDH/VOL.016/5). Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

ER: contributed protocol preparation, data collection, wrote the draft of the manuscript and critically reviewed the manuscript. DMM: contributed to protocol preparation, data collection and interpretation, and critically reviewed the manuscript. DEL: contributed to protocol preparation, data collection and interpretation, and critically reviewed the manuscript. CG: contributed to protocol preparation, data collection and interpretation, and critically reviewed the manuscript. LB: contributed to protocol preparation, data collection and interpretation, and critically reviewed the manuscript. GA: contributed to protocol preparation, data interpretation, and critically reviewed the manuscript. GP: contributed to protocol preparation, data interpretation, and critically reviewed the manuscript. AP: contributed to protocol preparation, data interpretation, and critically reviewed the manuscript. FC: conceived the study, contributed to data analysis, data interpretation, and writing of the manuscript. DT: conceived the study, and contributed to data interpretation, and writing of the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Adherence to WHO guidelines on severe pneumonia management in children and its impact on outcome: an observational study at Jinka General Hospital in Ethiopia

PAPER

Authors
La Vecchia A., Teklie B. G., Mulu D. A., Toitole K. K., Montalbetti F., Agostoni C., Hessebo T. T., Tsegaye A., Pietravalle A., Manenti F., Tognon F., Pisani L. and Hagos E.

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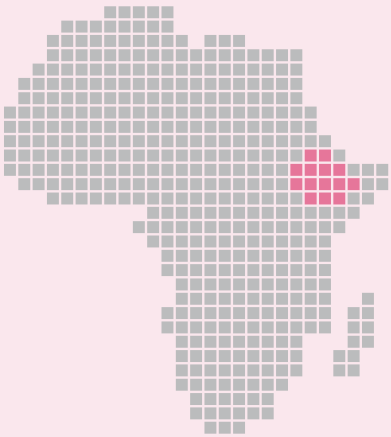

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EDITED BY
Richard Adegbola,
Nigerian Institute of Medical Research (NIMR), Nigeria

REVIEWED BY
Ozgur Kasapcopur,
Istanbul University-Cerrahpasa, Türkiye
Jakariya Md.,
North South University, Bangladesh

*CORRESPONDENCE
Carlo Agostoni
carlo.agostoni@unimi.it

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Adherence to WHO guidelines on severe pneumonia management in children and its impact on outcome: an observational study at Jinka General Hospital in Ethiopia

Adriano La Vecchia[1], Bereket Gebremedhin Teklie[2], Dagmawi Awoke Mulu[2], Kusse Koirita Toitole[3], Francesca Montalbetti[2], Carlo Agostoni[4,1]*, Tesfayesus Tefera Hessebo[2], Ademe Tsegaye[5], Andrea Pietravalle[6], Fabio Manenti[6], Francesca Tognon[6], Luigi Pisani[6] and Eleni Hagos[3]

[1]Department of Clinical Sciences and Community Health (DISCCO), University of Milan, Milan, Italy, [2]Jinka General Hospital, Jinka, South Omo, Ethiopia, [3]Doctors with Africa CUAMM, Jinka, South Omo, Ethiopia, [4]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Pediatric Area, Milan, Italy, [5]Doctors With Africa CUAMM, Addis Ababa, Ethiopia, [6]Operational Research Unit, Doctors With Africa CUAMM, Padua, Italy

Introduction: Poor adherence to guidelines during empirical antibiotic prescription in low-income countries could increase antimicrobial resistance without improving outcomes. Revised World Health Organization (WHO) guidelines published in 2014 on childhood (2–59 months) pneumonia re-defined the classification of severe pneumonia and changed the first-line treatment. The adherence to WHO guidelines in southern Ethiopia at the hospital level is unknown. We sought to determine the adherence to WHO guidelines on severe pneumonia first-line treatment in children in an Ethiopian referral hospital and assess the impact of non-adherence on patient outcomes.

Methods: An observational study was conducted on all children (2–59 months) clinically diagnosed with severe pneumonia and admitted to the Pediatric Ward of Jinka Hospital from 1 June 2021 to 31 May 2022. Exclusion criteria included a known HIV infection, ongoing antibiotic treatment before the event not related to acute pneumonia, or any other severe bacterial infection, confirmed or suspected. Adherence to guidelines was defined as first-line treatment with ampicillin or benzylpenicillin and gentamicin at the recommended dose. We compared the patients treated adherently vs. non-adherently. For categorical variables, the chi-square or Fisher's exact test was used, while for continuous variables, the Mann–Whitney U-test was used. Multivariate logistic regression was used to evaluate the association between adherence and demographic and clinical characteristics.

Results: During the observational period, 266 patients were registered as having severe pneumonia with an age between 2 and 59 months. After excluding 114 patients due to missing charts or other exclusion criteria, a total of 152 patients were included in the analysis. Of these, 78 (51%) were girls with a median age of 10 months (IQR 7–14). Overall, 75 (49%) patients received therapy according to the WHO guidelines. Compared to patients treated adherently to the guidelines,

patients not treated adherently had similar outcomes [median length of stay of 3 (IQR 3–5) and 4 (IQR 3–6) days], median duration of oxygen therapy of 2 (IQR 1–3) for both the groups, and self-discharge rates of 5% and 6.5%, respectively).

Conclusion: Adherence to the revised WHO guideline was limited and not associated with outcomes. Efforts should focus on reducing the gap between theory and practice.

KEYWORDS

Africa, children, Ethiopia, guidelines, pneumonia, treatment, WHO

1. Introduction

Sub-Saharan Africa has the world's highest rate of under-5 mortality, estimated in 2019 at 75.8 deaths per 1,000 live births, or one in every 13 children dying before reaching the age of 5 years (1). Among children aged 1–59 months, lower respiratory infections are the leading cause of death (2). Lower respiratory infections may present with different clinical symptoms such as cough, fatigue, obstruction, and respiratory distress with or without fever (3). Ethiopia is one of the five countries where nearly half of all under-5 deaths occurred in 2019 (1), and pneumonia causes 18% of all deaths in this age group (4).

The revised World Health Organization (WHO) guidelines on childhood pneumonia (2 months—5 years) published in 2014 re-defined the classification of severe pneumonia and changed the first-line treatment (5). Once diagnosed, pneumonia is classified as severe if one or more of the following symptoms are present: inability to drink, persistent vomiting, convulsions, lethargy or unconsciousness, stridor in a calm child, or severe malnutrition. The first-line recommended treatment for severe pneumonia is the parenteral combination of ampicillin or benzylpenicillin and gentamicin 7.5 mg/kg once a day for at least 5 days. Ceftriaxone should be used only as a second-line treatment in case of failure of the first-line treatment (5).

The WHO defined antimicrobial resistance (AMR) as one of the biggest threats to public health of the 21st-first century, and antibiotic misuse is one of the major drivers of AMR (6, 7). Antibiotics are the most frequently prescribed drugs worldwide (8), with a high rate of inappropriate prescriptions reported by various authors (9–11). In Ethiopia, most antibiotic prescriptions are empirically made, and the prescribing pattern is non-compliant with the WHO standards (12, 13).

Two previous studies, one in a northern region and another in a southern region of Ethiopia, found poor adherence to the Integrated Community Case Management of Newborn and Child Illness strategy in primary care settings (health posts and health centers), but the management of pneumonia at the hospital level was not investigated (14, 15). Little is known about adherence to guidelines on child pneumonia treatment at the hospital level in southern Ethiopia. Our study aimed to fill this knowledge gap, and the objectives were as follows: (1) to determine adherence to the WHO guidelines for severe pneumonia first-line treatment in under-5 children in a referral hospital in southern Ethiopia and (2) to compare the impact on patient outcomes of adherent and non-adherent empirical antibiotic treatments.

The findings will benefit local practitioners and health actors, as well as serve as a baseline study for any further studies on this topic in the area.

Abbreviations: AMR, antimicrobial resistance; CI, 95% confidence interval; COVID-19, Coronavirus Disease 2019; HIV, human immunodeficiency virus; IQR, interquartile range; OR, odd ratio, SAM, severe acute malnutrition; TFC, therapeutic feeding center, WHO, World Health Organization.

2. Materials and methods

2.1. Design, setting, and patients

We performed a retrospective observational study at Jinka General Hospital, a referral hospital located in Jinka Town, South Omo Zone, Southern Nations, Nationalities, and Peoples Region.

The South Omo Zone is an area of ~2.3 million hectares in southern Ethiopia, bordering Kenya and South Sudan. Based on the 2022 Ethiopian Statistical Service projections (16), the South Omo Zone has a population of more than 800,000 inhabitants living in a traditional agro-pastoral system of subsistence. The population pyramid has a large base with a high prevalence of children under the age of five (17). The Pediatric Ward at Jinka Hospital consists of 19 beds and admits an average of 850 patients annually.

The study examined clinical records of children admitted with pneumonia from 1 June 2021 to 31 May 2022.

In Jinka General Hospital, clinical information is recorded on paper. Patients to be included were identified from the admission register of the Pediatric Ward. Data were then extracted from the patient chart with the help of the chart room employee. Three trained physicians analyzed patient charts, collecting demographic, clinical, and therapeutic data in a standardized case report form.

The inclusion criteria were a pediatric ward admission of a patient aged 2–59 months with a clinical diagnosis of severe pneumonia during the observational period. The diagnosis was considered starting from the registry and was subsequently confirmed by the data from the medical record.

Exclusion criteria were (1) incomplete information (missing medical record), (2) a known HIV infection, (3) an ongoing antibiotic treatment before the admission not correlated with acute pneumonia, and (4) other concomitant severe bacterial infections confirmed or suspected (e.g., sepsis and meningitis).

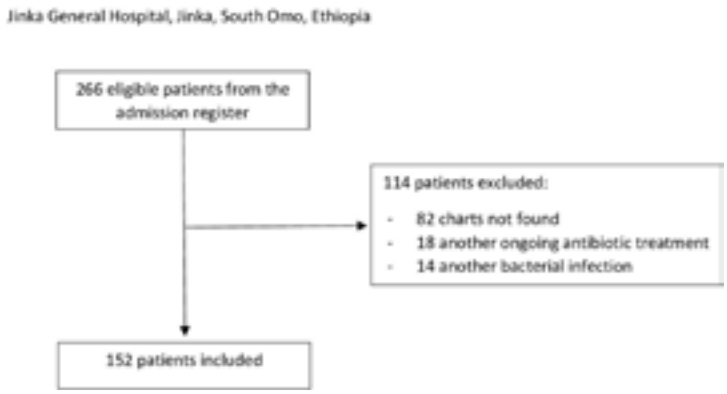

FIGURE 1
Inclusion/exclusion flowchart. The inclusion criteria were a pediatric ward admission of a patient aged 2–59 months with a clinical diagnosis of severe pneumonia during the observational period (1 June 2021 to 31 May 2022). Exclusion criteria were (1) incomplete information (missing medical record), (2) a known HIV infection, (3) an ongoing antibiotic treatment before the admission not correlated with acute pneumonia, and (4) other concomitants severe bacterial infections confirmed or suspected (e.g., sepsis and meningitis).

We evaluated the presence of concurrent chronic diseases, such as cardiovascular disease, pulmonary disease, neurologic disease, and metabolic disease, which were reported as comorbidities.

During data collection, the authors had access to information that could identify individual participants. The Jinka University Ethical Committee approved the study (reference number JKU/RCE/ERC/055/15), which included a waiver of informed consent because of the retrospective nature of the investigation.

2.2. Study endpoints

We evaluated the adherence to the WHO guidelines for first-line treatment with ampicillin or benzylpenicillin and gentamicin at the recommended dose (5).

Three different indicators were considered for the outcome evaluation: oxygen therapy days, hospitalization days, and death in the hospital.

2.3. Data analysis

Descriptive statistics were performed. Continuous data were presented as median and interquartile range and categorical data as numbers and percentages (18, 19). We compared the patients' outcome indicators between patients treated in adherence to the WHO guidelines and other patients. We also evaluated self-discharges as possible confounders. The chi-square test or Fisher's exact test was used for categorical variables, and the Mann–Whitney U-test was used for continuous ones. We used a non-parametric test after verifying that the continuous variables were not normally distributed using the Shapiro–Wilk normality test. We used multivariate logistic regression to evaluate the association between adherence to the guideline (as the dependent variable) and the independent variables such as sex, age, referral status, and patient severity (defined as the presence of central cyanosis/oxygen saturation <90%, severe respiratory distress, or lethargy). We found no significant sources of bias in the study's design. We performed analyses based only on the available data.

A p-value of <0.05 was considered statistically significant. Statistical analysis was performed using R software (version 3.6.3 for Windows).

3. Results

3.1. Patient cohort

During the observational period, 266 patients aged between 2 and 59 months were recorded in the pediatric ward registry as having severe pneumonia at admission. Considering the number of patients, they represent ∼30% of all admissions.

Among them, 114 patients were excluded: 82 patients' charts were not found, 18 patients were on another ongoing antibiotic therapy, and 14 had other suspected or confirmed severe bacterial infections (Figure 1). None of the patients was registered as HIV positive.

A total of 152 patients were included in the study, 78 (51%) girls and 74 (49%) boys, with a median age of 10 months (IQR 7–14). The included patients had no missing data. Five (3%) patients were referred from other health centers, and seven (5%) patients had comorbidities. Table 1 shows the demographic and clinical characteristics of the sample.

At least one of the WHO's severe defining symptoms was present in 133 (87.5%) patients. The most prevalent symptom was severe respiratory distress reported in 110 (72%) patients, followed by central cyanosis or oxygen saturation <90% in 78 (51%) patients, lethargy or unconsciousness in 30 (20%) patients, persistent vomiting in 20 (13%) patients, inability to drink in 2

TABLE 1 Sample characteristics divided by sex and total sample.

	F ($n = 78$)	M ($n = 74$)	TOT ($n = 152$)
Baseline characteristics			
Age, median [IQR]	9 [6–15.5]	10.5 [7–14]	10 [7–14]
Comorbidity	4 (5)	3 (4)	7 (5)
Referred	2 (3)	3 (4)	5 (3)
Clinical characteristics, *n* (%)			
Central cyanosis or oxygen saturation < 90%	45 (58)	33 (45)	78 (51)
Severe respiratory distress	64 (82)	46 (62)	110 (72)
Inability to drink	1 (1)	1 (1)	2 (1)
Persistent vomiting	9 (11.5)	11 (15)	20 (13)
Convulsions	0	0	0
Lethargy or unconsciousness	16 (20.5)	14 (19)	30 (20)
Stridor in a calm child	1 (1)	1 (1)	2 (1)
Severe malnutrition	1 (1)	1 (1)	2 (1)
No WHO severe defining symptoms	7 (9)	12 (16)	19 (12.5)
Outcomes			
Oxygen days, median [IQR]	2 [1–3]	2 [0–3]	2 [1–3]
Hospitalization days, median [IQR]	3 [3–6]	3.5 [3–5]	3 [3–6]
Recovery	77 (99)	66 (89)	143 (94)
Self-discharge	1 (1)	8 (11)	9 (6)

Data are presented as median [interquartile range] or as frequency (percentage).

(1%) patients, stridor in a calm child in 2 (1%) patients, and severe malnutrition in 2 (1%) patients. No patients presented with convulsion, and 19 (12.5%) of the patients did not report any severe defining symptom.

3.2. Adherence to WHO guidelines

Overall, 75 (49%) patients received therapy according to the WHO guidelines. The most commonly used antibiotic treatment was a combination of benzylpenicillin plus gentamicin in 72 (47%) patients, followed by ceftriaxone plus gentamicin in 42 (28%), and ceftriaxone alone in 20 (13%) patients. Table 2 shows the therapeutic schemes. Using a multivariate logistic regression model, we did not find any significant association between adherence to the WHO guidelines and sex (OR 0.8, CI 0.4–1.6), age (OR 1, CI 0.9–1), referral status (OR 1.4, CI 0.2–11.2), central cyanosis or saturation <90% (OR 1.1, CI 0.6–2.1), severe respiratory distress (OR 0.9, CI 0.4–2.1), and lethargy or unconsciousness (OR 0.8, CI 0.4–1.9).

3.3. Association with outcomes

No deaths were registered among the sample cohort, 143 (94%) patients recovered and 9 (6%) patients were self-discharged. The median duration of oxygen therapy was 2 (IQR 1–3) days, and the median length of stay was 3 (IQR 3–6) days.

TABLE 2 First-line antibiotic treatments used.

Antibiotic treatment	*n* (%)
Ampicillin + gentamicin	3 (2)
Benzylpenicillin+ gentamicin	72 (47)
Benzylpenicillin alone	3 (2)
Benzylpenicillin+ gentamicin+ azithromycin	3 (2)
Ceftriaxone alone	20 (13)
Ceftriaxone + gentamicin	42 (28)
Ceftriaxone + gentamicin + azithromycin	1 (1)
Ceftriaxone + azithromycin	7 (5)
Ceftriaxone + metronidazole	1 (1)

Data are presented as frequency (percentage). Ampicillin + gentamicin and benzylpenicillin+ gentamicin are the schemes suggested by the revised WHO guidelines.

TABLE 3 Baseline, clinical characteristics, and outcomes by adherence to the revised WHO guidelines.

	Non-adherent therapy ($n = 77$)	Adherent therapy ($n = 75$)	*p*-value
Baseline characteristics			
Female	38 (49)	40 (53)	0.6
Male	39 (51)	35 (47)	
Comorbidity	4 (5)	3 (4)	1
Primary admission	75 (97)	72 (96)	0.6
Referred	2 (3)	3 (4)	
Age in months, median [IQR]	10 [7–14]	9 [6–13.5]	0.1
Clinical characteristics, *n* (%)			
Central cyanosis or oxygen saturation < 90%	39 (51)	39 (52)	0.9
Severe respiratory distress	56 (73)	54 (72)	0.9
Inability to drink	1 (1)	1 (1)	1
Persistent vomiting	14 (18)	6 (8)	0.09
Lethargy or unconsciousness	16 (21)	14 (19)	0.7
Stridor in a calm child	1 (1)	1 (1)	1
Severe malnutrition	1 (1)	1 (1)	1
No WHO severe defining symptoms	7 (9)	12 (16)	0.2
Outcomes			
Oxygen days, median [IQR]	2 [1–3]	2 [1–3]	0.1
Hospitalization days, median [IQR]	4 [3–6]	3 [3–5]	0.5
Recovery	72 (93.5)	71 (95)	1
Self-discharge	5 (6.5)	4 (5)	1

Data are presented as median [interquartile range] or as frequency (percentage).

We compared patients who received therapy as adherent to the WHO guidelines vs. those who did not. Demographics, clinical characteristics, and outcomes were similar between the two groups (Table 3). We found no significant difference in oxygen days, hospitalization days, or self-discharges between patients treated according to the revised WHO guidelines and those who were not.

Regarding the other risk factors, we reported a significant association between male sex and self-discharge: eight (10%) male patients and one (1%) female patient self-discharged (OR 9.3, CI 1.6–175.4). When we evaluated the association between outcomes and adherence to guidelines adjusting for sex as possible confounders, we did not find a correlation (OR 0.9, CI 0.2–3.5).

4. Discussion

To the best of our knowledge, this is the first study to evaluate adherence to the WHO-revised guidelines on severe pneumonia in children at the hospital level in southern Ethiopia. We found that only half of the patients received an antibiotic treatment adherent to the guideline. Other studies evaluated adherence to the previous WHO guidelines in sub-Saharan Africa. A Sudanese study demonstrated poor adherence (18.8%) to severe pneumonia treatment during 2009–2010 in an urban children's referral hospital in Khartum (20). Similarly, a Kenyan study found a low level of adherence (27.7%) to the treatment of pneumonia in children in the Pediatric Department of Garissa Provincial General Hospital in Kenya (21). Our results do not allow us to understand the reason for the low adherence to guidelines, but we can exclude the lack of antibiotic supply since benzylpenicillin, ampicillin, and gentamicin were available continuously during the observational period.

We found no difference in hospitalization days, oxygen therapy, or outcomes when children were treated following the guidelines or using alternative antibiotics, most commonly ceftriaxone which is considered second-line treatment. These results are consistent with the Sudanese study (20). Our data show that outcomes of patients treated accordingly to the WHO guideline are not inferior to those treated with different antibiotic schemes and that physicians did not prescribe broader spectrum antibiotics to more severe patients.

We had no case fatalities in our sample cohort, although nine (6%) patients self-discharged. With a few exceptions, such as malnourished patients, patients older than 1 month in Ethiopia must pay for any treatment they receive, and sometimes the family cannot afford it. Moreover, in our experience when a patient is critical, the family prefers to bring him/her home to die in a family setting and to avoid payment that is considered pointless.

We observed that 43 (28%) patients received a combination of ceftriaxone plus gentamicin, which is not recommended by any international guidelines and indicated an antibiotic misuse/overuse issue. Neither the Sudanese study nor the Kenyan one reported cases treated with this antibiotic scheme (20, 21), suggesting that this kind of overtreatment could be a result of the changing of the guidelines or a regional issue. The misuse of antimicrobial agents is a critical factor associated with AMR, which is a major threat to human health in sub-Saharan Africa, a high-burden region (22). In Jinka General Hospital, as in many other hospitals and health centers in Africa, there is no possibility of etiologic diagnosis by cultural tests. In a setting like that, empiric treatment is the only choice, so strict adherence to guidelines is mandatory to fight AMR (23). Many of the patients treated could also have viral pneumonia which is hard to distinguish from bacterial pneumonia (24). While the change in respiratory virus epidemiology during the COVID-19 pandemic is well-described in Western countries (25, 26), only a few are known in low-income countries where the lockdown policies were different (27). In Africa, the second wave of the COVID-19 pandemic was more severe than the first, and Ethiopia implemented public health and social measures in March 2020, which were subsequently reduced throughout the year (28).

In order to fight AMR in a high-burden region, we recommend scaling up policies to increase adherence to antibiotic first prescriptions even at hospital levels, such as posters in emergency departments with guideline summaries and frequent courses for general practitioners. Moreover, we suggest periodic monitoring of guideline adherence at the hospital level.

According to the guidelines, more than 80% of the patients presented at least one severe defining symptom. This is consistent with a Kenyan study that found an adherence rate of 57% on disease classification vs. 28% on treatment (21). We found a low proportion of severely malnourished patients (1%) because we only analyzed the admission to the Pediatric Ward and did not include patients admitted to the therapeutic feeding center (TFC) where most of the malnourished patients are managed. We chose not to include the TFC patients since they are strictly managed using the Ethiopian National Guidelines for Malnutrition (29) which contain detailed indications of how to use antibiotics in those patients. A large retrospective study in 14 hospitals in Kenya found that a weight-for-age Z-score less than−3SD and any grade of pallor was associated with death in children 2–59 months diagnosed with pneumonia, suggesting clinicians consider these risk factors in addition to the WHO criteria (30).

Malnutrition is a major problem in the Horn of Africa, with South Omo being one of the most affected areas (31, 32). While we are writing about the "perfect storm" of the COVID-19 pandemic, climate change and the wheat crisis are worsening the risk for this already extremely frail population (31, 33). A study conducted in South-West Ethiopia before and during the COVID-19 pandemic found a recovery rate from severe acute malnutrition (SAM) of 68% in children aged 6–59 months, which was lower than the minimum accepted international standard of 75%, and a lower recovery rate when SAM was comorbid with pneumonia (34). In this scenario, where the malnutrition epidemic is likely to increase pneumonia cases and antibiotic use, a quality assessment of their use is essential to containing AMR.

Some limitations have to be acknowledged. Since we performed a retrospective analysis, we could not evaluate the clinical assessment properly but only use the handwritten reports of symptoms on the patient's chart. Moreover, nearly one-third of the patients admitted with severe pneumonia were not assessed because of missing charts. Research in low-income countries is made complex by the lack of resources to ensure data collection, which could be improved by the development of regional surveillance systems (35, 36). Anyway, this selection was random, and we believe it has not affected our results. Since this is a monocentric study, it is not generalizable to other Ethiopian hospitals, but other previous studies showed alarming results. The strengths of our research are the access to data from a remote area too often forgotten

by national and international policies but in desperate need of health improvement, methodological approach, and relatively large dataset.

5. Conclusion

Less than half of children received a treatment adherent to the WHO guidelines. Alternative antibiotic schemes did not prove superior to guideline-recommended schemes. Efforts should focus on understanding the causes and filling the gap between theory and practice. The fight against AMR should include a step up in quality monitoring systems in low-income countries where data are missing. However, none of the children admitted for pneumonia died.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Jinka University Ethical Committee. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

AL, EH, and LP conceptualized and designed the study. AL, EH, LP, BT, and DM designed the data collection instruments and collected data. AL and CA were responsible for the analysis and interpretation of data. AL drafted the manuscript. CA and KT performed a critical revision of the manuscript and gave a significant contribution in their field of expertise. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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A Clinical and Ethical Dilemma: Expectant Management for Ectopic Pregnancy with a Vital Fetus in a Low-Resource Setting

PAPER

Authors
Orsi M., Janneh F.M., Sesay A., Bah A.K., Tiru N.A.

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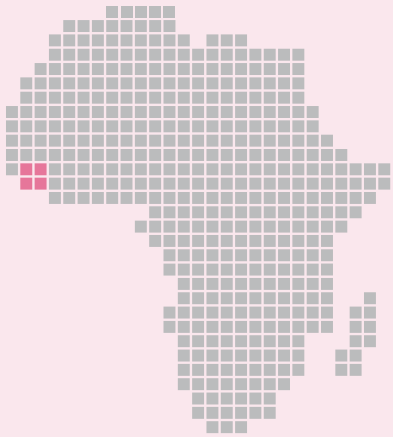

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Case Report

A Clinical and Ethical Dilemma: Expectant Management for Ectopic Pregnancy with a Vital Fetus in a Low-Resource Setting

Michele Orsi [1,*], Foday Musa Janneh [2], Amadu Sesay [2], Abdul Karim Bah [2] and Nitsuh Addis Tiru [2,3]

[1] Unit of Obstetrics, Department of Woman Newborn and Child, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Ca' Granda Ospedale Maggiore Policlinico, Via della Commenda, 12, 20122 Milan, Italy
[2] Princess Christian Maternity Hospital, University of Sierra Leone Teaching Hospital Complex, Fourah Bay Road, Freetown 00232, Sierra Leone
[3] Doctors with Africa CUAMM, Via San Francesco, 126, 35121 Padova, Italy
* Correspondence: michele.3@hotmail.it

Abstract: Background: Guidelines recommend the prompt surgical removal of any ectopic pregnancy (EP) in the presence of a vital embryo. This treatment impacts future fertility, particularly in low-resource settings where access to assisted reproductive techniques is limited. In addition, growing evidence is reporting live births after conservative management of initially undiagnosed abdominal pregnancies. Therefore, the discussion on the acceptability of expectant management in selected cases has been recently raised. Case: We present and discuss the case of a woman with vital first trimester EP who refused surgical treatment at Princess Christian Maternity Hospital, Freetown, Sierra Leone. She was initially diagnosed with a 12 week pregnancy located in the left adnexal region without hemoperitoneum. She refused both surgical treatment and hospital admission and did not come back to the hospital for antenatal care until 26 weeks of gestational age. Therefore, she was admitted and finally delivered, at 34 weeks of gestation, a 1.9 kg healthy baby which was alive. To disentangle the potential conflict between the ethical principles of medical treatment's beneficence and the patient's autonomy, we provide an update on counselling for a patient with early vital EP in a resource-limited setting and discuss the knowledge gap in this area. Conclusions: Limited access to fertility treatment in low- and middle-income countries may justify the discussion of expectant management as an option in selected cases of uncomplicated vital EP.

Keywords: ectopic pregnancy; expectant management; female infertility; medical ethics; assisted reproduction; low-resource setting; Sierra Leone

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1. Teaching Points

- Growing evidence reporting successful cases of abdominal pregnancy challenges the traditional assumption that ectopic pregnancy is non-viable by definition;
- The report provides an update regarding the potential conflict between the ethical principles of beneficence and the patient's autonomy while managing a vital ectopic pregnancy;
- The limited access to infertility treatment in low- and middle-income countries suggests bringing forward the debate regarding expectant management in uncomplicated cases of ectopic pregnancy.

2. Background

Ectopic pregnancy (EP) accounts for 1–2% of all pregnancies and is the medical emergency responsible for the majority of maternal deaths occurring during the first trimester of gestation [1–3]. Most cases arise from the tubal implantation of the embryo [4]. Signs and symptoms of an imminent or ongoing rupture, hemodynamic instability or the presence of a viable embryo are absolute indications for prompt surgical intervention [5].

However, the woman may sometimes refuse the operation for a variety of reasons [6,7]. First of all, the surgical treatment mainly entails salpingectomy. This intervention does not entirely hamper the chances of a future pregnancy, but inevitably may evoke in women thoughts of castration. In fact, in cases of previous contralateral salpingectomy, it may result in a sterilizing intervention. These aspects should be extensively discussed during the preoperative counselling [8,9]. Moreover, it must be considered that many women suffering from EP have a history of infertility, since several factors underlie both conditions [10–12]. Therefore, the choice of terminating a viable pregnancy may sound conceptually unacceptable, even if it is a life-saving procedure [13]. In some cases, it may also entail relevant psychological consequences, including post-traumatic stress disorder, depression or suicide [14,15].

This situation raises an ethical dilemma for healthcare providers [6,13]. A conflict may arise between the principles of patient autonomy and beneficence. The patient's wish to carry on the pregnancy collides with the healthcare providers' treatment proposal to mitigate risk and improve survival [16]. In low-resourced settings, challenged with low educational levels, cultural, and religious peculiarities; a fragile healthcare system and limited access to optimal infertility treatment, this conflict becomes more distinct [17–20].

Guidelines [5] recommend surgical removal of vital EPs based on the general assumption that they cannot generate a live birth while posing significant risk to patients' lives [13]. Nonetheless, growing evidence has shown favorable outcomes in cases of undiagnosed abdominal pregnancies (AP), some of which originated from tubal sites [21–23]. This has stimulated the discussion about expectant management of EP in selected cases [21,22].

Through the description of a challenging case with vital first-trimester EP, that refused surgery at the main teaching referral facility for obstetrics and gynecology in Freetown, Sierra Leone, we discuss some critical issues of concern in the shared decision-making process.

3. Case Presentation

A 26-year-old gravida 2 para 0, was referred to Princess Christian Maternity Hospital, Freetown, Sierra Leone, with amenorrhea of three months duration a three day history of worsening pelvic pain. She had a prior history of right salpingectomy performed 3 years before presentation as a result of ruptured right tubal EP. On examination, there was moderate tachycardia and lower abdominal tenderness; the pregnancy test was positive, and the transabdominal ultrasound scan revealed a 12-weeks left adnexal EP with a vital fetus and no free fluid collection in the pouch of Douglas (Figure 1). In this public academic hospital No other hematological diagnostic or imaging investigations were available, and they were not included in the free healthcare guaranteed by the national program. Blood tests and magnetic resonance imaging are carried out in other private institutions. A rapid test for hemoglobin was performed and the result was within the normal range. In the presence of the husband, the patient was offered detailed counselling for the management of her condition. Considering the vital fetus, the global consensus indicates the surgical removal of the pregnancy. As a symptom, pain could indicate impending or initial tubal rupture, and the consequent bleeding potentially threatens the patient's survival. Therefore, emergency exploratory laparotomy was proposed for suspicion of the imminent rupture of the EP.

Considering the previous salpingectomy and subsequent fertility implications, the patient outrightly refused both surgery and hospital admission, even after the proposal to only be hospitalized and remain monitored without immediate intervention. Analgesics and hematinics were then prescribed and a short-term outpatient follow-up was then advised. She defaulted on antenatal follow-up visits, and she avoided responding to repeated attempts of the medical staff to contact her. She only came to the hospital at 26 weeks of gestation. An ultrasound scan was then repeated (Figure 2). The fetus was still vital and growing within the normal range, with adequate amniotic fluid and normal umbilical flow at the Doppler ultrasound assessment. She was then admitted for close

J. Clin. Med. **2023**, *12*, 5642

monitoring and expectant management. Fetal lung maturation was induced by maternal intramuscular injection of corticosteroids at 28 weeks of gestational age, in order to reduce the risk of severe neonatal respiratory distress syndrome.

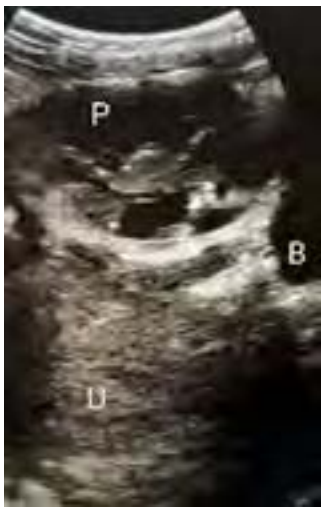

Figure 1. First trimester abdominal ultrasound scan showing the abdominal pregnancy, the empty uterus, and the absence of free fluid in the abdomino–pelvic cavity. P = pregnancy; U = uterus; B = bladder.

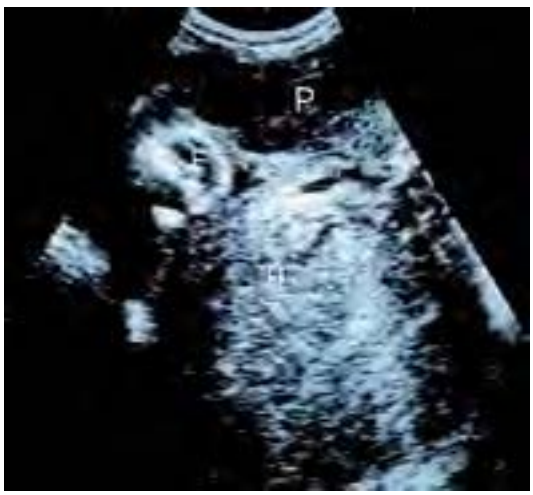

Figure 2. Third trimester abdominal ultrasound scan (left-lateral view) showing the fetal limbs, placenta, amniotic fluid, and the empty uterus. P = placenta; F = fetal limbs; U = uterus.

Eventually, a healthy baby girl weighing 1.9 kg was delivered by laparotomy at 34 weeks of gestational age, with an APGAR score of 8 in one minute and 9 in five minutes, and was referred to the special care baby unit. No major anatomical abnormalities of the newborn were noted, with the exception of mild contractures of the lower limbs. The placenta was firmly adherent to the left lower abdomino–pelvic wall, the annexus, the

broad ligament and the sigmoid colon on the same side. Therefore, a decision was made to provide essential hemostasis and leave it in situ in order to prevent a potentially dramatic hemorrhage. Total estimated blood loss was 1200 mL and 2 units of whole blood were transfused. Tranexamic acid and broad-spectrum antibiotics were therefore prescribed and 12 h after the surgery, when the patient was hemodynamically stable, anti-thrombotic prophylaxis with low molecular weight heparin was introduced. The mother and the baby recovered well and were discharged home 2 weeks later.

4. Discussion

The diagnosis of EP signifies a potentially life-threatening condition, and all possible efforts must be targeted at mitigating the related risks. Healthcare providers should offer such patients updated and evidence-based counselling for shared decision-making [24].

To the best of our knowledge, this is the first report discussing the potential role of conservative management of a first trimester ectopic gestation with a vital fetus. In our case, clinical and ethical challenges arose from the patient's refusal of the surgical treatment. There are no guidelines that suggest the management of a situation of this type. However, this case raises questions about the current recommendations in light of the peculiarity of the context, with limited resources, and the clinical characteristics of the patient.

Guidelines are designed on the basis of robust evidence mostly derived from randomized trials, while the role of case reports is to present insights or controversies that can inspire subsequent investigations and appropriate studies.

In view of the large number of human lives lost due to complications of ectopic pregnancy, prompt management is recommended to protect women's health [25]. Therefore, the discussion of expectant management is not currently an option, and in the event of a patient's request, it must be evaluated with caution while taking into account the available diagnostic and therapeutic resources as well as the socio–cultural context [6]. Furthermore, considering the high likelihood of complications, it is a shared opinion that emphasizing the very low chance of an EP resulting in a live birth facilitates the convergence of the patient–physician dyad towards the choice to immediately treat this condition. However, we believe that providing updated and detailed counseling to the patient with EP is an absolute priority in order to guarantee the patient's full decision-making autonomy [6]. In this regard, the now-no-longer anecdotal evidence of successful ectopic pregnancies should be cited, while emphasizing the risk of mortality and the high burden of maternal and fetal complications [21].

To support clinicians facing this condition and to deepen the ethical basis of the counselling while taking into account the recent evidence in this field, we focused the discussion on some typical questions that a patient diagnosed with EP may ask to the healthcare provider.

"Considering that the pregnancy is progressing, is there any actual risk for my life?"

The diagnosis of EP is itself a high-risk condition. In the presence of complications, such as hemoperitoneum or hemodynamic instability, there is an absolute indication for urgent surgical treatment [5]. This condition is potentially fatal and the risk increases in cases of failed diagnosis and delayed treatment [1,2,26]. Therefore, awareness of this condition and availability of prompt management are deemed to be protective factors. In the absence of hemoperitoneum, EP cannot be considered an immediate threat to the patient's life, but it is still a very high-risk condition. In keeping with the ethical principle of beneficence and in accordance with international guidelines, surgical removal should be proposed in the case of a viable EP [5,16].

"For my tubal pregnancy, is there any chance to success? In other words, what is the risk of rupture versus the chance to deliver a live baby?"

The thickness of the tube's mucosa and sub-mucosa are inadequate to sustain trophoblastic invasion and support the pregnancy progression. Therefore, most tubal EP are expected to rupture and cause intra-abdominal hemorrhage. However, after tubal

abortion or rupture, trophoblasts may sometimes invade adjacent abdominal organs, such as omentum, peritoneum, and others, to acquire sufficient blood and nutrients supply and survive beyond the first trimester without causing life-threatening bleeding [27,28]. The result is an AP, whose incidence remains currently unknown because most EPs are treated in the first trimester. Secondary AP remains a major diagnostic challenge [21,22], with an intraoperative diagnosis rate of up to 50% in both high- and low-income countries [29]. Ultrasound features of AP include absence of the uterine wall between the maternal bladder and the fetus; ectopic location of placenta; abnormal presentation of fetus; proximity of fetal parts to maternal abdominal wall; and absence of amniotic fluid between the placenta and the fetus [30]. The diagnosis of secondary AP can be made when the following criteria for primary AP are not verified: (1) normal tubes and ovaries; (2) absence of uteroplacental fistula; and (3) sufficiently early diagnosis to exclude the possibility of secondary implantation [31,32].

Since reports of advanced undiagnosed AP with successful outcome have been published, some authors started promoting a conservative management in selected cases [7,21,22]. A recently published case series from a South African referral center reported the outcomes of 118 advanced abdominal pregnancies [21] over a 22-year study period. Of these cases, 51 underwent immediate delivery for a viable fetus, while 46 underwent expectant management. In this wait-and-see group, 2 cases (4%) resulted in stillbirth, 11 (24%) in perinatal death, and 33 (72%) women were discharged from the hospital with a live newborn. Out of 46 cases, there were no maternal deaths, but 39 patients received hemotransfusions, 1 required relaparotomy and 1 had an intestinal lesion successfully repaired intraoperatively. Finally, the reported risk of congenital anomalies and severe prematurity is significantly higher than for abdominal pregnancies in comparison to intrauterine pregnancies [21,22].

Therefore, these reports as long as the existing knowledge gaps should be disclosed during the counseling, to fully guarantee the ethical principle of the patient's autonomy [16,24,33].

"But I'm infertile. What if this was my only chance? What if I refuse the surgery?"

In low- and middle-income countries, the vast majority of patients have limited access to assisted reproductive techniques (ART) for the treatment of infertility [34,35]. Therefore, the refusal of surgery in our case—in the patient who had previous contralateral salpingectomy—could be understandable from the fertility–preservation point of view. Although it is not possible to draw a full resemblance, if a pregnant woman with a preexisting high-risk medical condition—such as pulmonary arterial hypertension or heart failure—refuses to terminate her pregnancy, the situation would compel clinicians to design a new personalized care pathway [36]. Although these conditions correlate with a risk of maternal death of up to over 30%, detailed and comprehensive counseling on pregnancy success and failure rates in cases described in the literature should be offered. An even closer comparison could be made with cesarean scar pregnancy, which in the case of wait-and-see management exposes the patient to a significant risk of hemorrhage, uterine rupture, premature birth, hysterectomy, and death [37].

If a patient with an EP opts for conservative management against medical advice, we recommend close monitoring, including hospitalization, if necessary. Since most maternal deaths from EP occur as a result of delayed diagnosis or treatment [2,26,38,39], the awareness of this condition is expected to play a protective role and minimize mortality. Although this information is not available in the literature, we reasonably assume that the risk of severe outcomes is dramatically reduced if cross-matched blood units are prepared, and an adequately experienced surgical team is available on call. We are aware that these conditions require a considerable expenditure of healthcare resources. However, they are theoretically available as well as a basic requirement for referral centers even in low-resource countries.

5. Conclusions

According to guidelines, a patient with a first trimester vital ectopic pregnancy should promptly undergo its surgical removal. However, no recommendations are available to manage cases that refuse treatment. Furthermore, growing evidence is reporting successful cases of live births from AP, some of which originate from the fallopian tube. This evidence challenges the traditional assumption that EP is non-viable by definition and discloses a relevant knowledge gap in this area. In this case, considering the frequent coexistence of subfertility among cases of EP, the impact of its surgical treatment, and the limited access to ART in LMIC, clinicians should bring forward the debate regarding expectant management in highly selected cases. Providing the patient with comprehensive counseling would ensure the ethical principle of the patient's autonomy and foster the convergence with the principle of beneficence supported by the healthcare provider towards a shared decision-making process.

Author Contributions: A.S. and F.M.J. diagnosed and operated on the patient; M.O., N.A.T. and A.K.B. counselled and followed-up on the patient postoperatively; M.O. drafted the manuscript; A.S., F.M.J., A.K.B. and N.A.T. made useful critique of this manuscript. All authors read and approved the final version. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: According to the local ethics committee and the CARE Guidelines, ethical clearance was not required for this case report. However, to ensure patients' data safety, the Hospital Management of Princess Christian Maternity Hospital—University of Sierra Leone Teaching Hospital Complex—was consulted and provided the permission to access and publish clinical information for this case study. The patient was treated in agreement with the local and international guidelines and signed informed consent. Therefore, the manuscript fulfils the Declaration of Helsinki and its later amendments.

Informed Consent Statement: Informed consent was obtained from the patient for the publication of this manuscript.

Data Availability Statement: The data created during this current study are available from the corresponding author on reasonable request.

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Impact and burden of sickle cell disease in critically ill obstetric patients in a high dependency unit in Sierra Leone-a registry based evaluation

PAPER

Authors
Mortara M., Turay M.S., Boyle S., Caracciolo C., Bah S., Kargbo H., Hanciles E., John-Cole V., Scapini E., Benoni R., Dissanayake V., Beane A., Haniffa R., Adetunji A.O., Taylor W., Pisani L.

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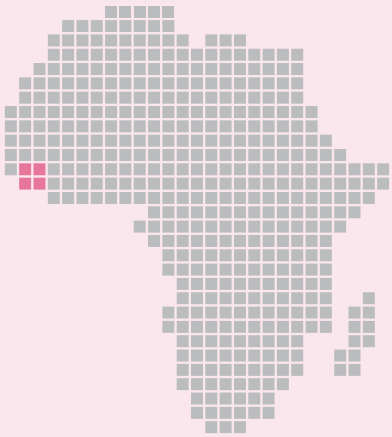

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Impact and burden of sickle cell disease in critically ill obstetric patients in a high dependency unit in Sierra Leone—a registry based evaluation

Milena Mortara[1,2], Momoh Sitta Turay[2], Sonia Boyle[2], Claudia Caracciolo[2,3], Sarjoh Bah[2], Henry Kargbo[2], Eva Hanciles[4], Valerie John-Cole[2], Ester Scapini[5], Roberto Benoni[3], Vishmi Dissanayake[6], Abi Beane[6], Rashan Haniffa[6], Adeniji O. Adetunji[2], Williamson Taylor[2] and Luigi Pisani[3,6,7*]

Abstract

Introduction Sickle cell disease (SCD) in pregnancy is associated with worse maternal and neonatal outcomes. There is limited available data describing the burden and outcomes of critically ill obstetric patients affected by SCD in low-income settings.

Objectives We aimed to define SCD burden and impact on mortality in critically-ill obstetric patients admitted to an urban referral hospital in Sierra Leone. We hypothesized that SCD burden is high and independently associated with increased mortality.

Methods We performed a registry-based cross-sectional study from March 2020 to December 2021 in the high-dependency unit (HDU) of Princess Christian Maternity Hospital PCMH, Freetown. Primary endpoints were the proportion of patients identified in the SCD group and HDU mortality. Secondary endpoints included frequency of maternal direct obstetric complications (MDOCs) and the maternal early obstetric warning score (MEOWS).

Results Out of a total of 497 patients, 25 (5.5%) qualified to be included in the SCD group. MEOWS on admission was not different between patients with and without SCD and SCD patients had also less frequently reported MDOCs. Yet, crude HDU mortality in the SCD group was 36%, compared to 9.5% in the non SCD group ($P < 0.01$), with an independent association between SCD group exposure and mortality when accounting for severity on admission (hazard ratio 3.40; 95%CI 1.57—7.39; $P = 0.002$). Patients with SCD had a tendency to longer HDU length of stay.

Conclusions One out of twenty patients accessing a HDU in Sierra Leone fulfilled criteria for SCD. Despite comparable severity on admission, mortality in SCD patients was four times higher than patients without SCD. Optimization of intermediate and intensive care for this group of patients should be prioritized in low-resource settings with high maternal mortality.

Keywords Sickle cell disease, Low-resource settings, Obstetric, High dependency unit

*Correspondence:
Luigi Pisani
luigipisani@gmail.com
Full list of author information is available at the end of the article

Introduction

Hemoglobin S (HbS) is a variant form of hemoglobin due to an abnormal beta globin chain. Homozygotes for this mutation (HbSS) as well as less common compound heterozygotes suffer from sickle cell disease (SCD), a severe form of anemia whose hallmarks are vaso-occlusive phenomena and hemolysis. Less common genetic variants associated with the disease are SCD is associated with premature death especially in low-income countries [1], while sickle cell trait is a benign carrier condition in which one allele of the beta globin gene carries the sickle hemoglobin mutation, producing hemoglobin AS (HbAS). Worldwide, the prevalence of SCD is highest in sub-Saharan Africa, as sickle cell trait condition has a protective effect against severe falciparum malaria [2]. In Sierra Leone the exact prevalence and incidence of SCD is unknown but the frequency of the trait is estimated at 20–25% [3].

People affected with SCD may require recurrent hospitalizations for acute pain crises, infections, cardiac problems, renal failure, and acute chest syndrome. Pregnant women with SCD experience these risks as well as vascular effects due to the gravid uterus and placenta. SCD in pregnancy is associated with infections, severe preeclampsia [4] and increased rates of cesarean delivery [5]. Pregnancies complicated by maternal SCD are also at increased risk of fetal complications such as increase in abortion, preterm labour, premature rupture of membranes, low birthweight, fetal distress in labour and increased perinatal mortality [6].

Despite the relevant prevalence and potential effects on mother and child, there is limited available data describing maternal burden and outcomes of critically ill obstetric patients affected by SCD in low income settings. A 2011 study reported how women with SCD suffer from a significant excess risk of dying in Jamaica, although it was not focused on critically ill patients and was limited to non-survivors case analysis [7]. There is scarce evidence on processes optimization to improve prevention or treatment of SCD-related complications in critically ill obstetric patients in low-resource settings. The aim of the current study is to define SCD burden in critically-ill obstetric patients and explore whether this condition significantly impacts outcomes in an urban referral hospital in Sierra Leone. The study leverages a recently developed cloud-based registry of critically ill patients in the largest maternal facility in the country [8]. We hypothesize that SCD burden is high in critically ill obstetric patients and independently associated with increased obstetrical complications and mortality.

Methods

Study design

We performed a registry-based prospective cross-sectional study from March 2020 to December 2021 in the high-dependency unit (HDU) of Princess Christian Maternity Hospital PCMH, Freetown, Sierra Leone. The HDU digital registry received ethical approval and a waiver of informed consent from the Sierra Leone Ethics and Scientific Review Committee in June 2020, with an extension granted in August 2022. (reference number 009/08/2022). The study was carried out in accordance with the declaration of Helsinki guidelines for medical research involving human subjects and the University of Sierra Leone ethical guidelines. The study is reported following the Strengthening of the reporting of Observational Studies in Epidemiology (STROBE) statement guidelines and checklists [9] (Table S1).

Setting

PCMH is the largest maternity referral hospital in Sierra Leone, receiving about 9000 admissions and 6500 deliveries per year [8]. The HDU is a 8-bed critical care ward in which critically-ill women receive basic critical care interventions, such as close monitoring of vital signs and renal output, intravenous fluid and vasopressor therapy management, blood transfusions, oxygen, antibiotics, essential point of care laboratory tests and pain management [10, 11]. Invasive mechanical ventilation, renal replacement therapy and other advanced organ support techniques were not available in this setting during the study period. The maternal mortality rate in Sierra Leone is the highest in the world with 1,120 mothers dying in every 100,000 live births, although a recent nation-wide survey reported this figure to be 510 per 100,000 live births [12]. Hospital maternal mortality rate during the study was 1049 deaths per 100.000 live births.

Population

Patients were included in the study if admitted to the HDU for any cause during the observation period. The sickle cell disease group was assigned to a patient whenever this condition was flagged in the patient hospital record by the treating team and thus captured by the electronic HDU registry. The registry code for SCD thus included any of the following: (i) patients patients being admitted with a clinical complication of SCD (such as "sickle cell crisis" or "acute chest syndrome") as reason for admission; (ii) patients with self-reported SCD as self- reported comorbidity on the parturient medical history, even if this was not the main reason for admission; (iii) patients having a positive point of care laboratory test for SCD (rapid detection test without differentiation

of genotypes). The current registry coding for SCD did not allow to differentiate between these three conditions. Patients with incomplete records, i.e. with missing admission diagnosis or outcome data were planned to be excluded from analysis. The non-SCD group was defined as all other patients admitted to the HDU during study period.

Registry structure and data collection procedures

The HDU in PCMH is part of the Critical Care Asia Africa (CCAA) federated network of registries, an international initiative enabling continuous evaluation of critical care services in low and middle income countries. Registry infrastructure and quality control processes were detailed in previous publications [13–15]. In brief, a dedicated data collector entered daily data on consecutive admissions on a secure cloud-based mobile or desktop portal. The clinical information was directly extracted from existing paper-based records and monitoring charts within the HDU. Validation of reporting and the opportunity for technical support were assured by regular contact with the registry platform curating team.

Data collection

Data collected on admission included demographic data, reported reason for hospital and for HDU admission, comorbidities, surgical status, the presence of a maternal direct obstetric complication (MDOCs), ongoing treatments for malaria or other infections. Vital signs were collected at admission, at 24 h and at discharge; they included pulse oximetry oxygen saturation (SpO_2), heart rate, respiratory rate, temperature, neurological status, systolic and diastolic arterial blood pressure, urinary output. Point of care laboratory measurement included glucose level and hemoglobin level. Total number of blood units transfused was recorded at discharge but only available in patients admitted after October 2021. Severity on admission was stratified through the Maternal Early Obstetric Warning Score (MEOWS; Table S2) [16]. Patient outcomes were recorded at HDU discharge.

Study definitions

The MEOWS uses core physiological parameters such as systolic and diastolic blood pressure, heart rate, respiratory rate and temperature to identify critical obstetric patients. The MEOWS ranges from 0 to 10 points, with a green color code granted with a total of 1–2, a yellow color code for total 3–5, and a red color code attributed to every patient with > 5 points or any danger sign. (Table S2). The AVPU coma scale was used to rapidly assess the patient's mental status in four categorical classes: alert (A), response to verbal stimuli (V), response to painful stimuli (P), unresponsiveness (U). Respiratory distress was defined as a respiratory rate on admission > 30 breaths per minute and/or a SpO_2 in air < 92% and/or when acute respiratory failure was recorded as the reason for admission.

Eight different maternal direct obstetric complications (MDOCs) were recorded, namely ante-partum hemorrage (APH), post-partum hemorrage (PPH), uterine rupture, puerperal sepsis, obstructed labour, severe pre-eclampisa or eclampsia, complications of abortion and ectopic pregnancy [17, 18].

Study endpoints

The co-primary endpoints were the proportion of patients identified in the SCD group and the crude HDU mortality of the SCD group compared to the non-SCD group. Secondary endpoints included meaningful clinical variables such as: severity of illness at admission, frequency of MDOCs and respiratory distress, hemoglobin levels, number of blood transfusions, malaria status on admission, HDU length of stay, organ support in terms of oxygen therapy and vasopressors.

Statistical analysis

Due to the descriptive nature of this analysis we did not perform a formal sample size calculation – instead, all available patients from registry inception were included in the study. Demographic data and outcomes were summarized as medians (interquartile range) for continuous variables and as frequencies (percentage) for categorical variables. In the case of normally distributed, continuous variables were compared between patients with and without SCD using t–test or ANOVA. When not considered normally distributed, continuous variables were compared between groups with Mann–Whitney U test or Kruskal–Wallis test, as appropriate. Categorical variables were compared between groups by chi–square analysis. Missing data imputation was not performed.

The association between the SCD group with HDU mortality as a time–to–event was analyzed with a Cox regression model, reporting the hazard ratio with 95%–confidence interval (CI). The SCD group was used as the grouping variable, while MEOWS (continous variable) was entered as covariate expressing the severity on admission based on physiological parameters. All analyses were performed using a two–sided superiority hypothesis test, with a significance level of 0.05 and presented with two–sided 95%–CI. No corrections were performed for multiple comparisons across secondary clinical outcomes. Analyses were performed using software R (version 4.0.2, R Core Team, 2016, Vienna, Austria).

Results

Case-mix

Of a total of 497 patients included in the HDU registry in the study period, 25 (5.5%) qualified to be included in the SCD group. No patients were excluded due to missing data. Baseline characteristics of patients with SCD as compared to the patients admitted to HDU without SCD are detailed in Table 1. Patients with SCD had comparable demographic characteristics to those without SCD, with an average age at admission of 25 years old. Patients

Table 1 Patients baseline case-mix characteristics

	All patients ($n=497$)	SCD group ($n=25$)	No-SCD group ($n=472$)	*P*-value
Age (years)	26 (21, 30)	23 (21, 28)	26 (21, 30)	0.417
Occupation status				
Employed	167 (33.6)	8 (32.0)	159 (33.7)	1
Unemployed	113 (22.7)	8 (32.0)	105 (22.2)	0.373
Homemaker	207 (41.6)	9 (36.0)	198 (41.9)	0.704
Type of admission				
Non operative	260 (52.3)	21 (84.0)	239 (50.6)	**0.002**
Operative	237 (47.7)	4 (16.0)	233 (49.4)	**0.002**
Emergency surgery	96 (40.5)	1 (25.0)	95 (40.8)	0.648
Reason for admission (Medical)				
Anemia	29/260 (11.2)	3/21 (14.3)	26/239 (10.9)	0.714
Acute respiratory failure	28/260 (10.8)	2/21 (9.5)	26/239 (10.9)	1
Malaria	26/260 (10.0)	4/21 (19.0)	22/239 (9.2)	0.143
Convulsive syncope	12/260 (4.6)	1/21 (4.7)	11/239 (4.6)	1
Reason for admission (Surgical)				
Cesarean section	76/237 (32.1)	3/4 (75.0)	75/233 (32.2)	1
Laparotomy	6/237 (2.5)	0	6/233 (2.6)	1
Hysterectomy	4/237 (1.7)	0	4/233 (1.7)	1
Evacuation of uterus	3/237 (1.3)	1/4 (25.0)	3/233 (1.3)	1
MDOCs on admission				
None reported	148/495 (29.9)	17/23 (73.9)	131/472 (27.8)	**< 0.01**
APH	40/495 (8.08)	0	40/472 (8.47)	0.243
PPH	125/495 (25.3)	3/23 (13.0)	122/472 (25.8)	0.257
Prolonged/obstructed labour	8/495 (1.62)	0	8/472 (1.69)	1
Complication of abortion	3/495 (0.606)	0	3/472 (0.636)	1
Pre eclampsia/Eclampsia	112/495 (22.6)	3/23 (13.0)	109/472 (23.1)	0.385
Puerperal sepsis	24/495 (4.85)	0	24/472 (5.08)	0.618
Ectopic pregnancy	11/495 (2.22)	0	11/472 (2.33)	1
Ruptured uterus	24/495 (4.85)	0	24/472 (5.08)	0.618
Comorbidities				
None (No comorbidity)	444 (89.3)	9 (36.0)	435 (92.2)	**< 0.01**
AIDS or HIV	10 (2.0)	2 (8.0)	8 (1.7)	0.085
Asthma	1 (0.2)	0	1 (0.2)	1
Diabetes	4 (0.8)	0	4 (0.8)	1
Hepatic disease	1 (0.2)	0	1 (0.2)	1
Hypertension	20 (4.0)	0	20 (4.2)	0.614
Renal failure	4 (0.8)	0	4 (0.8)	1
Respiratory disease, severe/moderate	1 (0.2)	0	1 (0.2)	1
Tuberculosis	1 (0.2)	0	1 (0.2)	1
Time from hospital to HDU admission				
Less than 24 h	379 (76.3)	18 (72.0)	361 (76.5)	0.786
More than 24 h	118 (23.7)	7 (28.0)	111 (23.5)	0.786

Abbreviations: SCD Sickle cell disease, *APH* Antepartum hemorrhage, *PPH* Vipost-partum hemorrhage, *AIDS* Acquired immunodeficiency syndrome

with SCD were less frequently post-operative patients (16% vs. 49%; $P=0.002$) with cesarean section being the most frequent surgery performed followed by laparotomy (Table 1). Time elapsed from hospital entry to HDU admission was not significantly different between the two groups, with roughly 70% of patients being referred to HDU within 24 h of hospital admission.

In the SCD subgroup, a major direct obstetric complication was reported in fewer cases than in the non-SCD group (26.1% versus 72.2%, $p<0.01$), with PPH and pre-eclampsia/eclampsia being the MDOCs reported. SCD patients were more anemic, with capillary Hb levels of 7.2 gr/dl in the SCD group compared to 8.6 g/dl in the non-SCD group ($p=0.02$) (Fig. 1). The severity level on admission was comparable with at least one red alert on the MEOWS recorded in > 75% in both groups (Table 2) and a total MEOWS of 4 (2–5) and 5 (3–6) in the SCD and non-SCD groups, respectively ($P=0.09$; Fig. 2). The main reasons for admission in the SCD group were anemia, severe malaria, respiratory distress, and eclampsia. Acute respiratory failure as a reason for admission was observed in one out of ten patients in the SCD group, with no difference compared to the general population of critically-ill obstetric patients.

Association with HDU mortality

Crude HDU mortality was higher in the SCD group compared to the group without (36% vs. 9%, $p<0.001$; Table 3). Overall, SCD affected one in five HDU deaths. Having SCD on admission was associated with an increased risk of death in HDU after adjustment for the severity level on admission expressed by MEOWS (HR for SCD group 3.40; 95%CI 1.57—7.39; $P=0.002$, Fig. 2 and model details in Table S3). Death in HDU was observed for SCD patients also at low levels of severity on admission and with normal hemoglobin levels (Fig. 3). Patients with SCD had a tendency to longer median length of stay in both survivors and non survivors, although these findings did not reach statistical significance.

Management features

Organ support features in the first 24 h for patients with and without SCD are detailed in Table 4. Oxygen therapy was required by 36% of SCD patients and by 14% of the non-SCD group ($P=0.002$). Antibiotic therapy was prescribed in 9 out of 10 patients in both groups, while SCD were three times more prone to receive anti-malarial treatment than patients without SCD. Vasoactive treatment was rarely required in the SCD group, yet reported in one fourth of patients without SCD, mainly for the management of hypertension in eclamptic patients. The data on total blood transfusions received during HDU stay was incomplete and only available for 14/25 SCD patients. Eleven out of 14 patients (79%) received a blood transfusion, with a median of 1 (1–4) units of whole blood per patient administered. No transfusion data was available for the non-SCD group.

Discussion

The main findings from this study were: (1) one in 20 critically ill obstetric patients referred to an obstetric HDU in a limited resource setting had assigned a SCD code; (2) these patients were mainly non-operative and had comparable severity on admission to patients without SCD; (3) yet SCD patients suffered from a four-fold higher HDU mortality, with SCD affecting one in five HDU deaths; (4) the association between group exposure and mortality was independent of baseline severity (5) context-specific HDU management for SCD patients comprises oxygen therapy, transfusions and antimicrobial therapy.

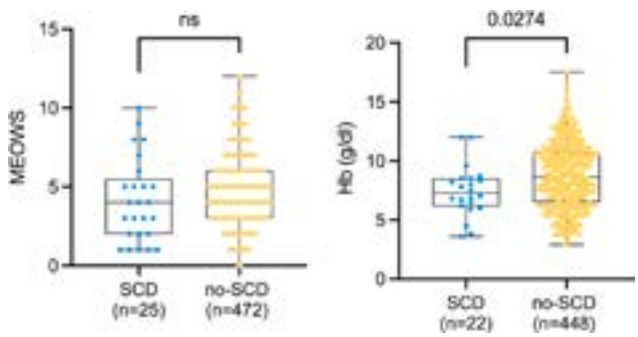

Fig. 1 Boxplot of modified early obstetric warning score and hemoglobin levels in patients with SCD as compared to patients without SCD. *P*-Value was computed through Mann–Whitney U test. Abbreviations: ns, non significant; MEOWS, modified early obstetric warning score; Hb, hemoglobin

Table 2 Clinical parameters on admission

	All patients (*n* = 497)	SCD group (*n* = 25)	No-SCD group (*n* = 472)	*P*-value
Severity of illness				
MEOWS	5 (3, 6)	4 (2, 5)	5 (3, 6)	0.089
Number of red alerts	407 (81.9)	19 (76.0)	388 (82.2)	0.432
Number of yellow alerts	404 (81.3)	18 (72.0)	386 (81.8)	0.221
Respiratory distress, yes	74 (14.9)	3 (12.0)	71 (15.0)	1
Vitals on admission				
SpO_2, %	97 (95, 98)	97 (94, 98)	97 (95, 99)	0.327
FiO_2, %	40 (22, 40)	40 (36, 40)	40 (22, 40)	0.963
SpO_2/FiO_2	242 (223, 289)	248 (242, 269)	242(220, 296)	0.406
Systolic BP, mm Hg	123 (105, 142)	122 (106, 132)	123 (105, 143)	0.547
Diastolic BP, mm Hg	77 (62, 94)	68 (61, 81)	78 (62, 94)	0.086
Respiratory rate, breaths per minute	30 (26, 38)	32 (28, 45)	30 (26, 37)	**0.042**
Heart rate, beats per minute	110 (98, 126)	100 (92, 112)	110 (98, 127)	**0.048**
Temperature, °C	36.8 (36.6, 37.3)	36.7 (36.5, 37.4)	36.8 (36.6, 37.3)	0.983
AVPU condition				
Alert	228 (45.9)	18 (72.0)	210 (44.5)	**0.012**
Voice	112 (22.5)	6 (24.0)	106 (22.5)	1
Pain	98 (19.7)	0	98 (20.8)	**0.007**
Unresponsive	58 (11.7)	1 (4.0)	57 (12.1)	0.340
Laboratory				
Capillary blood glucose, mmol/l	7.7 (5.8, 10.3)	5.7 (5.2, 6.6)	7.8 (5.9, 10.5)	**0.004**
Hemoglobin levels, g/dl	8.5 (6.5, 10.7)	7.3 (6.3, 8.5)	8.6 (6.5, 10.7)	**0.028**

Abbreviations: SCD Sickle cell disease, *MEOWS* Modified Early Obstetric Warning Score, *SpO2* Hemoglobin saturation from pulse oxymetry, *FiO_2* Fraction of inspired oxygen, *BP* Blood pressure, *AVPU* Alert, voice, pain, unresponsiveness score

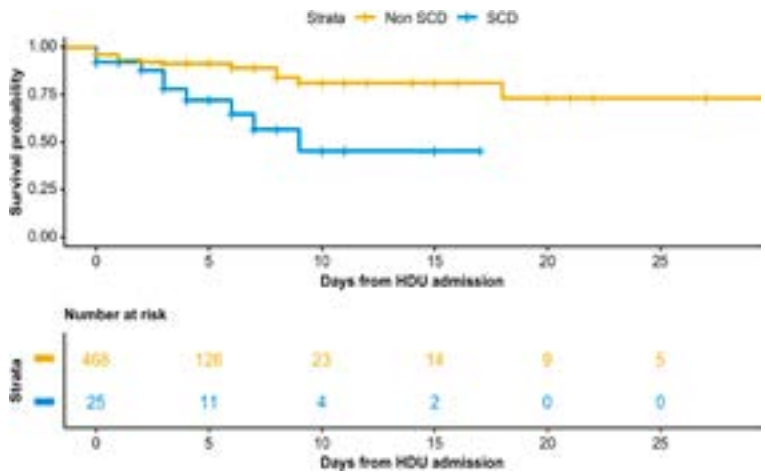

Fig. 2 Survival curve for the SCD group as compared to the general HDU population. Abbreviations. SCD, sickle cell disease group; HDU high dependency unit

Table 3 Patient outcomes

	All patients ($n=497$)	SCD group ($n=25$)	No-SCD group ($n=472$)	*P*-value
Death in HDU	54/494 (10.9)	9/25 (36.0)	45/469 (9.5)	**< 0.001**
Time from HDU admission to death, hours	13 (2, 69)	74 (34, 140)	9 (2, 51)	0.090
Length of stay in HDU for survivors, days	3.1 (1.8, 4.8)	4.5 (2.7, 8.2)	3.0 (1.8, 4.7)	0.068
Discharge destination for survivors				
Home	65/440 (14.8)	2/16 (12.5)	63/424 (14.9)	1
Ward	355/440 (80.7)	12/16 (75.0)	343/424 (80.9)	0.524
Transfer for specialist care	6/440 (1.3)	1/16 (6.3)	5/424 (1.2)	0.200
Referral to ICU or other hospital	13/440 (2.9)	1/16 (6.3)	12/424 (2.8)	0.386
Other	1/440 (0.2)	0	1/424 (0.2)	1

Abbreviations: SCD Sickle cell disease, *HDU* High dependency unit, *ICU* Intensive care unit

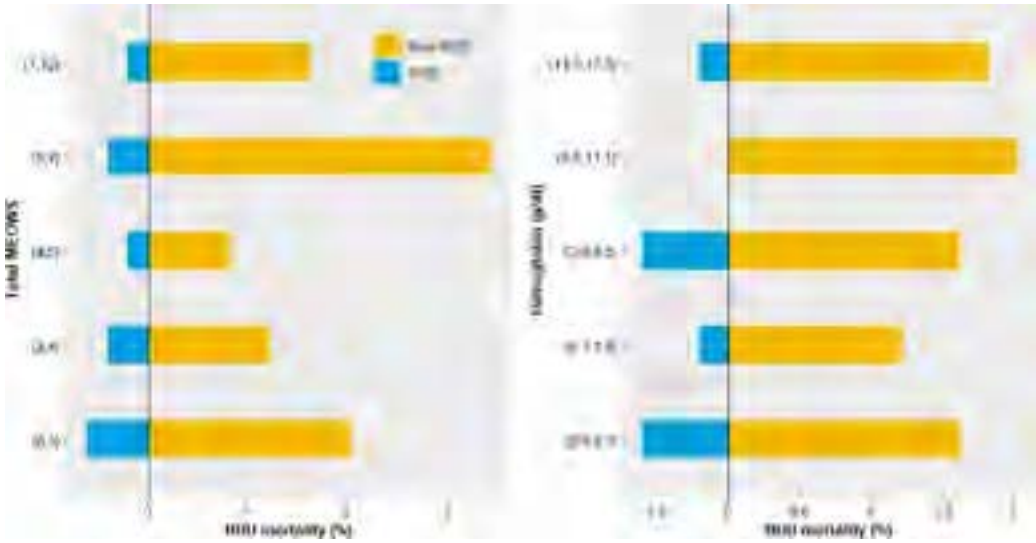

Fig. 3 Divergent bar plot showing the crude HDU mortality rate stratified by maternal early obstetric warning score and hemoglobin levels. Abbreviations: SCD, sickle cell disease; HDU, high dependency unit; MEOWS, modified early obstetric warning score

In our study one out of twenty patients admitted to the HDU had a history of SCD or was suffering from a complication of this disease. Studies reporting on the prevalence of SCD in obstetrical critical patients are lacking, as is robust local epidemiological data in Sierra Leone regarding prevalence of SCD in adults. In the United States, SCD complicates one out of 100 pregnancies, but does account for 1% of all maternal deaths [19]. Data on the frequency of SCD among HDU patients must be cautiously interpreted taking into account two context-specific considerations. Firstly, it is not very common for a SCD patient to become a mother, since 50 to 90% of children affected by SCD in Africa die before the age of 5 [20]. Secondly, being the study hospital a large referral hospital for complex obstetric cases, the number of patients with SCD may have been higher than in other settings. Yet, our study raises an alarming flag on the potential weight of SCD complications in pregnancy in the critically ill obstetric populations in limited resource settings with high maternal mortality.

SCD patients had similar baseline characteristics and management features to the general HDU population except for the need of oxygen, which was predictably higher in the SCD group. This can be attributed most likely to episodes of vaso-occlusive phenomena, pulmonary infections and severe anemia. Hemoglobin levels

Table 4 Management features

	All patients ($n=497$)	SCD group ($n=25$)	No-SCD group ($n=472$)	*P*-value
Oxygen therapy	73 (14.7)	9 (36.0)	64 (13.6)	**0.002**
Vasoactive treatment				
Vasopressors	40 (8.0)	2 (8.0)	38 (8.1)	1
Antihypertensives	121 (24.3)	1 (4)	120 (25.4)	1
Antihypertensive agent				
Intravenous hydralazine	8 (1.8)	0 (0.0)	8 (1.9)	1
Oral nifedipine	79 (18.3)	0 (0.0)	79 (18.2)	0.268
Any other	88 (20.4)	2 (8.0)	86 (20.1)	1
Urinary catheter	203/432 (46.9)	8/22 (36.4)	195/410 (47.4)	0.305
Antimicrobial use	445 (89.5)	22 (88.0)	423 (89.6)	0.737
Of which, antimalarial therapy	41/445 (9.5)	7/22 (31.8)	34/423 (7.2)	**<0.01**

Abbreviations: SCD Sickle cell disease

were, as expected, significantly lower in the SCD population. On the other hand, hemorrhagic complications such as APH and PPH were less common in SCD women, in line with previous literature [19, 21, 22]. This finding is probably attributable to the hypercoagulability state associated with SCD. In fact, vaso-occlusive crises as well as infections and thromboembolic events are well-known peripartum complications described in SCD making the low frequency of cesarean sections an unexpected finding. Malaria was a common condition in our cohort, a plausible finding as only SCT but not SCD is known to have a protective effect against the disease. On the contrary, the malaria infection can be accompanied by severe complications when affecting individuals with SCD [23]. Defining this burden was a relevant finding in our study, as early diagnosis and supportive treatment of malaria complications in patients with SCD may impact patient outcomes.

Our findings extend previous studies reporting that SCD in pregnancy increases the risk of maternal death [24–27]. Overall, crude mortality rate was extremely high in this setting with one in three patients with SCD dying in the HDU, as compared to one in ten patients in the non SCD group. It is important to note how SCD patients represented only 5% of admissions but almost 17% of total deaths. A 2011 study from Jamaica examined a sample of 42 deaths occurring in SCD patients over a 10-years-long period, in a setting with greater availability of diagnostic and treatment options[7]. In that study, SCD deaths suffered blood disorder, cardiovascular diseases and higher rates of post-partum complications – and more often died in an ICU. The study reported a significant excess risk of dying, underscoring the urge of further exploration of possible pathophysiological mechanisms to inform appropriate interventions. Our findings extend those from Asnani et al., describing how also in critically ill patients there is an increased probability of death which is independent from the baseline severity [7]. In our study, patients with SCD died roughly 48 h later than women in the non-SCD group, a time gap that may be attributed to the pathophysiology of the deadly cardiovascular events often seen in SCD, although we have no patient-level data to discern the exact causes of death.

A recent large cross-sectional study from the United States assessing outcomes of acute SCD admissions with black race suggested prenatal anemia to be a possible mediator associated with pregnancy risk in individuals with SCD [28]. In our cohort anemia as an admission criteria was equally prevalent among the two groups, and we could not distinguish between prenatal anemia versus acute hemorrhagic conditions. Yet, the hemoglobin level was markedly lower in the SCD group, in line with the hypothesis endorsing prenatal anemia as a mediator for adverse pregnancy outcomes.

The evidence for poor outcomes in this group of patients calls for specific optimization and escalation of care focusing on the life-threatening SCD complications. Patients with suspected acute chest syndrome require transfusions, antibiotics, adequate analgesia and and may need enoxaparin at therapeutic dosage in case of thromboembolism [29]. In low-resource settings the consistency of drug's and blood availability is often a problem, and sporadic scarcity of life-saving treatments may contribute to worsen mortality.

A major management issue is the prompt access to blood transfusions. Raising hemoglobin levels is recommended by current guidelines [30, 31], with the recommendation to avoid increasing Hb beyond 10 g/dl in patients receiving a transfusion, due to concerns with whole-blood viscosity-related complications [32]. Immediate and continuous availability of blood

products from the blood bank is a limiting factor in many African hospitals [33]. According to these findings, the implementation of strategies which lead to reliable blood supply in SCD patients to maintain Hb levels between 7 and 9 g/dl needs to become a primary concern. Moreover, as women with SCD have a steady state Hb level that is lower than average, routinary Hb screening in antenatal clinics may contribute to flag potential cases. This is even more important as prenatal anemia may be a mechanistic driver for organ dysfunction and complications associated with abnormal placentation [28]. In addition, the availability of reliable diagnostic methods based on electrophoresis or validated rapid detection kits should increase to allow correct diagnosis and phenotyping of SCD.

Our study has several strengths. It represents the first cloud-based registry-derived output from an obstetric HDU in a low-income setting. The registry structure allowed for a precise reporting of consecutive patient episodes, with a data collector dedicated to daily data entry and a registry infrastructure with inbuilt quality assurance features. Outcome follow-up at HDU discharge was completed for all patients, with an exact understanding of mortality and time-dependent endpoints.

The study also presents several limitations; the data collection was limited to obstetric HDU patients, therefore no information on neonatal outcomes was available. SCD diagnosis was acquired from self-reported anamnesis, patient records or clinically at HDU entry, and no electrophoresis confirmatory methods were available. Importantly, due to the unique coding for SCD we also lacked data on numbers for each defining category. Thus we cannot exclude potential miscategorization or the missing of patients affected by SCD with no prior knowledge. This limitation will be mitigated in the future by the implementation of a rapid detection test for SCD on all primigravidas. The outcomes were limited to patient HDU stay in immediate postpartum and we lacked the data to calculate a HDU-specific maternal mortality ratio. We also consider our study affected by a selection bias, since it was led in a large referral hospital, thus the findings cannot be generalized to district hospitals or different healthcare settings. Finally, this was a registry-based pragmatic study, with the systematic unavailability of some important variables conventionally used to specifically describe obstetric and SCD cohorts (e.g. parity and gravidity). This limited the patient-level characterization of conditions such as acute chest syndrome and other SCD related complications.

Conclusions

In this registry-based prospective study we show how SCD burden in critically ill obstetric patients is significant and is associated with poor outcomes, despite a similar severity on admission to patients without SCD. These findings call for the optimization of intermediate and intensive care for SCD patients, to be prioritized in low-resource settings with high maternal mortality.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12884-023-05888-9.

Additional file 1.

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Authors' contributions
MM, CC, LP and RH conceived and designed the paper. MST and HK collected the data. VS and RB performed the statistical analysis. MM and LP drafted the manuscript. LP, RH, AOA and CC supervised the project. CC, SB, VC, WT, AOA and SB supervised the registry data collection processes. All authors critically revised the manuscript. All authors provided final approval of the article. AB and RH obtained funding. LP and MM take overall responsibility for the work.

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Availability of data and materials
The datasets generated during and analyzed during the current study are not publicly available due to registry data sharing policies but are available from the corresponding author on reasonable request to the Critical Care Asia Africa (CCAA) data access committee. For further information and access to the data, please contact the CCAA data access committee (DAC@nicslk.com) and quote the manuscript, your institution and provide return correspondence information.

Declarations

Ethics approval and consent to participate
The HDU digital registry received ethical approval and a waiver of informed consent from the Sierra Leone Ethics and Scientific Review Committee in June 2020.

Consent for publication
Not applicable

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Anesthesia and Intensive Care, University of Piemonte Orientale, Novara, Italy. [2]Princess Christian Maternity Hospital, University of Sierra Leone Teaching Hospitals Complex, Freetown, Sierra Leone. [3]Section of Operational Research, Doctors with Africa–Cuamm, Padova, Italy. [4]Department of Anesthesia and Intensive Care, Connaught Hospital, University of Sierra

Leone, Freetown, Sierra Leone. [5]Anesthesia and Intensive Care Medicine, University of Bari, Bari, Italy. [6]Mahidol–Oxford Tropical Medicine Research Unit (MORU), Mahidol University, Bangkok, Thailand. [7]Intensive Care Unit, Miulli Regional Hospital, Acquaviva Delle Fonti, Italy.

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Publisher's Note

Indagine conoscitiva sulla violenza di genere tra i giovani residenti nel distretto di Oyam, Uganda

PAPER

Authors
Farina U., Coppola C., Dall'Oglio G., Alupu M., Ogwang E., Bingom C., Ogwal P., Di Gennaro F., Marotta C., Segala V.F., De Vita E., Iacob G., Tognon F., Putoto G., Martinelli D., Prato R., Fortunato F.

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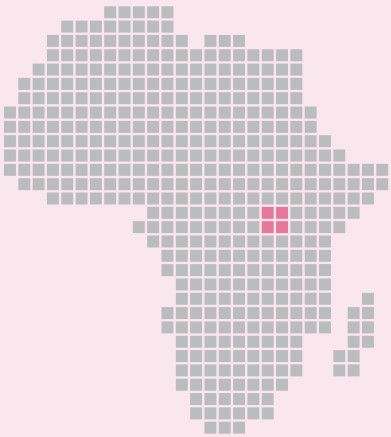

Recenti Prog Med 2023; 114: 541-542

Indagine conoscitiva sulla violenza di genere tra i giovani residenti nel distretto di Oyam, Uganda

UMBERTO FARINA[1], CRISTINA COPPOLA[2], GIOVANNI DALL'OGLIO[3], MONICA ALUPU[3], ERIC OGWANG[3], CHRISTOPHER BINGOM[3], POLYCAP OGWAL[3], FRANCESCO DI GENNARO[4,5], CLAUDIA MAROTTA[4], VLADIMIRO FRANCESCO SEGALA[5], ELDA DE VITA[5], GIULIO IACOB[3,6], FRANCESCA TOGNON[4], GIOVANNI PUTOTO[4], DOMENICO MARTINELLI[1], ROSA PRATO[1], FRANCESCA FORTUNATO[1]

[1]Scuola di specializzazione in Igiene e medicina preventiva, Dipartimento di Scienze mediche e chirurgiche, Università di Foggia; [2]Direzione sanitaria aziendale, Asl Bari; [3]Doctors with Africa, CUAMM, Uganda; [4]Operational Research Unit, Doctors with Africa CUAMM, Padova; [5]Clinica universitaria Malattie infettive, Università di Bari "Aldo Moro"; [6]Ospedale San Giuseppe Multimedica, Milano.

Poster presentato al Convegno "4words2023", Roma 11 maggio 2023.

Analogamente alle precedenti pandemie è stato osservato un aumento degli episodi di violenza di genere (Gbv) anche durante Covid-19[1]. In questo lavoro, sono state indagate le opinioni e le esperienze personali sul tema della Gbv nel distretto di Oyam.

Le informazioni sono state raccolte attraverso un questionario anonimo, somministrato tra maggio e settembre 2022 ai giovani partecipanti ai focus group organizzati dalla Ong Cuamm Medici con l'Africa nei centri di salute di Oyam.

Hanno risposto 129 soggetti, il 71,3% di sesso femminile (età media: 20 anni). Il 76,7% ha riferito un basso livello di istruzione, il 50,4% aveva un'occupazione, il 70,5% viveva in un'area rurale.

In merito alle opinioni sulla Gbv, il 72,8% era concorde che la forma di violenza più comune fosse quella fisica, seguita da quella economica (60,4%), psicologica (57,8%) e sessuale (49,6%) (figura 1).

Quasi l'80% dei rispondenti riteneva che a commettere più frequentemente abusi fossero gli uomini e i partner; oltre l'80% era d'accordo a parlarne con familiari e amici.

Il 12,4% era d'accordo che nulla potesse giustificare un atto di violenza, mentre oltre il 70% riteneva che la gelosia o l'inabilità della donna a ricoprire il ruolo di moglie o madre potesse legittimarlo.

In base all'esperienza personale, gli episodi di violenza sono risultati in aumento durante il lockdown (figura 2).

L'indagine conferma che la violenza e l'accettazione di essa rappresentano un problema ancora rilevante in Uganda e che le restrizioni dovute al lockdown hanno peggiorato la situazione. Appare indispensabile pertanto continuare l'implementazione di programmi di prevenzione e risposta alla violenza di genere da parte delle organizzazioni non governative e dai governi locali.

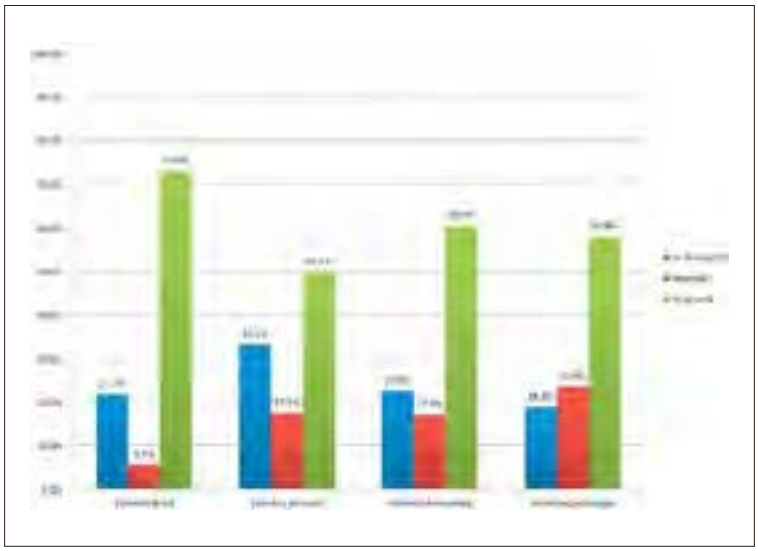

Figura 1. Tipi di violenza più frequente secondo l'opinione degli intervistati.

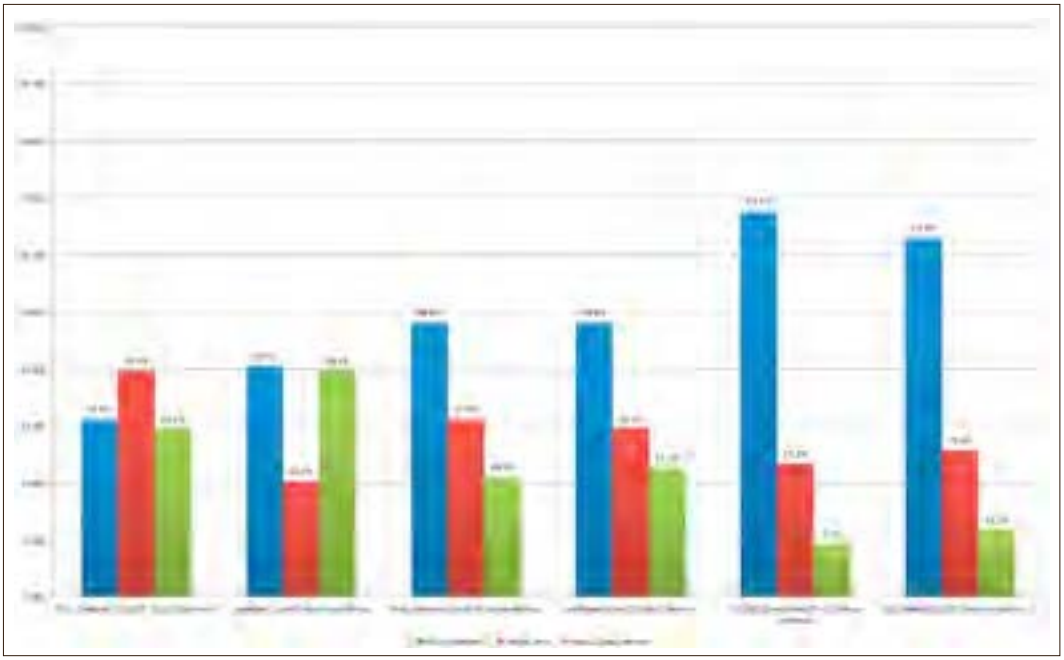

Figura 2. Esperienze sulla violenza: confronto lockdown Covid-19 vs post-lockdown Covid.

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Indirizzo per la corrispondenza:
Dott. Umberto Farina
E-mail: umberto.farina@unifg.it

A Good Start in Life: An Investigation on Basic ECD Knowledge and Practices in Two Districts of Zambezia Province

POSTER AND ORAL PRESENTATION

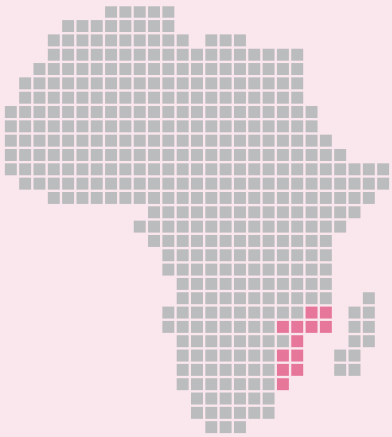
Conference
17th INTEREST Congress

Location
Maputo, Mozambique

Presentation date
9 - 12 May 2023

Authors
Occa E. et al.

Focus country
Mozambique



What if one of the biggest killers was even bigger? Hypertensive disorders of pregnancy underlying maternal death secondary to other direct and indirect causes

POSTER AND ORAL PRESENTATION

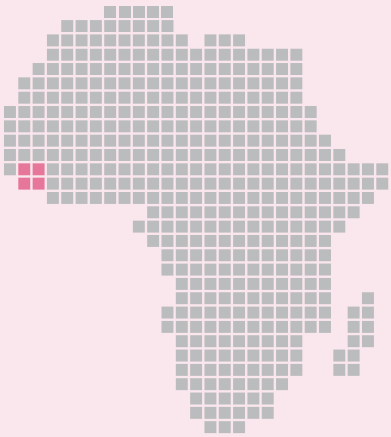
Conference
FIGO World Congress of Gynecology and Obstetrics

Location
Paris, France

Presentation date
9 - 12 October 2023

Authors
Orsi M. et al.

Focus country
Sierra Leone



Utilizing surgical Camps for clinical skills transfer: An experience of doctors with Africa CUAMM in Karamoja

POSTER AND ORAL PRESENTATION

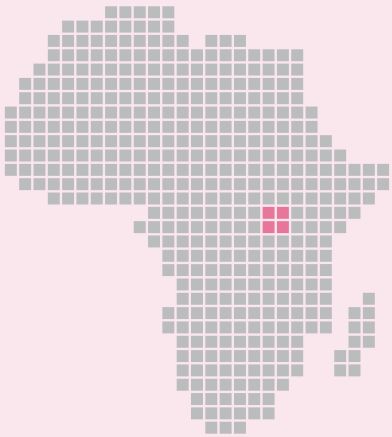
Conference
3rd National Safe Motherhood Conference

Location
Kampala, Uganda

Presentation date
23 - 25 October 2023

Authors
Boxtel A. L., et al.

Focus country
Uganda



Kangaroo Mother Care: Experience from Matany Hospital in Napak District Karamoja

POSTER AND ORAL PRESENTATION

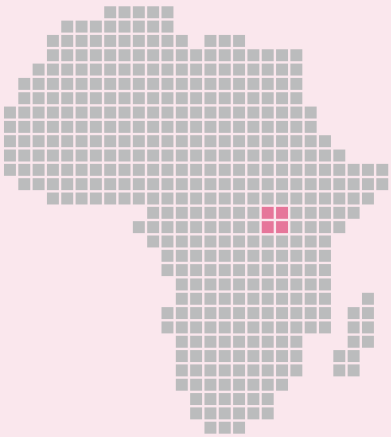
Conference
3rd National Safe Motherhood Conference

Location
Kampala, Uganda

Presentation date
23 - 25 October 2023

Authors
Christine M., et al.

Focus country
Uganda



Group ANC improves maternal and newborn outcomes. A case of Moroto RRH, Moroto District

POSTER AND ORAL PRESENTATION

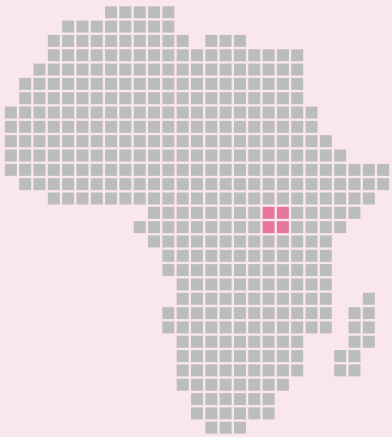
Conference
3rd National Safe Motherhood Conference

Location
Kampala, Uganda

Presentation date
23 - 25 October 2023

Authors
Pande S., et al.

Focus country
Uganda



Barriers to Care Mental Health Status and Impact of COVID-19 Pandemic on Adolescents and Young Adults Living with HIV in Shinyanga Region, Tanzania

POSTER AND ORAL PRESENTATION

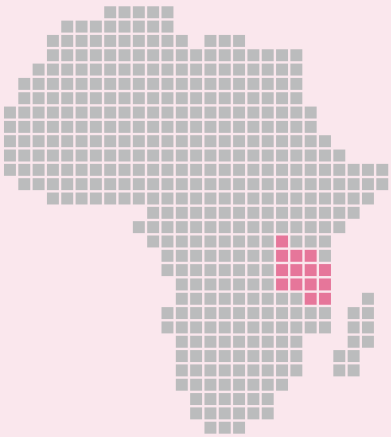
Conference
2nd Reproductive, Maternal, Newborn, Child, Adolescent health and Nutrition Scientific Conference

Location
Dar Es Salaam, Tanzania

Presentation date
15 - 17 November 2023

Authors
Didonè M. et. al.

Focus country
Tanzania



Pediatric Outpatient Services In Rural Tanzania: Retrospective Cohort Study On Predictive Factors For Hospitalization

POSTER AND ORAL PRESENTATION

Conference
2nd Reproductive, Maternal, Newborn, Child, Adolescent health and Nutrition Scientific Conference

Location
Dar Es Salaam, Tanzania

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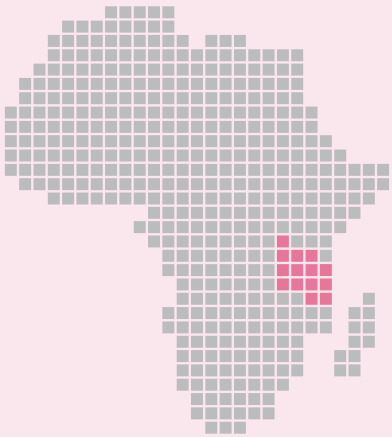
Authors
Mancini V. et al.

Focus country
Tanzania



Special Needs Population Of Malnourished Paediatric Patients In Tosamaganga Hospital, Rural District Of Iringa, Tanzania

POSTER AND ORAL PRESENTATION

Conference
2nd Reproductive, Maternal, Newborn, Child, Adolescent health and Nutrition Scientific Conference

Location
Dar Es Salaam, Tanzania

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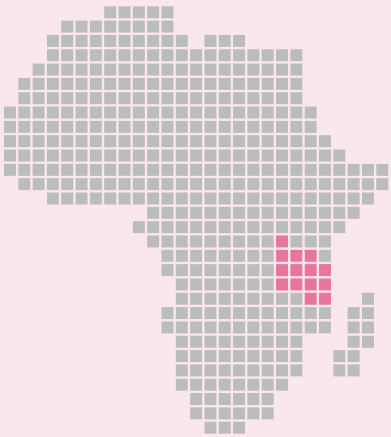
Authors
Dalla Porta F. et al.

Focus country
Tanzania



Public health and universal coverage

International medical electives in Sub-Saharan Africa: experiences from a 19-year NGO-driven initiative

PAPER

Authors
Quaglio G., Bosco Nsubuga J., Maziku D., Tsegaye A., Parise N., Cavagna C., Lochoro P., Strepparava M.G. , Da Dalt L., Okori S., Gatta A., Mbiya Kamunga A., Putoto G.

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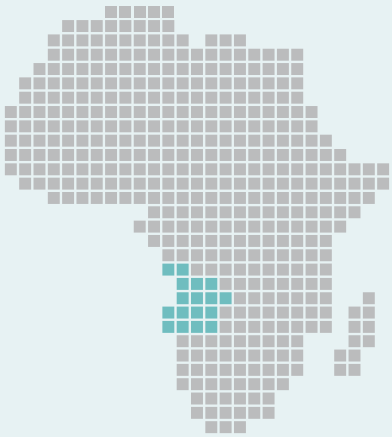

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BMC Medical Education

RESEARCH Open Access

International medical electives in Sub-Saharan Africa: experiences from a 19-year NGO-driven initiative

Gianluca Quaglio[1,2*], John Bosco Nsubuga[3], Donald Maziku[4], Ademe Tsegaye[5], Nicoletta Parise[6], Chiara Cavagna[2], Peter Lochoro[7], Maria Grazia Strepparava[8,9], Liviana Da Dalt[10], Sam Okori[11], Alessandra Gatta[2], Adrien Mbiya Kamunga[12] and Giovanni Putoto[2]

Abstract

Background Mainstream medical education remains largely focused on national health issues. Therefore, in order to expose medical students to international health issues, it is beneficial to facilitate international medical electives.

Methods This article describes the Junior Project Officer (JPO) program, a medical experience based on clinical electives in Sub-Saharan Africa, supported by a Non-Governmental Organisation (NGO). Residents spend 6 months as part of a multidisciplinary medical team in Africa. A post-elective online survey was administered to all who participated in the program in the period 2002–2020. The questionnaire comprised three domains: (i) general and pre-departure information; (ii) the experience; (iii) the post-experience.

Results Questionnaires were received from 157/241 subjects, a response rate of 65%. The most common specialties were pediatrics, public health, and internal medicine. Of all, 87% carried out clinical activities; 45% also worked in the management of health services, and 60% carried out research activities. About 64% reported difficulties linked to a lack of equipment, different ways of working (57%), and exposure to situations for which they did not feel technically prepared (56%). In 25% of cases, residents reported that their school's attitude to their doing the elective was not positive: upon their return, over 50% felt that their experience was not sufficiently valued by their institution. Respondents considered the experience important for professional and personal growth (93% and 80% respectively). Forty-two participants (27%) reported that the experience had a significant impact on their future career choices.

Conclusion Despite the difficulties encountered, a well-structured experience in international health can have a positive impact on residents, professionally and personally. Key factors behind the positive outcomes are the substantial length (6 months) of the experience, and the long term working relationships between the sending and receiving institutions. The schools in Italy that provide the students for the electives need to see more evidence that international electives are worth the investment.

Keywords Medical elective, International health, Sub Saharan-Africa, Global health

*Correspondence:
Gianluca Quaglio
gianluca.quaglio@europarl.europa.eu

Full list of author information is available at the end of the article

Background

The provision of global health training through international clinical experiences for medical students is now a necessity. This may be traced back to two fundamental causes: the first is that globalization affects many aspects of public health, as has been underscored by the COVID-19 pandemic [1]. The second is that mainstream medical education is substantially focused on national and not global health issues [2, 3]. An increasing number of medical students are undertaking electives in low- or middle-income countries (LMICs) [4]. Medical experiences in LMICs give hands-on understanding of working in under-resourced conditions and in a different cultural environment. Medical electives increase diagnostic skills in conditions where medical technology is often non-existent. They bring a greater appreciation for public health interventions on community health [5–7]. However, medical electives have brought to light multiple concerns, including navigating an unfamiliar health system with different workflows [8, 9], health risks associated with electives [8, 10], and possible doubts about how meaningful and positive the impact on host communities may be [11–14]. International guidelines have been developed for best practices in electives. These guidelines aim to better understand local cultures, ethical implications, personal motivations, and to ensure that elective activities improve local health capabilities [15–17].

Global health is a concept and reality that has emerged almost entirely from western institutions. This base in the traditions of the west has even led to the claim that 'global health' is neo-colonialist [18]. This has led to current international electives facing rigorous monitoring and criticism [19–21]. Cole noted how international medical electives are carried out predominantly by privileged groups, which assume that, 'they can make a difference without understanding the complexities of context of those being helped' [22], perpetuating the notion that, 'some care is better than none' [23]. Sullivan observed that electives, 'commonly arrive lacking contextual and cultural knowledge, let alone specific notions of what precisely they will do. Volunteers thus arrive and interact in an ad hoc fashion' [21]. Dowell, and Merrylees (2009) [24] pointed out that, 'electives in developing countries tend to be popular and memorable, but are generally so unstructured that they raise a number of moral issues and perhaps fail to fulfil all the educational opportunities they seek to offer'. These criticisms highlight the need to ensure that international electives should be well prepared for the experience. In addition, critics require that elective activities meaningfully mitigate against the global and local factors that drive imbalances in terms of knowledge, resources, and level of healthcare. Instead of focussing only on biomedical and clinical capacity, global health practices should adopt multidisciplinary approaches, acknowledging social and economic inequity at community and global level [25].

In order to develop a well-structured elective experience, Dowell and Merrylees observed it is important to establish, 'institutional partnerships between the sending and receiving institutions'. They also emphasise that, 'the continuity of student presence provided by a partnership allows more comprehensive student preparation', and that the preparation of students for electives, 'is easier to organise and of more direct relevance for groups of students who are going to the same place as part of an institutional partnership' [24]. In short, a stable relationship with the host institution helps prepare residents for the elective experience and can lessen the potential concerns relating to host institutions in LMICs [26, 27]. We reviewed over two-hundred articles on international medical electives, and to the best of our knowledge, there has been no systematic analysis of how institutions that provide residents begin their involvement with international medical electives. Typically, providers engage through personal connections and by joining faith-based medical mission teams. Academic institutions more often begin their involvement by establishing or participating in bilateral academic partnerships [9].

This paper sets out the experience called the Junior Project Officer (JPO), driven by the Non-Governmental Organization (NGO), Doctors with Africa - CUAMM (DwA) [28]. A resident international elective requires that the time needed for participants to adapt to the hosting site be carefully balanced with the issues arising from time spent away from the home institution. The JPO offers doctors-in-training the chance to undertake a six-month health elective in Sub-Saharan Africa. The six-month elective allows residents enough time to adjust psychologically to a challenging environment, and to better understand the different aspects of global health related to the experience. In its 19 years of activity, the JPO has collaborated with 37 Italian medical schools. With 12 of these, the relationship is governed by a memorandum of understanding. A memorandum of understanding has also long been established by DwA with each of the African health facilities hosting JPO residents. The experience is clinically focused, and includes public health practices and research components. Continuity of care between hospitals, peripheral health centres, and communities is key to the organization's activities. Accordingly, in addition to hospital work, residents carry out visits to peripheral health centres and communities. These activities are mediated by government health staff (District Health Management Teams and Community Health Workers). The meetings with communities, especially with women, are aimed at learning about healthcare-seeking behaviours and the cultural, geographical, and financial barriers that prevent populations

from accessing health services. DwA also organises pregraduate medical elective international experiences, as described elsewhere [29].

DwA is the first NGO working in the international health field to be recognised in Italy and is the largest Italian organisation for health promotion in Africa. DwA is present with offices and staff in eight Sub-Saharan African countries; Angola, Central African Republic, Ethiopia, Mozambique, South Sudan, Uganda, Sierra Leone, and Tanzania [28, 30]. At clinical level, the organisation supports 23 main hospitals and 761 health facilities. The major areas of intervention are maternal and child health, nutrition, infectious diseases, and chronic diseases. DwA provides training support to one university and four schools of nurses and midwives. In 2021, DwA had 4,518 health professionals and technicians on the ground. The organisation works with a long-term development perspective, often undertaking projects that will last for decades. It receives national and international private and public funding.

The 19 years' experience of the JPO is reported in this paper, using the results of a survey distributed to all residents who participated in the JPO.

Managerial and recruitment process for JPO residents

The screening process for the selection of residents for the JPO consists of several steps aiming at assessing motivation, cultural sensitivity, and commitment to working in a setting with limited resources. Prospective JPO candidates fill in an application form, eliciting basic information, including professional profile, academic record, and reasons for participating in the elective. Residents are required to attend pre-departure training courses organised by DwA, during which the selection of candidates is finalised. Over the 19 years of the project, the training has been progressively revised, based on the feedback from the participants and from the African hospitals hosting the residents. At present, it consists of four main sections. The first is devoted to the objectives of the JPO. The second section provides information management on specific clinical fields, along with concepts of hospital management and public health in poor resource settings. The third section aims at educating the participants regarding the socio-cultural context of the host country. This preparation is tailored to each location, and is generally taught by people from the relevant countries. It includes information on how historical factors, such as colonisation and exploitation of resources, have affected health services. In addition, the third section contains a module dedicated to health. This follows the LEARN medical anthropology framework (Listen, Explain, Acknowledge, Recommend, Negotiate) [15]. The fourth section provides bureaucratic and practical information. The trainers are health professionals with previous experience in LMICs.

Before departure, the most suitable location in Africa is identified and a personalised job description is prepared for each resident, in line with the needs of the host institutions and the training objectives of the specialty school. All the locations where DwA works are potential destinations, provided that the presence of the tutor as well as logistical and safety conditions are guaranteed. These conditions may vary over time depending on the evolution of DwA's intervention and the situations in the countries where it operates.

Upon their return, residents are asked to complete an evaluation form and attend debriefing sessions with DwA staff. Debriefing provides an opportunity for residents to reflect on the frequently mixed emotions experienced, and on the challenges faced, thus allowing for further personal and professional development. Often, residents are invited to share their experience during an ad hoc seminar in their school of speciality and encouraged to elaborate upon their experience through reflective writing, which is published on the DwA website.

Methods

Study design

The study design was a cross-sectional online survey.

Setting and on-site activities

There are 8 countries and different potential destinations: Angola (Chiulo hospital, Luanda); Ethiopia (Wolisso hospital); Mozambique (Beira central hospital); Central African Republic (Bangui hospial); Sierra Leone (Freetown hospital and hospital and health centres in the Pujehun district); South Sudan (Yirol hospital and Lui hospital); Tanzania (Tosamaganga hospital); Uganda (Aber hospital and Matany hospital). Travel costs are incurred directly by residents (Table 1). DwA provides insurance coverage, accommodation and logistical support.

In Africa, the residents are required to participate in all the daily activities of the service, including patient visits, case discussion, making diagnosis and management of illnesses, meetings with nurses and families, and on-site formularies. This brings familiarisation with local disease patterns and the limitations of local health resources. The clinical care process is mediated by the local health staff in charge, such as medical doctors, nurses, and hospital managers. The main way of communicating with the patients and their relatives is through the national language (e.g. Kiswahili, English, French, Portuguese, etc.). At the community level, where people commonly speak local dialects, language barriers are overcome by local district health managers and community health workers. Senior doctors act as tutors, helping residents to deal with the difficulties that are inevitably encountered in

Table 1 Major sites of activities of the JPO programme

Major sites of electives	Beds	Out-patients visits	In-patients admissions	Health location
Ethiopia: Saint Luke H[1], Wolisso	200	80.282	12.183	Regional referral H, urban area; Community; Districts
Central African Republic: Bangui Pediatric H	257	71.065	16.309	National referral H, urban area
Mozambique: Beira Central H	823	126.150	17.159	National referral H, urban area
South Sudan: Yirol H and Lui H	105	54.470	10.391	National referral Hs, urban area; Community; Districts
Angola: Chiulo H, Luanda	234	25.055	4.510	District referral H, rural area; Community; Districts
Uganda[2]: Aber H and Matany H	428	64.948	26.259	District referral Hs; rural area; Community; Districts
Tanzania: Tosamaganga H	165	31.963	6.354	District referral H, rural area; Community; Districts
Sierra Leone[2]: maternity H, Freetown and H in the in Pujehun district	184	20.162	12.501	National and district referral hospitals; urban and rural areas; Community; Districts

[1] H: Hospital; 2: cumulative data

this type of situation. Tutors are involved in drafting the training objectives approved by the University, providing monthly feedback and a final evaluation of each resident's activity. Since the start of the project, over 50 professionals have been tutors, both expatriates and locals, most of them being head of a hospital ward or department, and specialised in the same or a closely related speciality as the resident. Typically, they have more than 10 years of experience as consultants. Motivation for the tutors is multifaceted. There are no financial incentives, however teaching trainees brings its own rewards. In addition, tutors familiarise themselves with new procedures, and can network with international academia. Also of value is that residents help share the burden of clinical work.

Sample, eligibility and data collection

The survey, carried out in July 2021, was electronically distributed to all subjects who participated in the JPO program during the period 2002–2020. Participants were informed that the data would be used exclusively for research purposes and that the data were collected in conditions of complete anonymity. The questionnaire encompassed three sections: (i) general and pre-departure information; (ii) the experience; (iii) the post-experience (Annex I). The study was approved by the Ethics Committee of DwA.

Statistical analysis

All statistical analysis was performed using SPSS v.26. The variables were of two types: categorical variables, such as characteristics of individuals or of their experience (year of departures, destination, main motivation, etc.); ordinal variables (values from 1 to 10), used by participants to assess their professional or training experience. Categorical variables were recapitulated using frequency tables (percentage distribution). Ordinal variables were summarised using quartiles. Bivariate analyses were carried out to identify associations between variables (or differences) between groups of respondents. In order to evaluate the association between categorical variables, cross tables and Pearson's chi-square test were conducted. For example, analysis was conducted to see if there were differences in different periods (2002–2013 vs. 2014–2019) or in different working areas (medical vs. surgical). A number of paired t-tests was used to test if the means of two paired measurements (pre-departure score and post-departure score) were different. A value of $p<0.05$ was considered significant.

Results

Progressive increase in the number of participants

Over the period of the study, the JPO program received an average of 30 requests per year, and there were on average 12 departures per year. However, the number of residents doing a medical elective progressively increased over the years. In the first 5 years of the project, there was an average of 7 applications per year: this increased to 56 per year in the last 5 years of the project. During the course of the project, there was a corresponding increase in the number of departures, from an average of 4 per year in the first five years to 27 per year in the final five years (data not shown).

General and pre-departure information

Of the 241 subjects who took a medical elective during the study period, 157 completed the survey (65% response rate). The majority of the questionnaires (54%) were completed by those who had had the elective experience in the last 5 years of the study period. The majority of participants were female and carried out the electives at Wolisso, Tosamaganga, and Beira hospitals. The most frequent specialties were pediatrics, public health, internal medicine and subspecialties. At the time of departure, most participants were in year 4 or year 5 of their residency (Table 2).

Table 2 General and pre-departure information

Topic	No	%
Gender		
Female	116	74%
Male	41	26%
Year of departure		
2002–2007	20	13%
2008–2014	41	26%
2015–2020	96	61%
Post-graduate year of residency		
PGY-1	3	2%
PGY-2	5	3%
PGY-3	36	23%
PGY-4	71	45%
PGY-5	42	27%
Specialisation		
Pediatrics	47	30%
Hygiene and preventive medicine	25	16%
Internal medicine and subspecialties	25	16%
General surgery	19	12%
Gynecology and obstetric	17	11%
Infectious diseases	14	9%
Emergency medicine	7	4%
Anasthesia	3	2%
Location of the elective		
Wolisso (Ethiopia)	28	18%
Tosamaganga (Tanzania)	27	17%
Beira (Mozambique)	27	17%
Chiulo (Angola)	19	12%
Matany (Uganda)	12	8%
Aber (Uganda)	9	6%
Freetown (Sierra Leone)	8	5%
Others	27	17%
Motivations		
To serve less privileged populations	91	58%
To enhance my professional experience	47	30%
Others	19	12%
Effectiveness of pre-departure training		
Yes	118	75%
No	39	25%
Response of the school to the JPO		
Very well	52	33%
Moderate	66	42%
Neutrally	27	17%
Not well	12	8%
In Africa before		
Never	68	43%
As a volunteer	61	39%
As a tourist	28	18%
Activity carried out in current work*		
Clinical activity	126	80%
Research activity	33	21%
Organisation of services and health planning	25	16%
Didactic and training activities	25	16%
Current place of work		

Table 2 (continued)

Topic	No	%
Italy	141	90%
Abroad	16	10%

* More than one answer was possible

Table 3 The experience

Topic	No	%
Health location of the elective*		
Hospital	125	87%
Community	49	31%
District	22	14%
Others	9	5%
Clinical activities*		
No	20	13%
Hospital	119	76%
Outpatient clinic	68	43%
Emergency	41	26%
Others clinical activities	30	19%
Didactic/training activities*		
No	30	19%
General population	146	93%
Community health workers	137	87%
Doctors and/or clinical officers	99	63%
Nurses	55	35%
Other didactic/training activities	143	91%
Organisation of health services*		
No	86	55%
Health centres	49	31%
Villages	24	15%
Districts	22	14%
Other organisational services	16	10%
Research activities*		
No	63	40%
Research for the specialisation thesis	52	33%
Research for posters/abstracts/presentations	24	15%
Research for articles in peer review journals	22	14%
Other research activities	27	17%

*More than one answer was possible

The desire to serve less privileged populations and to improve one's professional preparation were the major reasons behind the decision to undertake the experience. There were no statistically significant variations between the motivations and the year of the experience.

As a whole, the support received in preparing for departure is evaluated positively by 75% of respondents. Further analysis of the pre-departure training shows that the major criticisms were related to the preparation for clinical activities, with a lack of specific information related to the location (hospital) of medical elective; the available resources for clinical care and the internal organisational arrangements (data not shown).

About one in 4 respondents (25%) stated that their medical school of specialisation did not welcome the choice to participate in the JPO.

The experience

Most of the activities were carried out in hospitals or community health centres (87% and 31% respectively). Clinical activities were mainly done in hospital, with in-patient and out-patient levels at 76% and 43% respectively. The educational and training activities were carried out mainly with the general population (93%) and with community health workers (87%), while the organisation of health services was carried out in health centres and villages (31% and 15% respectively) (Table 3).

About 64% reported difficulties linked to a lack of equipment (materials, devices, drugs, etc.), different ways of working (57%), and exposure to situations for which they did not feel technically prepared (56%). The share of those who reported difficulties due to exposure to situations for which they were not psychologically prepared was also significant (39%). A minority had difficulties in integrating with colleagues (19%) and in relationships outside the workplace (14%) (Fig. 1). A further analysis was made to see if there was a relationship between any of these obstacles, the host institutions, the host countries, and the working area (divided between medical and surgical). No statistically significant differences emerged with the host institutions and host countries. The obstacle 'exposure to technically challenging situations' was reported by 85% of those who worked in the surgical area and by 49% of those who worked in the medical area ($p<0.01$). For the other obstacles, no significant differences between the two groups were identified.

The post-experience

Training objectives included management of the clinical field in poor resource settings, understanding health inequities and other public health issues, improving health services management, and achieving professional and personal growth. In total, 58% of respondents felt that the training objectives were fully achieved. Only 2% stated that they were not. A significant percentage (40%) declared that the training objectives were only partially achieved. Notably, trainees considered the JPO experience important for professional and personal growth (respectively 93% and 80% of respondents). The analysis of these responses in relation to the period of departure

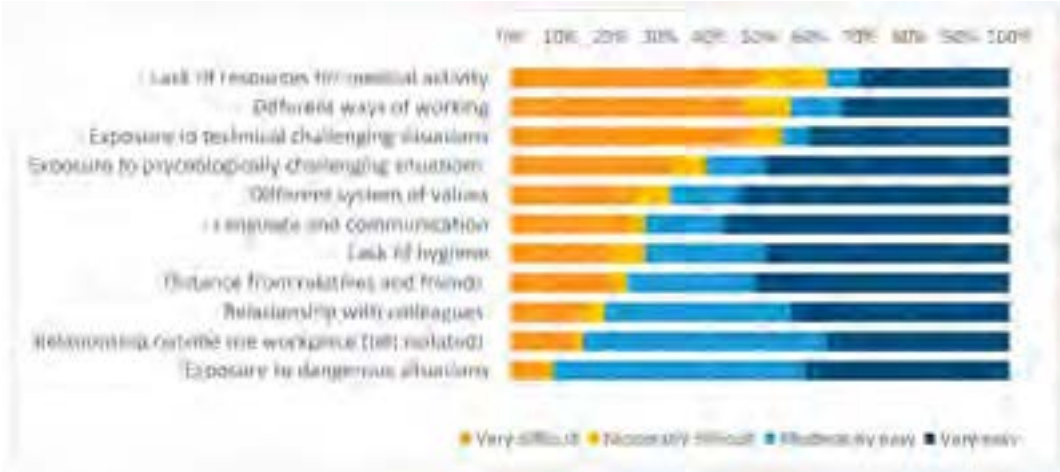

Fig. 1 Obstacles reported during the medical elective

and the working area (medical versus surgical), revealed no statistically significant differences.

Forty-two participants (27%) reported that the experience had an impact on their future career choices.

The experience positively influenced the medical approach of the residents. Respondents say they gained in terms of autonomy at work and self-confidence (79%) and in resilience (77%) (Table 4). The analysis of these responses in relation to the period of departure and the working area (medical versus surgical), revealed no statistically significant differences.

Other questions explored how the experience affected residents' interest in health inequalities, commitment to reducing environmental damage, awareness of wasting health resources, and interest in health services management. These questions compared pre and post-experience data (Fig. 2): the comparisons were statistically significant ($p<0.01$).

Subsequent to their elective, 29% have spent additional time in a medical setting in Africa, and 33% consider having other similar experiences in LMICs in the future. After their elective, 50% of residents have maintained contact with the African setting; 91% have maintained some form of contact with DwA (training, activities of cooperation, etc.).

Discussion

Principal findings

Mutchnick et al. [2] observe, 'living in alternative social environments creates an educational experience unmatched in any textbook or classroom exercise'. Residents in this study reported benefits from their experience which fall into three categories. First, at the professional level, residents declared that they returned home with an improved medical self-confidence, a greater sense of empathy towards patients, and an increased awareness of problems concerning the use of resources. This contributed to better cost-effectiveness and resource utilisation on return home [27, 31, 32]. Second, at the educational level, residents reported a deeper interest in health services management, and a greater appreciation of issues such as health inequalities, environmental damage, and the wasting of health resources. Third, the electives resulted in long-term behavioural change among residents. Consistent with prior reports, the experience seemed to influence the careers of a significant percentage of residents, increasing their interest in public service [7, 27, 32].

A stable relationship between sending and hosting institutions

As observed by Ackerman [33], 'on-site supervisors, the back-bone of most electives, are only possible with a reciprocal, long-term relationship either through a local university and medical school, a Nongovernmental Organization (NGO), or an International Nongovernmental Organization (INGO) working in the area. The educators must ensure that the host organization is appropriately integrated into the community and that community goals are at the forefront'. Willott et al. [34] highlight that, 'students frequently want to be able to decide for themselves where they go and how they spend their electives, but this may not be what is best for hosting institutions, nor for global health more generally'. As pointed out by Edwards et al. [35], a major concern regarding medical electives is that students may practice, 'beyond their competence, to their own and their patients' detriment. This may be more common in developing countries

Table 4 The post-experience

Topic	No	(%)
Achievement of formative objectives		
Fully	91	58%
Partially	63	40%
No	3	2%
Contribution of elective on personal growth		
Very much	146	93%
Fair	9	6%
Slight	2	1%
None at all	0	0%
Contribution of elective on professional growth		
Very much	125	80%
Fair	25	16%
Slight	5	3%
Not at all	2	1%
Impact on future career choices		
Yes	42	27%
No	115	73%
Impact of elective on medical practices*		
Autonomy at work and self-confidence	124	79%
Resilience	121	77%
Empathy with the patient	104	66%
Patience	89	57%
Aptitude to work with others	85	54%
Respect for others	78	50%
Valued by your school of specialisation upon returning		
Very much	20	13%
Fair	46	29%
Slight	55	35%
Not at all	36	23%
Maintained contact with the hospital in Africa		
Yes	78	50%
No	79	50%
Other experiences in LMICs after the elective		
Yes	46	29%
No	111	71%
Other work experiences in LMICs in the future		
Very much	52	33%
Fairly	89	57%
Slightly	14	9%
Not at all	2	1%
Maintained contact with DwA after the elective		
Yes	143	91%
No	14	9%

*More than one answer was possible

where supervision is scant and students may assume that limited health care resources justify their adopting roles or performing procedures which would be restricted to fully trained staff at home'. These reflections highlight the benefits of an experience like the JPO, which is organised and implemented by an NGO with long-term working relationships with the African populations and is well integrated into the community. The project is carried out in health facilities where DwA staff have been working for many years. Having well-known locations for electives reduces the potential risks connected with this type of experience, and better ensures a satisfactory level of supervision, a lack of which is a serious problem in many similar experiences [36]. A stable relationship between sending and hosting institutions may take several years to establish. The positive results of the JPO program were made possible by the continuous on-site presence of DwA. As observed by Luchett et al., 'this continuity provides a larger framework for residents so that they can contextualize their knowledge and understand their role' [37].

Length of experience and obstacles encountered

A resident international elective requires a balance between the time required to adapt to the hosting site and the organisational constraints associated with being away from the resident's home institution. Drain et al., suggest that residents in international rotations should spend at least six weeks working at the host institution [5]. It is a unique feature of the JPO project that the residents spend 6 full months on the elective. This gives JPO residents a much better sense of global health than is possible from most international rotation programs, which typically last between one and three months. Furthermore, this time frame is more likely to accommodate a more thorough psychological adjustment to a new and challenging environment. The six-month period is counted as equal to any other mandatory rotation that residents undertake during their training.

Consistent with prior reports, the major obstacles and frustrations reported are related to the working conditions: limited resources (e.g. fewer human resources, lack of medication and equipment, a lack of laboratory and imaging support, etc.), different ways of working (e.g. team structures or clinical roles that differ from what residents are used to), and clinical situations for which residents were technically unprepared (e.g. managing unfamiliar medical conditions) [9, 38]. The exposure to situations for which residents were not psychologically prepared was also significant. The emergence of mental health problems arising from coping with culture shock and working in problematic settings, often with high morbidity and mortality, are recognised elsewhere [9, 38, 39].

A less direct problem is how the providing school of specialisation reacted to the resident's departure and return. In 25% of cases, residents reported the school's response to departure was not positive. In addition, over 50% reported that upon their return their experience seemed insufficiently appreciated by their institution. These data must not be overlooked. This may be

Fig. 2 Residents' interest in health inequalities, commitment to the environment, awareness of wasting health resources, and interest in health services management (post-experience data)

explained by the shortage of health personnel in Italy and many European Member States, which is an ongoing barrier to pursuing international clinical rotations. The providing schools of specialisation need to see more evidence that it is worth their investing in international electives. A more rigorous evaluation of the effectiveness of elective experience is needed to demonstrate the value added to medical training [40], and what impact it may have on the communities and institutions involved [41]. Long-term follow-ups of elective participants after medical school in relation to their career choices (e.g., type of medical practice, career developed in public or private sectors) can also persuade medical schools that it is worth their investing in medical electives [32].

Activities in research and public health

Conducting research in Africa is not easy, for several reasons. Health institutions in Africa are often reluctant to support research efforts. This hesitation may stem from difficulties in data gathering, chronic shortcomings in clinical service provision, and fear that the research results may expose poor performance [42]. Additional frustrations arise from difficulties in understanding whom the research activities most benefit - the host institution in Africa, or the academic home institution. Over recent years, research has gained increasing importance in the DwA organisation and the JPO program. Research activities are embedded in the interventions meant to improve access and quality of care, or in stand-alone projects, which are promoted by DwA and the host institutions. About a third of the residents develop a research topic in line with their own specialty thesis, using locally available data. All JPO research-based initiatives must obtain both home and host site approval, as well as ethical approval from the ethics committees of the host institution and national research authorities. In addition, presentations and articles must recognise the contributions from African partners. In the years 2018–2020, DwA published 91 articles in peer-reviewed journals: of these, 44 had medical electives as co-authors [43]. While research collaboration between residents and host institutions is promising, the process is still far from optimal.

Residency programs often have difficulty teaching issues such as cost awareness and health inequity. To address the issue of paucity of resources, problem-solving ability was developed by the residents through alternative diagnostic and therapeutic solutions. Local resources including semeiotic knowledge, simple point of care testing, basic drugs regimen, and essential care for critical patients, were the main factors affecting residents' autonomy, self-confidence, and resilience. Since the clinical services are not provided for free, the residents developed a "cost awareness" attitude, searching out the most beneficial and cost/effective clinical pathways. This also contributed to seeing the severity of inappropriate care in western countires, where the wasting of health resources is significant and even dangerous. For instance, over prescription of antibiotics has led to increased antimicrobial resistance [44]. Patient delay causes severe, often fatal medical complications. To respond to this common phenomenon in Africa, residents developed a capacity to act quickly in dealing with critical patients, and increased their resilience in working under stressful conditions. Through attending death audit sessions, they see that to assure continuity of care, it is essential that health systems operating at different levels are sufficiently interconnected.

The interconnection of climate change and health needs to be addressed at global and local levels. International electives make residents confront environmental issues with an immediacy not possible in the home environment. For example, in 2019, when Mozambique was hit by Cyclone Idai, residents remained in the field, and provided humanitarian and clinical support to Beira Hospital and surrounding HIV health services [45, 46]. When Angola was hit drought, exacerbating child malnutrition, JPO residents similarly remained in post [47]. Such experiences make residents more aware of the interconnectedness of global environmental and health issues.

Study limitations

Although common to other reports of this type, it cannot be overlooked that this study has several shortcomings. Although the majority of questionnaires were completed

by those who underwent the JPO experience in recent years (2016–2020), there was significant variation in the time elapsed between the experience in Africa and the administration of the questionnaire. The JPO is carried out in eight countries with over a dozen potential destinations. Significant disparities exist on economic activities, welfare, health policies and social indicators across these countries. Furthermore, geographic settings are dynamic, constantly evolving in terms of socio-economic and political aspects, access to basic services (such as education and infrastructure) and public health policies. Therefore, it is challenging to examine whether and how changes in the African settings might have influenced the experiences of the residents during the nearly two decades of the JPO program. While this was not the goal of this study, it is an intrinsic limitation of it. A further limitation of this study is its retrospective design, with no comparison control group. The study utilised a self-administered questionnaire, without measures to address potential self-reporting bias. Although hosting institutions generally gave positive feedback, the information has not yet been systematically collected. An additional limitation is related to the lack of systematic collection of the feedback provided by residents after their experience. There is a need to better quantify the impacts of JPO on clinical knowledge and patient care. Future objectives of the JPO are to collect structured feedback from local communities, including additional outcome measures, other than self-reports, focusing on provider behaviour, clinical knowledge, and patient care.

Conclusion

This study reveals the results of structured and ongoing medical elective experiences carried out by an NGO in Sub-Saharan Africa. The ever-increasing globalisation deepens the need for physicians to be culturally broad-minded and to be effective communicators. International electives are an important means towards engaging with the diversity of patients physicians will encounter along their careers [27, 48]. The JPO has enabled elective experiences to people from 37 Italian universities (there are 43 faculties of medicine in Italy). The program seems to be making up for the lack of international experience in sub-Saharan Africa offered by Italian universities [49]. This is confirmed by the steadily increasing number of agreements between DwA and Italian universities. Further, this work highlights the need for Italian academic institutions and medical schools to nurture a medical education approach that is able to train doctors internationally competent and with a professional profile sensitive to global health issues. Ensuring adequate supervision and stable partnerships with hosting sites in Africa is mandatory, in order to respond to the unique logistic and ethical challenges that arise. The experience may present residents with practical and emotional challenges. A stable relationship with host institutions can also provide a continuous chain of residents over many years, contributing to the capacity building of the host institutions. Our findings support previous research about the value of international electives for residents. The mission of the medical school should be not only to train good clinicians, but also to be more community oriented, reconciling the health needs of the individual and the community.

Abbreviations

LMICs	Low- or Middle-Income Countries
JPO	Junior Project Officer
NGO	Non-governmental Organization
DwA	Doctors with Africa
CUAMM	Collegio Universitario Aspiranti Medici Missionari
INGO	International Nongovernmental Organization

Supplementary Information

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Questionnaire of the study

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Author Contribution

GP, GQ, CC and NP contributed to the conception and design of the study. CC, AG, DM, PL, and AL contributed to data acquisition. GQ and GP provided the literature review. GQ, AG, AT, NP, GP, SO, AK, and JN contributed to the data analysis and interpretation. GQ, AG, MS, LD and GP drafted and revised the article. GQ and GP prepared Tables 1, 2, 3 and 4 and NP prepared Figs. 1 and 2. All authors approved the final manuscript for publication.

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Data Availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request. The questionnaire used in the study was developed specifically for this study (in Italian). An English version is available as a supplementary file.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of DwA-CUAMM (reference number: 2556). All potential participants were sent brief details of the study and offered a more detailed standard information sheet. The informed consent obtained from study participants was in a written format. The data collection was carried out in accordance with relevant guidelines and regulations.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Disclaimer

The views expressed in this publication are the sole responsibility of the authors and do not necessarily reflect the views of the affiliated organisations.

Author details
[1]Medical Preparedness and Crisis Management Unit (MPCMU), Directorate-General for Personnel, European Parliament, Rue Wiertz, 60, B-1047 Brussels, Belgium
[2]Operational Research Unit, Doctors with Africa Cuamm, Padova, Italy
[3]Saint Kizito Hospital, Matany, Uganda
[4]Tosamaganga Hospital, Iringa, United Republic of Tanzania
[5]Saint Luke Hospital, Wolisso, Ethiopia
[6]Department of Statistical Sciences, Padova University, Padova, Italy
[7]Doctors with Africa Cuamm, Kampala, Uganda
[8]Clinical Psychology Unit, San Gerardo Hospital, Monza, Italy
[9]School of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy
[10]Division of Paediatric Emergency Medicine, Department of Women's and Children's Health, University of Padova, Padova, Italy
[11]Aber Hospital, Aber, Uganda
[12]Doctors with Africa Cuamm, Pujehun Hospital, Pujehun, Sierra Leone

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Knowledge, attitudes and practices for blood safety in a worldwide perspective

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COLLECTION, PRODUCTION AND STORAGE OF BLOOD COMPONENTS

Editorial

Knowledge, attitudes and practices for blood safety in a worldwide perspective

Massimo La Raja[1,2]

[1]*Transfusion Medicine Department of Azienda Sanitaria Universitaria Giuliano Isontina (ASU GI), Trieste, Italy;*
[2]*Doctors with Africa Cuamm, Padua, Italy*

"The KAP (Knowledge, Attitude, and Practice) survey on bacterial contamination of blood components"[1] addresses a crucial aspect of blood safety: raising awareness among healthcare staff regarding the risk of bacterial contamination in blood components and the importance of safe preventive practices. This becomes even more critical in the context of developing countries, such as the Democratic Republic of Congo, where some facilities (reliable cold chains, sterile connection devices, digital check systems, bacteriological controls, etc.) may not always be available, leading to a higher risk of infection transmission, whether viral or bacterial.

In recent years, blood transfusion practices have increasingly relied on the implementation of procedures and operational instructions that have significantly improved blood safety. However, a question arises: are frontline operators sufficiently aware of the root causes from which these procedures originated? More recent approaches to quality systems in healthcare necessitate that health professionals perform detailed and documented risk assessments when introducing significant changes or new activities[2]. This is essential to implement all effective and feasible preventive measures before it's too late. In complex systems, all actors, regardless of their roles, are key informants in identifying possible "points of failure" in the process itself.

Hence, a thorough understanding of the transfusion process is crucial for ensuring transfusion safety. This understanding is derived from both formal and informal training, along with individual experience. Effective training depends on evidence-based content, suitable teaching methodologies, and regular re-evaluation within a continuous education program. Numerous relevant online training tools are available globally, regularly updated, and issued by international institutions such as WHO[3] and ISBT[4]. A survey on transfusion medicine training facilities and programs in Africa[5] revealed a persistent gap between training needs and available resources, particularly in remote areas. Similar gaps might exist in other regions worldwide. Over the last decade, accelerated by the pandemic, accessible online training packages have become valuable supplementary educational opportunities[6]. However, face-to-face exchanges and practical sessions are irreplaceable by digital tools, as training content needs real-world contextualization, and education is inherently a bidirectional process requiring mutual understanding.

But if safe practice implies knowledge and understanding what about the importance of attitudes?

Inclusive teamwork, participatory approach, sharing knowledge and doubts, paying attention to critical steps, and accepting corrections in a continuous improvement cycle

Correspondence: Massimo La Raja
e-mail: massimo.laraja@asugi.sanita.fvg.it

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are all elements that require positive attitudes from all healthcare personnel, and this is for the sake of patient and operator safety[7].

Procedures and technologies may vary based on available resources in different healthcare systems. Nonetheless, assessing and strengthening knowledge and encouraging proactive attitudes and critical thinking towards transfusion safety are universal assets that can be promoted in all settings. It's crucial to remember that the most important resources are human resources. This underlies the strong message conveyed by the paper from Heroes and colleagues from the Democratic Republic of the Congo, which is applicable to all.

Nevertheless, this should not overshadow the shortages of structural, technological, and financial resources in the field of blood safety and availability in developing countries, particularly in Sub-Saharan Africa (SSA). In recent times, programs like PEPFAR funded by the US and other projects funded by EU countries have provided substantial support to National Blood Bank services in SSA[8,9]. These efforts have had a significant impact on blood safety, even though the centralized and top-down approach has been the subject of criticism due to high costs and limited availability of safe blood in peripheral areas[10]. In any case, reliable and sufficient funding, coupled with appropriate implementing strategies, should be maintained and strengthened in contrast to signs of "donor fatigue" that have emerged in recent years[11]. Blood transfusion from voluntary non-remunerated donors is considered an essential medicine by the WHO, but it remains challenging for healthcare services in the lowest-income countries, especially if we aim to continue asserting that blood safety is a global health objective.

Keywords: bacterial contamination, Africa South of the Sahara, allogenic blood transfusion.

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Mixed methods study protocol for combining stakeholder-led rapid evaluation with near real-time continuous registry data to facilitate evaluations of quality of care in intensive care units

PAPER

Authors
Rashan A., Beane A., Ghose A., Dondorp A.M., Kwizera A., Vijayaraghavan B.K.T., Biccard B., Righy C., Thwaites C.L., Pell C., Sendagire C., Thomson D., Done D.G., Aryal D., Wagstaff D., Nadia F., Putoto G., Panaru H., Udayanga I., Amuasi J., Salluh J., Gokhale K., Nirantharakumar K., Pisani L., Hashmi M., Schultz M., Ghalib M.S., Mukaka M., Mat-Nor M.B., Siaw-Frimpong M., Surenthirakumaran R., Haniffa R., Kaddu R.P., Pereira S.P., Murthy S., Harris S., Moonesinghe S.R., Vengadasalam S., Tripathy S., Gooden T.E., Tolppa T., Pari V., Waweru-Siika W., Minh Y.L.

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STUDY PROTOCOL

Mixed methods study protocol for combining stakeholder-led rapid evaluation with near real-time continuous registry data to facilitate evaluations of quality of care in intensive care units [version 3; peer review: 2 approved]

The Collaboration for Research, Implementation and Training in Critical Care in Asia and Africa (CCAA),
Aasiyah Rashan[1], Abi Beane[2-4], Aniruddha Ghose[5], Arjen M Dondorp[3,4,6], Arthur Kwizera[7], Bharath Kumar Tirupakuzhi Vijayaraghavan[8], Bruce Biccard[9], Cassia Righy[10], C. Louise Thwaites[6,11], Christopher Pell[4], Cornelius Sendagire[12,13], David Thomson[9], Dilanthi Gamage Done[14,15], Diptesh Aryal[3,13,16], Duncan Wagstaff[9,17], Farah Nadia[18], Giovanni Putoto[19], Hem Panaru[16], Ishara Udayanga[14], John Amuasi[20], Jorge Salluh[13], Krishna Gokhale[15], Krishnarajah Nirantharakumar[15], Luigi Pisani[3], Madiha Hashmi[3,21], Marcus Schultz[22], Maryam Shamal Ghalib[23], Mavuto Mukaka[3,6], Mohammed Basri Mat-Nor[18], Moses Siaw-frimpong[24], Rajendra Surenthirakumaran[25], Rashan Haniffa[2,3,14], Ronnie P Kaddu[26], Snehal Pinto Pereira[27], Srinivas Murthy[28], Steve Harris[29], Suneetha Ramani Moonesinghe[27], Sutharshan Vengadasalam[30], Swagata Tripathy[2,31], Tiffany E Gooden[15], Timo Tolppa[14], Vrindha Pari[32], Wangari Waweru-Siika[26], Yen Lam Minh[11]

[1]Institute of Health Informatics, University College London, London, UK
[2]Centre for Inflammation Research, University of Edinburgh, Edinburgh, UK
[3]Mahidol Oxford Tropical Medicine Research Unit, Bangkok, Thailand
[4]Amsterdam Institute for Global Health and Development, Amsterdam, The Netherlands
[5]Department of Medicine, Chittagong Medical College Hospital, Chattogram, Bangladesh
[6]Nuffield Department of Medicine, University of Oxford, Oxford, UK
[7]Department of Anaesthesia and Intensive Care Medicine, Makerere University, Kampala, Uganda
[8]Department of Critical Care Medicine, Apollo Hospitals Educational and Research Foundation, Chennai, India
[9]Department of Anaesthesia and Perioperative Medicine, University of Cape Town, Cape Town, South Africa
[10]National Institute of Infectious Diseases, Oswaldo Cruz Foundation, Rio de Janeiro, Brazil
[11]Oxford University Clinical Research Unit, University of Oxford, Ho Chi Minh City, Vietnam
[12]Uganda Heart Institute, University of Makerere, Makerere, Uganda
[13]D'Or Institute for Research and Education, Sao Paulo, Brazil
[14]Nat-Intensive Care Surveillance, Mahidol Oxford Tropical Medicine Research Unit, Colombo, Sri Lanka

[15]Institute of Applied Health Research, University of Birmingham, Birmingham, UK
[16]Department of Critical Care, Nepal Intensive Care Research Foundation, Kathmandu, Nepal
[17]Centre for Preoperative Medicine, University College London, London, UK
[18]Department of Intensive Care Anaesthesiology, International Islamic University Malaysia, Kuala Lumpur, Malaysia
[19]Department of Planning and Operational Research, Doctors with Africa CUAMM, Padova, Italy
[20]Department of Global Health, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana
[21]Department of Critical Care Medicine, Ziauddin University, Karachi, Pakistan
[22]Intensive Care Medicine, University of Amsterdam, Amsterdam, The Netherlands
[23]General Surgery, Wazir Akbar Khan Hospital, Kabul, Afghanistan
[24]Department of Anaesthesiology and Intensive care, Komfo Anokye Teaching Hospital, Kumasi, Ghana
[25]Department of Community and Family Medicine, University of Jaffna, Jaffna, Sri Lanka
[26]Department of Anaesthesia, The Aga Khan University, Nairobi, Kenya
[27]Department of Targeted Intervention, University College London, London, UK
[28]Department of Pediatrics, Faculty of Medicine, University of British Columbia, Vancouver, Canada
[29]Department of Critical Care, University College London Hospitals NHS Foundation Trust, London, UK
[30]Teaching Hospital Jaffna, Jaffna, Sri Lanka
[31]AII India Institute of Medical Sciences, New Delhi, India
[32]Chennai Critical Care Consultants Private Limited, Chennai, India

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Abstract

Background

Improved access to healthcare in low- and middle-income countries (LMICs) has not equated to improved health outcomes. Absence or unsustained quality of care is partly to blame. Improving outcomes in intensive care units (ICUs) requires delivery of complex interventions by multiple specialties working in concert, and the simultaneous prevention of avoidable harms associated with the illness and the treatment interventions. Therefore, successful design and implementation of improvement interventions requires understanding of the behavioural, organisational, and external factors that determine care delivery and the likelihood of achieving sustained improvement. We aim to identify care processes that contribute to suboptimal clinical outcomes in ICUs located in LMICs and to establish barriers and enablers for improving the care processes.

Methods

Using rapid evaluation methods, we will use four data collection methods: 1) registry embedded indicators to assess quality of care processes and their associated outcomes; 2) process mapping to provide a preliminary framework to understand gaps between current

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1. **Maryati Mohd Yusof**, Universiti Kebangsaan Malaysia, Bangi, Malaysia
2. **Heather Schacht Reisinger**, University of Iowa Carver College of Medicine, Iowa City, IA, USA

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and desired care practices; 3) structured observations of processes of interest identified from the process mapping and; 4) focus group discussions with stakeholders to identify barriers and enablers influencing the gap between current and desired care practices. We will also collect self-assessments of readiness for quality improvement. Data collection and analysis will be led by local stakeholders, performed in parallel and through an iterative process across eight countries: Kenya, India, Malaysia, Nepal, Pakistan, South Africa, Uganda and Vietnam.

Conclusions

The results of our study will provide essential information on where and how care processes can be improved to facilitate better quality of care to critically ill patients in LMICs; thus, reduce preventable mortality and morbidity in ICUs. Furthermore, understanding the rapid evaluation methods that will be used for this study will allow other researchers and healthcare professionals to carry out similar research in ICUs and other health services.

Keywords
rapid evaluation, quality of care, intensive care, critical illness, low- and middle-income countries, learning health systems

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Corresponding author: Abi Beane (abi@nicslk.com)

Author roles: Rashan A: Conceptualization, Writing – Review & Editing; **Beane A**: Conceptualization, Funding Acquisition, Methodology, Supervision, Writing – Original Draft Preparation, Writing – Review & Editing; **Ghose A**: Conceptualization, Writing – Review & Editing; **Dondorp AM**: Conceptualization, Funding Acquisition, Methodology, Writing – Review & Editing; **Kwizera A**: Conceptualization, Methodology, Supervision, Writing – Review & Editing; **Vijayaraghavan BKT**: Conceptualization, Methodology, Supervision, Writing – Review & Editing; **Biccard B**: Conceptualization, Writing – Review & Editing; **Righy C**: Conceptualization, Writing – Review & Editing; **Thwaites CL**: Conceptualization, Methodology, Supervision, Writing – Review & Editing; **Pell C**: Conceptualization, Writing – Review & Editing; **Sendagire C**: Conceptualization, Methodology, Supervision, Writing – Review & Editing; **Thomson D**: Conceptualization, Methodology, Supervision, Writing – Review & Editing; **Done DG**: Conceptualization, Writing – Review & Editing; **Aryal D**: Conceptualization, Methodology, Supervision, Writing – Review & Editing; **Wagstaff D**: Conceptualization, Methodology, Supervision, Writing – Original Draft Preparation, Writing – Review & Editing; **Nadia F**: Conceptualization, Writing – Review & Editing; **Putoto G**: Conceptualization, Writing – Review & Editing; **Panaru H**: Conceptualization, Writing – Review & Editing; **Udayanga I**: Conceptualization, Writing – Review & Editing; **Amuasi J**: Conceptualization, Writing – Review & Editing; **Salluh J**: Conceptualization, Writing – Review & Editing; **Gokhale K**: Conceptualization, Writing – Review & Editing; **Nirantharakumar K**: Conceptualization, Writing – Review & Editing; **Pisani L**: Conceptualization, Methodology, Writing – Review & Editing; **Hashmi M**: Conceptualization, Methodology, Supervision, Writing – Review & Editing; **Schultz M**: Conceptualization, Writing – Review & Editing; **Ghalib MS**: Conceptualization, Writing – Review & Editing; **Mukaka M**: Conceptualization, Writing – Review & Editing; **Mat-Nor MB**: Conceptualization, Methodology, Supervision, Writing – Review & Editing; **Siaw-frimpong M**: Conceptualization, Writing – Review & Editing; **Surenthirakumaran R**: Conceptualization, Writing – Review & Editing; **Haniffa R**: Conceptualization, Funding Acquisition, Methodology, Writing – Review & Editing; **Kaddu RP**: Conceptualization, Methodology, Writing – Original Draft Preparation, Writing – Review & Editing; **Pereira SP**: Conceptualization, Writing – Review & Editing; **Murthy S**: Conceptualization, Writing – Review & Editing; **Harris S**: Conceptualization, Writing – Review & Editing; **Moonesinghe SR**: Conceptualization, Writing – Review & Editing; **Vengadasalam S**: Conceptualization, Writing – Review & Editing; **Tripathy S**: Conceptualization, Methodology, Supervision, Writing – Review & Editing; **Gooden TE**: Conceptualization, Project Administration, Writing – Original Draft Preparation; **Tolppa T**: Conceptualization, Writing – Review & Editing; **Pari V**: Conceptualization, Writing – Review & Editing; **Waweru-Siika W**: Conceptualization, Methodology, Supervision, Writing – Review & Editing; **Minh YL**: Conceptualization, Methodology, Supervision, Writing – Review & Editing

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REVISED **Amendments from Version 2**

No major changes have been made to this manuscript. As a response to reviewer comments, the following minor changes were made:

1. We moved text from 'study design' to 'data collection' to make the methods described easier to follow and understand.
2. We added text to clarify what data the registry holds, how care processes will be chosen for the process mapping and how the MUSIQ 2 calculator will be used.
3. We made minor changes to text in the introduction and discussion regarding the potential impact of this research, and the benefits of using the described participatory research methods and patient-centred stakeholder-led evaluation for ICU care in LMICs.

Any further responses from the reviewers can be found at the end of the article

Introduction

An estimated five million deaths per year worldwide could be avoided by improving the quality of the delivery of healthcare[1]. The Institute of Medicine[2] defines quality of healthcare as "the degree to which health care services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge". Quality of care is reflected in structures of healthcare services, patient-level processes undertaken, and the outcomes of healthcare interactions[3,4]. Recommendations from the Lancet High Quality Health Systems (HQSS) report called for greater investment in systems and processes that strengthen evaluation and improvement of care in low and lower middle income countries (LMICs), and that these systems should reflect and be sensitive to the diverse needs of communities they serve[4].

Critical care encompasses healthcare provided to patients with, or at risk of, immediately life-threatening, potentially reversible conditions, irrespective of age, diagnosis, specific patient group or location[5]. Improving the safety and effectiveness of care for critically ill patients has the potential to substantially reduce preventable mortality[1]. Efforts to improve the quality of critical care[6] in intensive care units (ICUs) internationally, have increasingly focused on ameliorating risk of complications associated with both the critical illness itself, and the healthcare interventions delivered to treat it. These efforts have included minimising duration of invasive therapies, optimising infection control practices and increasing adherence to antimicrobial stewardship practices. Whilst each of these interventions has an established evidence base of improving outcomes across the heterogeneity of critical illness[7], such interventions are often poorly implemented and, or consistently adopted in resource constrained healthcare institutions; notably concentrated in LMICs. In addition, patient-centred care and engagement with families and patients to share experiences of critical care is often overlooked despite being of itself, associated with improved outcomes[8].

Healthcare providers, including the National Health Service in the UK, have long relied on models of healthcare evaluation including Donabedian's which measures care provision through the framework of structures, processes and outcomes[9]. Classically, critical care services have evaluated and benchmarked care using comparisons of this framework between different hospitals (often annually) and within the same institutions over time (often years)[10,11]. However, such methods of evaluation rarely provide the granularity of information or the specific contextual factors needed to determine the reasons for poor care and identify opportunities for improvement. Systematic improvement in quality requires identification of the gaps in care (i.e. the differences between care as intended and care as delivered) and an understanding of the underlying determinants. Furthermore, effectiveness of current care delivery, and the likely success of any quality improvement interventions are dependent on the ability to positively and sustainably influence the behaviour of relevant stakeholders[12].

Quality of care and success of interventions to improve care is directly attributable to the behaviour of healthcare providers, organisational culture within hospital settings and external factors affecting healthcare accountability[3,12,13]. In LMICs[14], further exploration is needed to understand what factors determine healthcare provider behaviours, organisational cultures and patient and public expectations. Acquiring a better understanding of these determinants is essential to inform the design[3,12] and increase the effectiveness of interventions targeted at improving care both in individual ICUs, and more widely within a healthcare system[15].

This project aims to leverage the system infrastructure and community of practice established by The Collaboration for Research, Implementation and Training in Critical Care in Asia and Africa (CCAA) to: evaluate the quality of existing care processes in the ICU; identify individual, team and organisational factors determining current care delivery; and assess the likely influence of these factors on future improvement interventions[3]. This protocol describes the novel methods proposed to undertake this multi-layered, multi-centre evaluation.

Protocol

Study design

This is a multi-centre mixed methods rapid evaluation comprising: registry-enabled assessment of care quality using selected process and outcome metrics, stakeholder-led rapid evaluation of the organisational and contextual factors influencing care (process mapping, structured observations and focus group discussions); and an assessment of local quality improvement capabilities (Figure 1). Together these methods will provide a replicable, comparable and context-specific evaluation of the quality of care processes and their associated outcomes. This evaluation will help stakeholders identify and understand the underlying factors enabling or impeding the delivery and improvement of high-quality care within their departments.

Rapid evaluation (RE) methods[25,26] were chosen for their ability to empower healthcare stakeholders to identify and understand the determinants of existing practice within their own setting[15]. Process mapping[27] conducted by clinical

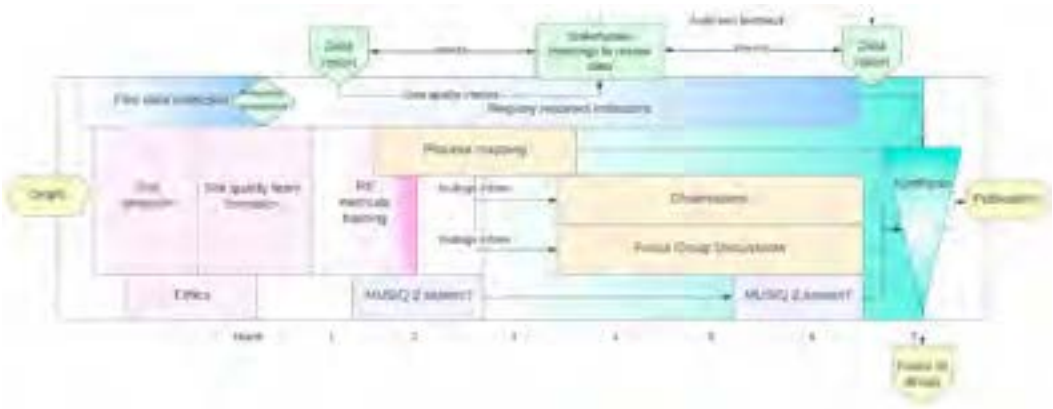

Figure 1. Schema of activities throughout the project.

teams, with participation where possible from patients and care receiver representations, will provide a preliminary framework[28] to understand gaps between care as intended and care delivered. This information will inform the scope, location and timing of structured observations[25] and topics for focus group discussions[29,30].

Structured observations of care will enable the study team to document and describe team and patient-provider interactions relevant to the care process(es) under evaluation. These observations will enable the teams to identify practices of communication, team working and environmental factors (space, location etc) that may affect care delivery.

Focus group discussions, conducted in parallel to the observations, will be used to further explore and enrich the team's understanding of the care process(es) of interest from the participants' view, including their perceptions of barriers to, and enablers of, effective care delivery.

Assessment of organisational readiness for care improvement. The findings of this multi-centre international evaluation of care will be used to inform future co-design of a toolkit for quality improvement in ICUs. As such, the evaluation will include a replicable assessment of the readiness of participating ICU teams and their institutions to undertake quality improvement activities. The international-validated Model for Understanding Success in Quality (MUSIQ 2)[31] calculator designed to identify likelihood of success of future improvement interventions, will be used to gather individual experiences of quality improvement, the site-level data needed to create a shared understanding of local practice and identify local quality improvement capabilities.

Setting

The CCAA is supported by a Wellcome Innovations Flagship Programme and UKRI/MRC award, established in 2020, and currently funded until January 2026. The CCAA's aim is to establish a community of practice equipped with the infrastructure required for a learning health system capable of providing continuous reliable service evaluation, supporting measurable care improvement and facilitating high quality clinical research which translates to practice change. At its core is the ICU digital registry platform which supports a distributed network of clinician-led registries across 17 LMICs, which capture data on case mix, population characteristics, organisational features, care processes and clinical outcomes contemporaneous to the delivery of clinical care for all ICU (and some emergency, perioperative and acute medicine) encounters. The harmonisable data provides near real-time information for service evaluation, clinical research and contextualised sustainable improvements in care delivery (Figure 2). The registry data set, data collection methods, data quality assurance processes and research impact are described elsewhere[16,32–37].

CCAA collaborators from ICUs in seven country networks have self-selected to participate in this project. The self-selected countries are Kenya (CCSK), Ghana (KCCR), India (IRIS), Malaysia, Nepal (NICRF), Vietnam and South Africa. Each national network will identify three to six ICUs that have ambition to use their registry for regional and international care quality evaluation, build capacity for health systems research methods and participate in quality improvement interventions. Each participating ICU will also have demonstrated ability to use the ICU registry platform for near real-time daily data collection of ICU encounters inclusive of over 95% of all admissions[16]. Pluralistic health systems co-exist in each of these countries, whereby private, government and non-governmental organization providers offer critical care services within secondary and tertiary facilities. The CCAA is non-discriminatory in its inclusion of institutions and no representation of diversity of providers is being sought. All country networks and ICUs participate by choice and no financial incentives are used. Factors including care provision and financial models of care may influence organisations' care quality and ability to engage in quality improvement[38]. These will be captured and quantified

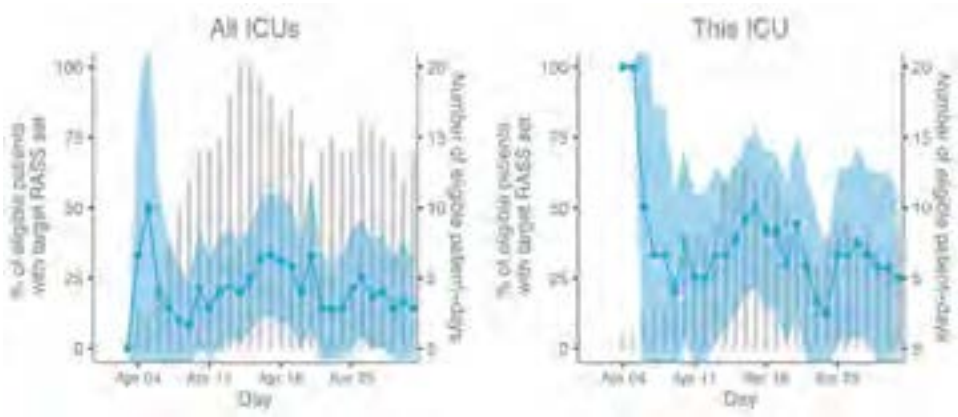

Figure 2. Process evaluation p-charts of Richmond Agitation-Sedation Scale (RASS) rates. The blue line and shaded 95% CI area (left y-axis) display the daily percentage of eligible patients who had a target RASS set and the bars (right y-axis) represent the number of eligible patients. Patients are eligible if they are mechanically ventilated on that day.

during the project using the mixed methods described above and a future network-wide process evaluation.

Study team, participants, sample size and recruitment

Study team. Each site will have an ICU quality team consisting of (as a minimum), an ICU nurse, a senior doctor and a data collector. Each ICU team will be supported by their existing national registry coordination team (who include a national lead, coordinator and research assistant). Working alongside these site level and national teams are the already established registry implementation team which includes data scientists, statisticians and clinician researchers with a track record in mixed methods evaluation and service improvement. Together they will provide continued support to the ICU quality team in methods, statistical analysis and overall study conduct. This support is provided where possible remotely, using the Zoom (Zoom Video Communications Inc, San Jose, CA, USA) conferencing application.

Study participants. A wide range of ICU stakeholders will be invited to participate. This will include patients and carers in addition to those responsible for both the strategic service development and delivery of clinical care. We will aim to have balanced representation from each of the stakeholder groups[39]; however, we recognise the possible limitation of scope from the ICUs in healthcare settings, whereby allied clinical disciplines (e.g. microbiologists, pharmacists, and dieticians) may be limited or poorly represented. Invitation to participate in the project will be sought through the national registry leads and the ICU quality teams.

Stakeholders invited to participate ('participants') in the rapid evaluation will have study information made available prior to participation[17]. Participants will have an opportunity to review the participant information sheet a minimum of 72 hours prior to participation to allow sufficient time for them to consider and seek advice from the ICU or national team or other independent parties. All data collection will be in the language commonly used to deliver healthcare in the setting.

Sample size and recruitment. Sample size will be guided by similar studies and based on achieving sufficient data to explore a range of stakeholder perspectives to understand the factors affecting the specific process of care under evaluation. The combination of purposive sampling of key stakeholders[25], including patients, the focused scope of inquiry[40] defined by process mapping, and flexible, rapid iterations of data collection and analysis conducted in parallel by teams (a feature of RE method design[25]) means that the research question may be addressed with estimated 2–3 process maps, 2–3 observations and 2–3 focus groups per ICU[41].

Data collection

The sequence and timings of the five discrete but complementary sources of data are described in Figure 1.

Registry enabled continuous evaluation of care. The components of a learning health system (continuous data for evaluation and new knowledge generation, rapidly integrated into practice) already established by the CCAA will be enhanced by the rapid evaluation, facilitating future practice improvement. The CCAA already has an ICU registry with an established core data set which enables comparable description of case mix, severity of illness and benchmarking of clinical outcomes; the details of the core dataset are described elsewhere. Additionally, the CCAA recently completed a scoping review of ICU quality metrics used internationally and undertook a four round modified Rand Delphi study to identify a set of indicators for evaluation[21]. Indicators were assessed for their feasibility, reliability, validity to predict outcome and sensitivity to change.

They have been classified according to the High Quality Health Systems Framework[4]: foundations (encompassing human resources, governance structures, accessibility and tools), quality impacts (including clinical and economic outcomes) and care processes (descriptions of care and systems as well as user-experience). These indicators were then prioritised and defined for implementation through the registry. The care processes associated with these priorities are already endorsed by healthcare policy makers in all but the most resource constrained health systems in LMICs[22].

The selected metrics are described in Table 1 and reflect previously identified research priorities for improvement: reducing avoidable harms; improving delivery of interventions and processes already proved to improve outcomes and measuring and improving patient-centred outcomes[21]. Avoidable harms include deep venous thrombosis, stress ulcer, ICU delirium, neuromuscular decline, pressure injury and healthcare-acquired infections. These harms are all associated with prolonged organ support including mechanical ventilation[8]. The associated daily care processes and interventions proven to ameliorate these harms include optimising sedation and pain management using objective assessment tools (RASS, CPOT); daily assessment of readiness to wake (SAT), assessment of ability to breath spontaneously (SBT) and passive or active mobilization[23]. Foundations of care, for example nurse:patient ratios, have also been shown to influence these harms. In addition, engagement of family members in daily care in the ICU and their involvement in interventions including respiratory physiotherapy and mobilisation has been demonstrated to improve not only the effectiveness of the interventions, but also to increase both provider and patient compliance, and promote better experience for families and patients[8]. The feasibility of these measures (three foundation, eight quality impacts and eight care processes) and their definitions[17] are currently being assessed[9,18] for feasibility of collection (using the Khan quality framework assessment criteria for conformance and completeness)[19] in pilot ICUs in collaborating registries including IRIS (Indian Registry of IntenSive care), NICRF (Nepal Intensive Care Research Foundation), CCSK (Critical Care Society of Kenya) and South Africa.

Table 1 data are captured each day, extracted from patient charts or directly observed by trained data collectors and entered to the registry platform daily during ICU stay. A comprehensive field specification and data collection guide are made available to all ICU teams through the platform and 24-hour online support is available. Data collectors are trained using already published methods. Weekly follow up meetings with the national registry teams and the site quality teams will provide feedback and troubleshooting for data collection and data quality during weeks 1–4, thereafter monthly meetings using a published quality assurance framework[16]. Census checks with independent admission data are used to monitor cohort inclusion weekly.

Rapid evaluation. Process mapping will be locally-led by the ICU quality teams, with the support of the national

Table 1. Selected measures for registry enabled evaluation.

Foundations	1. Nursing staff to patient ratio 2. Intensivist staffing to bed ratio 3. ICU medical night coverage
Quality impacts	1. Antimicrobial usage, (days of therapy, duration of empirical antimicrobial use) 2. Incidence of ICU-acquired drug resistant organism of interest (DRI) 3. Incidence of HAI (Central Venous Catheter Associated Infection, Catheter Associated Urinary Tract Infections & Infection-related Ventilator-Associated Complication (IVAC)) 4. Incidence of unplanned ICU discharge due to financial constraints 5. Unplanned readmission to ICU 6. Standardised mortality rate (ICU & hospital) 7. Length of stay (ICU & hospital) 8. Quality of life at 30 days post ICU
Care processes	1. Venous thromboembolism prophylaxis 2. Duration of mechanical ventilation 3. RASS score (target and actual) 4. Stress ulcer prophylaxis 5. Spontaneous awakening trial 6. Spontaneous breathing trial 7. Incidence of new pressure sores 8. In-bed mobilisation

ICU: intensive care units; HAI: hospital acquired infection; RASS: Richmond Agitation-Sedation Scale[20]

registry teams who have experience in rapid evaluation methods, and remote support will be provided by experienced researchers in the implementation team. Process mapping will be conducted in months 2–3 of the evaluation and will inform the priorities for observations and focus group discussions. We will use a general process mapping technique rather than one allied to a specific improvement methodology[42]. Stakeholders will be asked to map out the discrete activities (tasks) associated with locally-selected care processes from the list in Table 1, identify the actors and equipment involved, the interactions, decision making and who are the decision makers, for care as intended, and for care as it is actually delivered. A mapping guide[17] will be used as a template. The mappings will provide a structured, visual representation of each care process which will identify deviations from intended practice and inefficiencies in existing care processes.

Structured observations will be conducted by the ICU quality team, in the clinical area relevant to the processes of interest identified through the process mapping (months 3–6). Data from the observations will be collected using a structured observation guide[17] to ensure consistency across study teams and sites. Observations will usually take place within the ICU but may on occasion extend to other locations in local pathways for critically ill patients such as emergency departments and inpatient wards.

Focus group discussions will be conducted by the national registry teams familiar with the context but not directly responsible for care, with support of experienced researchers. Separate focus group discussions will be conducted for healthcare providers and patients/carers so as to limit the impacts of social hierarchies of healthcare within the communities participating[29,30]. Focus group discussions will be conducted with between six and eight stakeholders at any one discussion. A template to guide discussions has been designed[17] but may be iteratively modified based on the findings of the process mapping and structured observations.

Assessment of organisational readiness. The national registry teams will work in partnership with the ICU quality teams to complete an assessment of readiness for quality improvement using the MUSIQ 2 calculator[31]. ICU quality teams will have an orientation session to the tool led by the national leads, and then complete the MUSIQ 2 calculator online. The MUSIQ 2 will be assessed at the start of the evaluation period (month 1) to help the ICU teams to identify the existing contextual factors which may promote or inhibit the success of the quality evaluation and future improvement initiatives. Scores will be reviewed together with the research team to identify opportunities where the CCAA infrastructure could be leveraged to improve quality improvement capability, for example capacity for quality improvement, data infrastructure, workforce focus and resources for quality improvement. The MUSIQ 2 will be reassessed at month six to describe changes in the micro, environmental and organisational factors as a result of engagement in the evaluation. Scores will be collated and stored on an electronic shared drive for each ICU. Scores will be validated by the registry implementation team for consistency.

Data analysis and data management

Data collection and iterative analysis will occur in parallel[25]. Discovery of information will be a reflexive process in which local knowledge is reconstructed through a cycle of data collection, analysis and planning what to examine next[25]. Given the evaluations will in part be conducted by the ICU quality teams directly responsible for care, the registry implementation team will facilitate debriefing sessions following each data collection procedure to ensure internal biases (present as a result of priori knowledge of the subject area) are discussed and resolved as data collection/analysis continues and conclusions are drawn[43].

Data pertaining to case mix and demographics will be reported using standard descriptive statistics. Diagnosis will be classified from SNOMED CT and mapped to APACHE IV[44]. Risk adjusted outcomes and predicted mortality will be determined using standardised mortality ratio (SMR). Observed mortality is defined as the percentage of ICU patients who die within hospital (same encounter) as a proportion of all ICU admissions. Observed ICU mortality represents the numerator for risk-adjusted ICU mortality (SMR). The ratio between the observed number of deaths and the predicted number of deaths for the case mix of each ICU, computed by indirect standardisation. Predicted mortality will be determined using APACHE II or e-TropICS (a priori selected by the contributing registry)[45]. Compliance to process measures will be reported for individual patients based on eligibility each day during the ICU encounter. Composite measures of outcome or event indicators will be calculated as per their published and a priori chosen definitions, using data captured either daily, or by event, as appropriate.

Data arising from the process mapping, observations and focus group discussions will be triangulated[25] and analysed using an interpretive analysis approach[46]. Data will be deconstructed and barriers and facilitators to care quality coded using the Consolidated Framework for Implementation Research (CFIR) framework[47]. The CFIR was chosen for its ability to facilitate exploration of the individual, and team characteristics, and the in ICU organisational and external factors that promote and inhibit the routine incorporation of interventions into everyday clinical practice[28,47,48]. The findings of each round of analysis will be reconstructed using a Rapid Assessment Process (RAP) sheet[17], to repackage the different categories and discover the high level themes that cross cut different care processes within and between individual ICUs. The validity of findings will be discussed and checked with process mapping, observation and focus group participants at every site[49].

The Zoom conferencing application will be used to automatically save the audio files (as a MP4 file) from the process mapping exercises to a project-designated, password-protected and automatically backed-up shared drive storage space. The Zoom conferencing application will be used as set out by the University of Oxford ‘Guidelines for using Zoom’[50]. The titles of video files will not include a participant’s name, but rather the date of the interview and a site code.

Data management will be overseen by the investigators (DW and AB) and the wider CCAA project team. Data from the

process mapping, observations and focus group discussions will be captured digitally and identifiers will be removed. RAP sheets will contain anonymised data only and will also be completed digitally. All data will be retained for five years after the publication of the results. All data will be held on a project-designated, password-protected and automatically backed-up shared drive storage space. All data in the UK will be managed in accordance with EU General Data Protection Regulation (GDPR)[51] and if outside the UK, in line with country-specific data protection regulations.

Ethical and regulatory considerations

The focus of the research is on improvement of healthcare services and is not of a sensitive nature, and thus unlikely to evoke feelings of discomfort or emotional distress for participants. The project will be conducted in accordance with relevant national and international guidance and regulations, including the Global Code of Conduct for Research in Resource-Poor Settings[52]. To ensure that the project is conducted in an ethical manner, this protocol has been submitted to the Oxford Tropical Research Ethics Committee (OxTREC)[53]. National registry leads in each collaborating country will be responsible for coordinating with their institutional or institute review boards for relevant approvals. All participants will be given a participant information sheet prior to providing written informed consent.

Public engagement & involvement. National leads were consulted in the design of this project. There is existing literature to support the use of the methods proposed for research inclusive of patients including within the populations considered in this context[14,26,54].

The registry reports were co-designed and developed with national registry leads and piloted for feedback with the multidisciplinary teams in Kenya, Nepal and India. The research team members are currently being trained in process mapping, observations and focus group discussions by investigators (DW and AB) via video conferencing and using a purpose-build quality improvement resource platform made freely available to all CCAA members[55].

Quality improvement initiatives designed to improve care for patients and the public will be explored in subsequent research. The findings of this project will be accessible to patients and the public via the MORU Tropical Health Network website (www.tropmedres.ac).

Dissemination

The findings will be used to directly inform the development of a toolbox for implementation of quality improvement interventions in LMICs led by clinician- researchers. The findings will be developed into country-specific manuscripts for publication and also shared across the CCAA collaborating countries. A report will be developed for the funders, Wellcome and UKRI/ MRC. Findings will be published as academic publications as open access and presented at academic conferences.

The country network teams with the support of the lead investigators (DW and AB) will lead writing and reviewing of manuscripts, abstracts and any other publications arising from the overall project. These will be equitably published in academic, peer-reviewed literature as open-access and will offer practical learning for others seeking to utilise similar methods in healthcare institutions worldwide for service improvement. Authorship will be based on the set of criteria outlined by the journal and where possible follow the CredIT Taxonomy[56], and will acknowledge that this work is on behalf of the collaborating clinicians, patients and families representing healthcare services within the CCAA. The project results will also be published online ahead of peer review using a free access preprint platform in response to the global academic movement to increase equity and access to healthcare research.

Study status

The study started in August 2022. Due to staggered start-times between countries, data collection will continue until August 2023. No country has yet completed data collection.

Discussion

Measurement of key quality indicators, which include patient-centred outcomes, to drive forward improvement is increasingly being promoted as part of benchmarking healthcare quality. Continuous evaluation (driven by data generated each day during routine care delivery) undertaken contemporaneously to stakeholder-led exploration of organisational cultures to inform improvement interventions provides the potential to accelerate service improvement. In this study, we aim to simultaneously lay the foundations for a culture of healthcare improvement and establish capacity for future institution-led research through which healthcare providers, families and patients reflect and appraise current practice, to identify problems and seek possible solutions. As a result, this research has the potential to inform sustainable and effective ICU quality improvement in LMICs for both clinical outcomes and patient-family experiences.

Rapid evaluations (REs) can be characterised as: an intensive, team-based investigation that uses multiple methods of data collection; having an iterative process for collection and analysis; and following the principles of participatory action in order to quickly develop a holistic understanding of a programme from the perspective of key stakeholders, providing a potentially effective methods for institution-led but scalable improvement[25]. Stakeholder-led rapid research can provide timely insight into specific, complex processes and systems from locally-defined perspectives, which if attempted using more traditional ethnographic methods may take many months before conclusions are made, risking disengagement of stakeholders and delaying service improvement[57]. RE methods, increasingly used in healthcare[58] are amenable to enabling involvement of patient and public stakeholders, representation from whom is often absent in research and which is essential if healthcare providers are to better understand the impact of critical illness on individual families and on wider social and economic population metrics[3]. Attaining understanding of the

context[13,26] in which care is delivered allows tailoring and embedding of any subsequent quality improvement interventions with increased opportunity for their success[13].

We anticipate that the combination of traditional benchmarking data from the established near real-time clinical registries together with the qualitative approaches of RE which stem from disciplines including anthropology and business, will enable understanding of existing ICU care processes and how organisational factors and health system structures may influence quality of care both at facility level and in relation to individual patient outcomes. For example, objective replicable daily time series data on the completeness of assessment of sedation use, and readiness to breath spontaneously, in each eligible patient, along with daily changes in ICU case mix, acuity, turnover and staffing numbers, will enable stakeholders to unpack (using iterative cycles of analysis and feedback) how internal and external factors affect aggregate and individual quality of individual care processes and their impact on patient outcomes. The multi-dimensional registry data will be fed back in parallel to ongoing evaluation, thereby providing a reliable and replicable measure of process change over time as future improvement interventions are implemented and evaluated for impact[59].

The findings of the project will directly inform subsequent local projects aimed at improving patient care and the development of the CCAA registry to enable effective utilisation of data to drive quality improvement for stakeholders and their ICUs. By understanding organisational readiness for improvement, we will enable stakeholders to plan interventions best suited to their local cultures, needs and resources. Further to this, given this project's participatory nature, and having been co-designed by clinical stakeholders, novice researchers and clinicians will be exposed to new methods. We anticipate this approach will facilitate the building research and quality improvement capacity in the CCAA which will extend beyond this project.

Data availability

Underlying data

No underlying data are associated with this article.

Extended data

Figshare: Supplementary materials for 'Mixed methods study protocol for combining stakeholder-led rapid evaluation with near real-time continuous registry data to facilitate evaluations of quality of care in intensive care units'. https://doi.org/10.6084/m9.figshare.21763325[17]

This project contains the following extended data:

- File 1: Data Completion Guide
- File 2: Mapping Session Guide
- File 3: Focus Group Discussion Topic Guides
- File 4: Invitation Email to CCAA Country Site Leads
- File 5: Participant Information Sheet: Observations
- File 6: Participant Information Sheet: Interviews
- File 7: Observation Template Sheet
- File 8: Rapid Assessment Process (RAP) Sheet

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Comparative Insights to Advance Political Economy Analysis: A Response to Recent Commentaries

PAPER

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Correspondence

Comparative Insights to Advance Political Economy Analysis: A Response to Recent Commentaries

Maria Nannini[1,2*], **Mario Biggeri**[1,2], **Giovanni Putoto**[3]

***Correspondence to:** Maria Nannini, Email: maria.nannini@unifi.it

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We are pleased to advance the debate on health coverage and financial protection in Uganda through a political economy perspective. Firstly, we express gratitude to the authors of the commentaries pertaining to our article "Health Coverage and Financial Protection in Uganda: A Political Economy Perspective."[1] These commentaries serve to draw attention to methodological aspects as well as context-specific political dynamics that impact the outcomes of the analysis. In this correspondence, we present key points from each commentary that we believe facilitate advancing the debate and catalysing a thoughtful analysis on health coverage and financial protection.

Basaza and colleagues[2] delve into the analysis of political economy, focusing on the introduction of the National Health Insurance Scheme (NHIS) in Uganda. The trajectory for implementing this scheme represents a distinctly political process and should be understood as part of the country's long-term strategy for development; indeed, the NHIS is part of the national agenda "the Uganda Vision 2040."[3] Moreover, the government has officially committed to achieving the Sustainable Development Goals (SDGs), and there exists a roadmap aimed at attaining universal health coverage (UHC) in Uganda.[4] As argued by the authors, political elites play a crucial role in determining the timing of reform implementation, also based on the existing consensus regarding the need for structural changes among policy makers and general public. Therefore, it is important not to perceive the current government position as permanent. Simultaneously, given the inherently political nature of the process, conducting interviews with political leaders belonging to the ruling party would enable the incorporation of central elements concerning interests and ideologies influencing the process. To facilitate the advancement of the discourse, it is beneficial to refer to recent data regarding misconceptions and fears. As articulated by the authors, the difficulty in mobilizing the informal sector to collect insurance premiums, as well as the low level of willingness to pay among the population, do not appear to genuinely hinder the design of the reform. In light of these new insights, it would be valuable to conduct a careful and updated analysis of the reform path to implement the NHIS, considering both the voice from the political elite as well as other important stakeholders.

Croke[5] directs attention to two elements that could strengthen the analysis of political economy, offering a clearer understanding of the dynamics characterizing the Ugandan case study. Firstly, the author suggests integrating the analysis with evidence from comparative politics focused on the current Ugandan regime. It is particularly useful to consider that, as concluded by various studies,[6-9] the highly personalized nature of the regime in Uganda, centred around President Museveni, constitutes a significant aspect influencing choices related to priority reforms and allocation of budget across different sectors. Consequently, drawing from comparative politics literature, greater emphasis could be placed on the interplay between regime dynamics and state capacity. Secondly, the commentary delves into the concept of "political settlement" understood as "*the social order based on political compromises between powerful groups in society that sets the context for institutional and other policies.*"[10] Referring to specific studies on the healthcare sector in Uganda,[11] it is crucial to consider the role of political bargaining among influential actors and how it shapes health services delivery. These considerations also allow for advancing the specific discourse on the NHIS and the future prospects for healthcare sector financing.

Eusebio and colleagues[12] build upon our political economy analysis to delve into the pro-UHC forces that can expedite the political discourse and implementation of structural reforms in the healthcare sector. Firstly, the authors argue for the potential of reframing the UHC debate in order to catalyse effective change. They consider positioning UHC as a component of "nation-building" as an instrumental strategy to solidify a national identity and foster economic growth. Secondly, the commentary emphasizes the necessity of identifying or creating a window of political opportunity for health sector reforms, to be seized by relevant stakeholders. This could encompass leveraging the United Nations' 2030

Full list of authors' affiliations is available at the end of the article.

Agenda; harnessing the historical momentum generated by establishing a COVID-19 preparedness and response plan represents an additional opportunity to stimulate reforms for health coverage. Thirdly, the authors underscore the pivotal issue of mobilizing resources to drive meaningful change. They highlight the potential for progress through enhancing both the ownership of local communities in health financing programs and advocacy efforts by academic experts and civil society representatives aimed at overcoming existing barriers to UHC. Given the pluralistic nature of the Ugandan healthcare system, the political process should be open to engagement with all stakeholders, including, for instance, the Private Not-For-Profit sector.

Fox proposes several potential methodological and theoretical improvements to enable deeper claims through political economy studies of health reforms in low- and middle-income countries. Firstly, the author underscores the significance of historicizing analyses. Taking into account past policies and the historical trajectory within specific contexts allows for easier identification of potential political decisions and structural reforms proposed by governments, considering the so-called policy feedbacks effects. Secondly, Fox suggests, whenever feasible, adopting a comparative perspective that examines various case studies aiming to move beyond describing a single case: indeed, more observations of different case studies would facilitate providing more generalized explanations of political economy dynamics according to a causal logic. Lastly, the commentary advocates for testing theories by verifying whether evidence supports or contradicts the expectations derived from the theory. This approach aims to avoid relying solely on a theory-light approach that risks not reaching meaningful conclusions to advance policy or practice.

Kim[13] applies a political economy approach to the case study of the Republic of Korea, identifying the most significant elements driving the reform process toward achieving UHC. The author traces the historical path followed by the country regarding its National Health Insurance system, identifying the primary obstacles hindering the actual attainment of UHC-related objectives. It is important to note that the analysis considers a relatively extensive period of reforms, starting from the 1960s, intending to present a more historically contextualized and in-depth study of the health insurance scheme.

Tangcharoensathien and colleagues[14] offer additional insights into the political economy processes aimed at achieving UHC in African low-income countries. Initially, the authors suggest a concise review of the available evidence concerning the impact of the pandemic and the recovery efforts in these nations. Secondly, they pinpoint the primary factors that adversely influence the attainment of health-related SDGs. Finally, the commentary highlights opportunities and provides recommendations for low-income country governments to implement effective reforms for UHC.

Ssennyonjo[15] delves into various aspects of analysis and suggests methodological enhancements to delve deeper into key concepts of political economy, thereby offering a better understanding of the ongoing dynamics in Uganda. Firstly, the author presents the "structure-agency" debate, emphasizing the crucial bidirectional interaction between structure and agency to enhance political economy analysis. Secondly, the commentary proposes additional considerations and existing theories to avoid oversimplifications concerning the meaning of ideas, interests, and institutions. For instance, when referring to "institutions," formal or informal rules shaping or impacting human action[16] should be considered.

In conclusion, the analytical framework proposed in the article could benefit from several enhancements. Further to adopting terminologies and definitions more aligned with political economy analysis (for instance, rectifying the usage of the term "institutions"), embracing a more comparative approach represents a potential improvement. This approach would consider, on one hand, the overall architecture of different sectors and strategic priorities pursued by the most influential stakeholder groups in Uganda, thus disentangling the crucial aspect of trust and consensus towards political elites. On the other hand, it would encompass experiences from other countries regarding similar reforms in healthcare financing. Expanding the analysis in these two directions entails broadening the study's focus, considering also a longer historical period to capture "policy feedback" effects. The broader scope is functional to understand the potential for change, overcoming existing barriers to achieve UHC.

Ethical issues

Not applicable.

Competing interests

Authors declare that they have no competing interests.

Authors' contributions

Conceptualization: Maria Nannini and Mario Biggeri.
Formal analysis: Maria Nannini, Mario Biggeri, and Giovanni Putoto.
Investigation: Maria Nannini, Mario Biggeri, and Giovanni Putoto.
Validation: Maria Nannini, Mario Biggeri, and Giovanni Putoto.
Writing–original draft: Maria Nannini.
Writing–review & editing: Maria Nannini, Mario Biggeri, and Giovanni Putoto.

Authors' affiliations

[1]ARCO (Action Research for CO-development), PIN Educational and Scientific Services for the University of Florence, Prato, Italy. [2]Department of Economics and Management, University of Florence, Florence, Italy. [3]Doctors with Africa CUAMM, Padova, Italy.

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From “reproductive” to “generative” health. Anthropology as a tool for an epistemological review of health development strategies in Africa

POSTER AND ORAL PRESENTATION

Conference
Association of Social Anthropologist (ASA) of the UK Conference

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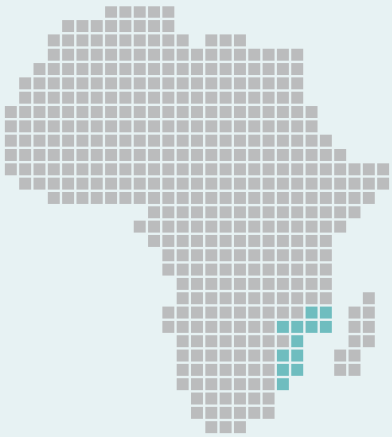
Authors
Occa E.

Focus country
Mozambique



Perception of Services and Barrier to Retention in Care for Girls and Young Women in Beira, Mozambique. Doctors with Africa CUAMM INGO

POSTER AND ORAL PRESENTATION

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17th INTEREST Congress

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Authors
Occa E. et al.

Focus country
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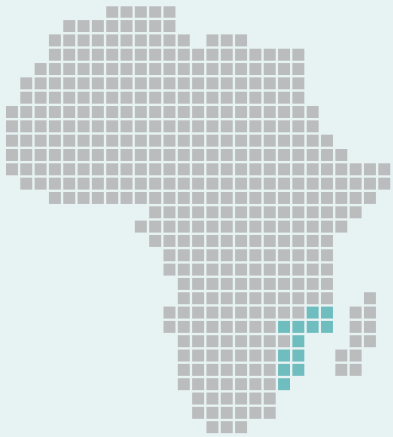

Taxonomic Criteria and Creation of Imaginaries; Field Experience on the Definition of “Beneficiary” in Humanitarian Interventions in Mozambique

POSTER AND ORAL PRESENTATION

Conference
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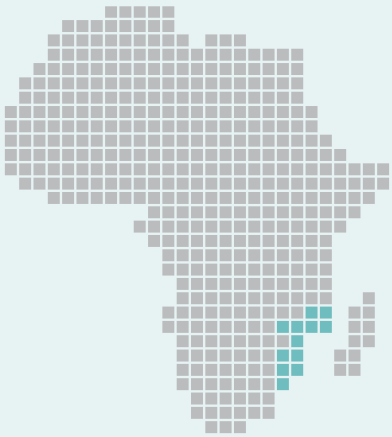
Authors
Occa E.

Focus country
Mozambique



“Gli squali non stanno nei fiumi”. L’esperienza di risposta umanitaria al ciclone Freddy in Mozambico come paradigma di una nuova ecologia del pensiero antropologico e della cooperazione sanitaria

POSTER AND ORAL PRESENTATION

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Congresso della Società Italiana di Antropologia Applicata

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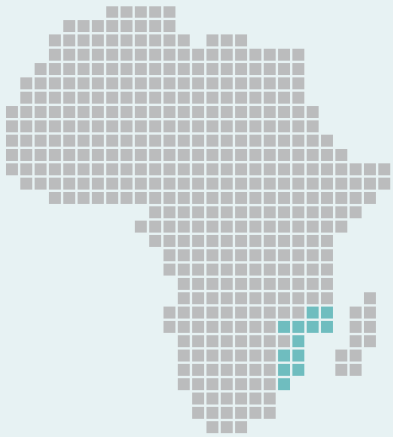
Authors
Occa E.

Focus country
Mozambique



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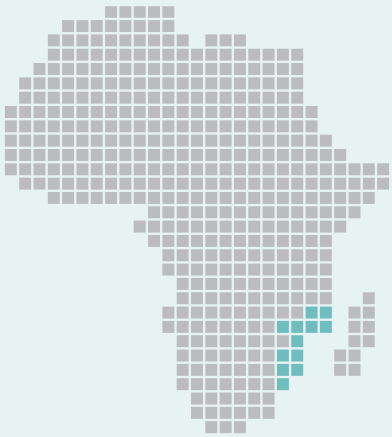
Focus country
Mozambique



Comunicações Breves

A percepção da qualidade do atendimento das gestantes nos centros de saúde apoiados pela Médicos com África CUAMM

Cássimo Manuel Saide[1], Simone Cadorin[1], Ilaria Onida[1], Edoardo Occa[1]

[1]Médicos com África CUAMM Moçambique

Cássimo Manuel Saide
Médicos com África CUAMM Moçambique | m.saide@cuamm.org

Resumo

Introdução: Moçambique é um Pais em vias de desenvolvimento cujo maior desafio é diminuir a mortalidade materno e infantil, tanto que actividades conjuntas entre a comunidade e o serviço de saúde são essenciais para uma assistência e bem-estar da população. Foi desenvolvido no distrito de Montepuez e Balama de 2020 a 2022 um projecto "Os primeiros 1000 dias**"** que visava proporcionar cuidados básicos para a mulher e a criança. **Metodologia:** Na avaliação recorreu-se ao método quali-quantitativo. Foi conduzido em grupos focais compostos de 10 mães que tiveram parto no período entre Junho de 2021 a Junho de 2022, totalizando 60 mulheres. **Resultados:** Relativo a idade um (2%) era menor de 14 anos e 23 (38%) tinham 19 a 25 anos. 36.7% (22/60) sabiam do significado e importância do CPN, 21.7% (13/60) sabiam e não frequentavam, 3.3% (2/60) sabiam, mas não acharam importante. Sobre acessibilidade aos serviços, 46.6% (28/60) referiram que a distância associada a questões logísticas condiciona o acesso. 70.0% (42/60) referiram que estão totalmente satisfeitas pelos serviços prestados. Sobre disponibilidade de recursos e insumos no dia do parto, 46.7% (28/60) elogiaram, 33.3% (20/60) referiram falta de alguns serviços como água, electricidade, banheiros e camas. Sobre aceitabilidade e vontade de poder frequentar a US face ao comportamento dos profissionais de Saúde e aos cuidados oferecidos, 73.3% (44/60) tiveram uma resposta totalmente positiva no que diz respeito a usar a mesma unidade sanitária caso estejam grávidas. **Conclusão:** As mulheres dos distritos de Balama e Montepuez estão satisfeitas pelos serviços prestados pelas US. Tanto que, 73.3% (44/60) garantem que voltariam ao mesmo hospital para receber cuidados de saúde.
Palavras-chave: maternidade, parto, qualidade, satisfação, barreiras culturais

Abstract

Introduction: Mozambique is a developing country whose biggest challenge is to reduce maternal and child mortality, so much so that joint activities between the community and the health service are essential for the assistance and well-being of the population. A project "The first 1000 days" was developed in the district of Montepuez and Balama from 2020 to 2022, which aimed to provide basic care for women and children. **Methodology:** In the evaluation, the qualitative-quantitative method was used. It was conducted in focus groups made up of 10 mothers who gave birth between June 2021 and June 2022, totaling 60 women. **Results:** Regarding age, one (2%) was under 14 years old and 23 (38%) were between 19 and 25 years old. 36.7% (22/60) knew the meaning and importance of the CPN, 21.7% (13/60) knew and did not attend, 3.3% (2/60) knew, but did not think it was important. Regarding accessibility to services, 46.6% (28/60) reported that the distance associated with logistical issues affects access. 70.0% (42/60) reported that they were completely satisfied with the services provided. Regarding the availability of resources and supplies on the day of birth, 46.7% (28/60) praised it, 33.3% (20/60) reported a lack of some services such as water, electricity, bathrooms and beds. Regarding acceptability and desire to be able to attend the US in light of the behavior of healthcare professionals and the care offered, 73.3% (44/60) had a completely positive response with regard to using the same healthcare unit if they are pregnant. **Conclusion:** Women in the districts of Balama and Montepuez are satisfied with the services provided by the US. So much so that 73.3% (44/60) guarantee that they would return to the same hospital to receive healthcare.
Keywords: maternity, delivery, quality, satisfaction, cultural barriers

Introdução

Moçambique é um Pais em vias de desenvolvimento cujo maior desafio é diminuir a mortalidade materno e infantil, tanto que actividades conjuntas entre a comunidade e o serviço de saúde são essenciais para uma assistência e bem-estar da população.[1] No entanto, a falta de informação sobre a atenção a ter durante a gravidez, os cuidados de mulher grávida, a importância da assistência ao parto, a necessidade de ter consulta pós-parto e o seguimento da criança nos primeiros anos de vida, contribui negativamente para o aumento das mortes maternas e infantis. Segundo a Organização Mundial de Saúde, "morte materna" é todo falecimento causado por problemas relacionados à gravidez, ao parto ou ocorrido até 42 dias depois do parto. [2] Um projecto denominado "os primeiros 1000 dias", financiado pela Agência Italiana de Cooperação para o Desenvolvimento (AICS) foi implementado em Montepuez e Balama entre os anos 2020 e 2022, com o objectivo deaumentar a demanda na assistência das mulheres e crianças incluindo sua qualidade. Durante a vigência do projecto, as enfermeiras do projecto 1000 dias que dava o apoio técnico nas Unidades Sanitárias (US), encontraram gestantes que não passaram por nenhuma consulta pré-natal facto que contribui para que o parto seja assistido às cegas, pelo facto de não ter o histórico gestacional da mulher, nem o estado de saúde do bebé. Os indicadores de saúde materno-infantil (SMI) em Moçambique mostram uma tendência crescente em relação as consulta pré-natal (CPN) com destaque para a primeira consulta facto que não se verifica nas consultas pós-parto (CPP) onde tem se verificado a redução no atendimento das mulheres e crianças. [3]

Métodos

Foi desenvolvida uma avaliação do tipo qualitativa e usado ométodo quali-quantitativo quanto à abordagem e descritivo quanto aos objectivos. A análise estava focada nos cuidados prestados na US para perceber a satisfação dos beneficiários directos do projecto. Foram conduzidos 6 grupos focais repartidos em 3 para Montepuez (Nairoto, Namueto, Centro Urbano) e 3 para Balama (Impire, Balama sede, Metata) com 10 mulheres cada, que tiveram parto entre Junho de 2021 a Junho de 2022. As participantes foram reunidas numa área da comunidade onde se sentiam a vontade. As discussões tiveram aduração média de 30 minutos. Com recurso a umum guião pré estruturado para orientar a discussão foram colhidos dados como demográficos, Conhecimento, Accesso, Percepção da qualidade e Comportamento e acções e realizadas 10 questões sobre qualidade dos serviços oferecidos na CPN, Maternidade, CPP, Neonatologia e Pediatria, qualidade no atendimento na CPN, Maternidade, CPP, Neonatologia e Pediatria, importância de frequentar a CPN, acesso aos cuidados de saúde e melhoria do serviço.

Aspectos éticos: Foi obtida autorização da Direcção Provincial de Saúde, e na colecta de dados foi enfatizada a participação voluntária e foram respeitados os princípios básicos da ética.

Resultados

Dados sociodemográficos

De um total de 60 mulheres entrevistadas, uma (2%) era menor de 14 anos de idade e 23 (38%) tinham idade entre 19 a 25 anos. Sessenta e cinco por cento tinha frequentado ensino primário, 25% não tinham instrução e 10% o ensino secundário. Ao longo do período uma mulher (2%) teve dois partos e 59 (98%) tiveram um parto e 62% têm mais de dois filhos vivos.

Tabela 1: Apresentação de dados demográfico

Idade			Escolaridade			Nº de Partos			Filhos vivos		
	Nº	%		Nº	%		Nº	%		Nº	%
Menos 14 anos	**1**	**1.7**	**S/Intr***	**15**	**25**	**1 parto**	**59**	**98.3**	**1 filho**	**13**	**21.6**
14-18	13	21.7	Ens 1º**	39	65	2 partos	1	1.6	2 filhos	10	16.6
19-25	23	38.3	Ens 2º***	6	10	3 partos	0	0	Mais 1 filhos	37	61.6
26-35	13	21.7	Ens. Sup****		0	Mais de 4 Partos	0	0			
36-45	3	5									

* Sem instrução, ** Ensino primario, *** Ensino secundário **** Ensino Superior

Análise de dados qualitativos

Chegada tardia a CPN: Oitenta e dois por cento das mulheres referiu razões sócio culturais porque seus parceiros condicionam a ida ao centro de Saúde (CS). E 13.3% (8/60) referem por razões logísticas. Os resultados mostram que as mulheres vão tardiamente a CPN por questões socio culturais elacionadas aos seus parceiros que não se fazem aos hospitais acompanhando a sua parceira para a primeira CPN.

Feita a pergunta "Sabem o que significa a CPN qual é a importância e porque devemos fazer as CPN muito cedo?" 36.7% (22/60) afirmaram que tinham conhecimento do significado e da sua importância de fazer por isso frequentam. 221.7% (13/60) sabiam, mas não frequentavam por motivos sociais, 3.3% (2/60) sabiam, mas não acharam importante.

"uma mulher gravida deve vir muito cedo no hospital porque aqui nos controlam a saúde, nos medem a barriga, nos pesam e quando temos doenças eles nos dão medicamentos para tomar no hospital e em casa."

Acesso aos cuidados de Saúde:, 46.6% (28/60) referiram que a distância associadas a questões logísticas contribuem no acesso aos cuidados básicos de Saúde. 38.3% (23/60) refere a equidade e 15% (9/60) referiram questões associadas à qualidade de serviços.

"aqui nós somos bem atendidas, o que nos preocupa é a servente, quando nós chegamos a US e abordamos a ela, diz que primeiro tem de me cumprimentar e depois ela nos deixa muito tempo sem nos dar a senha e isso nos atrasa para ser atendida, isso me preocupa bastante (…) mas o atendimento dos profissionais de saúde está tudo bem. Mas a servente tem nos desrespeitado, ela nos goza nos atende a hora que ela quer."

Percepção da Qualidade dos serviços oferecidos na CPN, Maternidade, CPP, Neonatologia e Pediatria: 70.0% (42/60) referiram que estão totalmente satisfeitas pelos serviços que se beneficiaram e 30.0% (18/60) criticaram os serviços prestados pelo CS.

"eu não tenho nenhuma queixa pois eu sempre tive filhos neste hospital e as minhas consultas também faço aqui eu nunca fui maltratada por isso eu digo que sou bem tratada"

Relacionamento interpessoal: 70.0% (42/60) referiram que tiveram um bom atendimento e boa interação com osprofissionais de Saúde. 18.3% (11/60) criticam o relacionamento com os profissionais de Saúde e 11.7% (7/60) referem que sentiram falta de protecção psicológica e de segurança.

"eu tinha vindo aqui, não tive nenhuma dificuldade, fui atendida com uma enfermeira jovem e nova, ela me recebeu me observou e disse que teria parto em uma hora e na verdade no tempo que ela disse eu tive o parto. Fui bem cuidada e bem observada, eu e meu bebé e logo que amanheceu fomos dispensados e fui para casa.

Disponibilidade de insumos e recursos: 46.7% (28/60) elogiaram os serviços, 33.3% (20/60) referiram falta de alguns serviços como, água, electricidade, banheiros e camas. 20.0% (12/60) relatam abandonos das enfermeiras na US.

"(…) neste hospital o que mais nos preocupa é por falta de camas, nos deixarem aqui duas pessoas ou três na mesma cama não é bom, será que não vamos carregar doenças? Aqui falta camas, só tem duas e uma esta estragada. Falta luz e se você não traz lanterna, vai passar mal para ter parto."

"eu quando fui ao hospital senti-me bem a única coisa que sei que tem faltado é casa de banho, luz e água, a água aqui esta longe e não tem recipientes para colocar. No dia do meu parto eu queria beber água e depois me disseram que o balde não podíamos por água de beber porque poem ali coisas com sangue."

Tempo de espera para o atendimento: 86.7% (52/60) referiram que foram atendidas logo que chegaram na Maternidade e 13.3% (8/60) queixaram-se de ter esperado por muito tempo.

"eu quando cheguei no hospital me receberam e

me deram cama e fui atendida logo porque encontrei a enfermeira ali no hospital."

Comportamento e acções: Se estivesse gravida agora voltaria ao mesmo hospital para fazer a CPN, ter o Parto, internar o seu bebé?

Retorno a mesma US: 73.3% (44/60) disseram que voltariam aquela US caso estivessem gravidas, 21.7% (13/60) tiveram resposta proactiva e 5.0% (3/60) condicionaram o seu regresso.

"quando cheguei no hospital desde a consulta pré-natal, parto e até a vacinação nunca me trataram mal, sempre foram bons comigo e gosto do jeito que eles me tratam todos os meus filhos tive neste hospital e com diferentes enfermeiras, mas elas sempre me trataram bem, cuidaram do meu bebé e me fizeram limpeza e deram-me alta, aqui para mim sempre foi bom.

Conclusões

As consultas pré-natais são pouco frequentadas, por razões socio culturais, pois o CS recomenda que as mulheres venham com o seu parceiro para a CPN e eles simplesmente não acompanham as suas esposas e isso condiciona com que elas tenham o mínimo de consulta recomendadas. Concluimos que as mulheres têm conhecimento do significado e importância da CPN, mas a sua frequência é condicionada como antes foi referido, mas também a distâncias, a equidade relacionado a igualdade no direito a assistência sem distinção de poder económico e ou posição social, foram apontados como elementos que contribuem no condicionamento em CS identificados.

As mulheres de Balama e Montepuez estão satisfeitas pelos serviços de saúde oferecidos visto que maior parte das entrevistadas garantem retomar a mesma unidade sanitária para receber os cuidados de saúde. Tanto que a maioria 73.3% (44/60) das mulheres mostraram satisfação em relação os serviços prestados e garantem voltar a mesma unidade sanitária. Com estes resultados mostra a confiança que os profissionais de saúde demonstraram pela boa prestação e apontam como a falta de insumos, como camas, iluminação, água, e ainda o comportamento de alguns profissionais de saúde em CS e profissionais de saúde identificados no atendimento das gestante condicionam a oferta integral dos cuidados de saúde e satisfação das mesmas.

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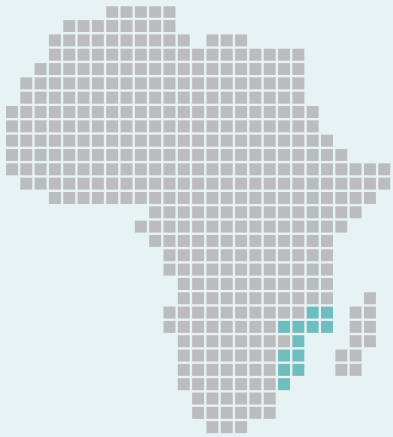
Implementação da Linha de Base de Pré-intervenção do Programa Governamental Família Modelo para Adoção de Comportamentos Preventivos da Cólera e outras Doenças Transmissíveis, em seis Distritos da Província de Cabo Delgado



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Implementação da Linha de Base de Pré-intervenção do Programa Governamental Família Modelo para Adoção de Comportamentos Preventivos da Cólera e outras Doenças Transmissíveis, em seis Distritos da Província de Cabo Delgado

Elsa Chambisse[1], Simone Cadorin[1], Edoardo Occa[1], Angelo Ghelardi[2], Inusso Chuau[2], Ketan Chitnis[2], Mussa Ally[3]

[1]Médicos com África CUAMM Moçambique; [2]Unicef Moçambique; [3]NIOP (Núcleo Investigativo Operacional de Pemba)

Elsa Chambisse

Médicos com África CUAMM Moçambique | e.chambisse@cuamm.org

Resumo

Introdução: No âmbito da implementação de uma das estratégias de comunicação para a mudança de comportamento do MISAU intitulado "família modelo" que visa a prevenção de doenças como malária, cólera, desnutrição e COVID-19 usando acções de sensibilização das famílias para a adopção de práticas saudáveis ao nível do País através das instituições da saúde. Em Cabo Delgado particularmente é implementada pela Médicos com África CUAMM em colaboração com a UNICEF. Foi definida uma linha de base em seis distritos da província de Cabo Delgado antes da implementação da mesma estratégia. A linha de base faz uma breve análise descritiva dos parâmetros encontrados nas famílias visitadas e se espera que ao longo do seguimento aconteça alteração positiva dos mesmos.**Métodos:** Foi realizada uma análise descritiva do estado das famílias em relação às práticas caracterizadas como sendo dos parâmetros da família modelo através da observação directa dos mesmos. Foram feitas entrevistas domiciliares dirigidas aos chefes dos agregados de 1890 familiares, aleatoriamente, sem discriminação de sexo, idade, bem como se é deslocado ou população nativa. Foram entrevistadas famílias nos distritos de Chiure, Ancuabe, Ibo, Mueda, Balama e Montepuez, de Outubro a Novembro de 2022. **Resultados:** os resultados estão em período de analise estatística detalhada e neste estudo apresenta-se os cumulativos preliminares (dados colhidos ao nível dos distritos) e desagregados estatisticamente; os dados cumulativos disponíveis mostram-nos uma média de menos de 50% de adesão dos parâmetros, com diferenças notáveis entre aldeias e entre tipos de população (nativos e deslocados). **Conclusões:** A maior parte das famílias ainda estão distantes de alcançar os parâmetros. A intervenção através do programa, tem evidenciado que será necessário um longo seguimento das mesmas para alcançar os parâmetros definidos pelo MISAU. Os dados sugerem que as intervenções no âmbito da família modelo requerem maior conjugação de esforços e associá-los aos fatores socioculturais, ambientais, económicos.

Palavras-chave: Prevenção, Comportamento, Saúde comunitária, Doenças transmissíveis, Deslocados

Abstract

Background: As part of the implementation of one of the MISAU's communication strategies for behavioural change, entitled "model family", which aims to prevent diseases such as malaria, cholera, malnutrition and COVID-19 using actions to raise awareness among families to adopt healthy practices at country level through health institutions. In Cabo Delgado in particular, it is implemented by Médicos con África CUAMM in collaboration with UNICEF. To this end, a baseline was defined in six districts of Cabo Delgado province before the strategy was implemented. The baseline makes a brief descriptive analysis of the parameters found in the families visited and it is hoped that over the course of the follow-up there will be a positive change in these parameters. **Methods:** A descriptive analysis of the state of the families in relation to the practices characterised as the parameters of the model family was carried out through direct observation. Household interviews were conducted with the heads of 1890 households, randomly, without discrimination as to gender, age or whether they were displaced or native. Families were interviewed in the districts of Chiure, Ancuabe, Ibo, Mueda, Balama and Montepuez from October to November 2022. **Results:**

The results are in the process of being analysed in detail and this study presents preliminary cumulative data (data collected at district level) and statistically disaggregated; the cumulative data available shows an average of less than 50% adherence to the parameters, with notable differences between villages and between types of population (natives and displaced persons). **Conclusions:** Most families are still far from achieving the parameters. The intervention through the programme has shown that it will be necessary to follow them up for a long time in order to achieve the parameters defined by the MoH. The data suggests that interventions in the context of the model family require a greater combination of efforts and the association of sociocultural, environmental and economic factors.
Keywords: Prevention, behavior, community health, communicable diseases, displaced persons.

Introdução

A saúde de uma comunidade ou sociedade não depende apenas da genética e da condição socioeconómica, mas também do meio ambiente a que a mesma é acometida. Segundo Ministério da Saúde (MISAU), no Plano Estratégico do Sector de Saúde (PESS) 2019-2024, a maioria das condições de saúde, senão todas, é passível de ser prevenidas com intervenções de promoção de saúde e/ou de prevenção da doença e sendo parte dos pilares do PESS, destacam-se a aceleração da prevenção da malnutrição e redução do peso das doenças endémicas nomeadamente a Malária, HIV, Tuberculose e Doenças Não Transmissíveis. [1]
Em cabo Delgado, a promoção de saúde é também feita a partir da abordagem das famílias modelo, concebida pelo MISAU e parceiros para a promoção de comportamentos saudáveis para a prevenção de doenças tais como COVID-19, Malaria, Desnutrição, Cólera através de 14 indicadores pré-definidos. Estas actividades de promoção através da abordagem das famílias modelo decorrem em seis distritos da província de Cabo Delgado desde Setembro de 2022.[2]
Segundo a OMS, citada no PESS (2019-2024), 10% do peso global da doença poderia ser prevenido através da melhoria da disponibilidade de água potável, saneamento, higiene e gestão dos recursos hídricos.
A definição da linha de base traz uma leitura sobre quais têm sido as atitudes e práticas das famílias perante os parâmetros definidos como sendo da família modelo descritos pelo MISAU. A condução dos parâmetros da família modelo é uma nova adopção do MISAU como estratégia de melhoramento da saúde das famílias que está sendo implementada ao nível de todo o País através do governo e dos parceiros de cooperação. Em Cabo Delgado, embora com os desafios enfrentados como a indisponibilidade da água potável, o êxodo constante das famílias por factores ligados a ataques nas suas zonas de origem a linha de base apreciou algumas atitudes e práticas positivas das famílias como resposta da importância e pertinência da adopção dos parâmetros pré-definidos apesar de sugerir uma média <50% em muitas famílias.

Situação de saúde no contexto de emergência

Cabo Delgado é a província nortenha do país que desde o ano de 2017 vive situações de violência armada. De acordo com o relatório de apelo humanitário produzido pela UNFPA para Cabo Delgado , 669.256 pessoas foram deslocadas internamente e vizinhança. Com unidades de saúde que oferecem serviços abrangentes de saúde sexual e reprodutiva com necessidade crítica de suprimentos médicos essenciais, equipamentos e pessoal.[3]
Para o aspecto ligado a continuidade da educação das crianças face ao período de emergência que também consta dos parâmetros da família modelo, deve se encorajar as crianças a voltar à escola, quer seja por meio do acesso à educação formal ou proporcionando espaços seguros de aprendizagem mais próximos de seus reassentamentos.[4]
A elevada prevalência de sintomas respiratórios em crianças desnutridas confirmou a conhecida correlação entre a desnutrição e a infeção respiratória.[5]
Em contextos sociais severamente desconstruídos, a educação contínua e a sensibilização comunitária são cruciais para alcançar e manter atitudes positivas de prevenção da cólera.[6]
A linha de base realizada espelha as atitudes e práticas encontradas nas famílias para a prevenção das doenças através da implementação dos parâmetros da família modelo, contudo ainda existe vários aspectos estruturais que são necessários para que a promoção de saúde seja efectiva.

Métodos

Trata-se de uma análise descritiva de uma linha de base realizada previamente à implementação da estratégia família modelo do MISAU, onde foram visitadas 49 aldeias das quais algumas são centros de reassentamentos e aldeias designadas por acolhedoras, com colheita de dados quantitativos de forma presencial através de questionário contendo as perguntas dos parâmetros definidos segundo o guião das famílias modelo, (MISAU, 2021). Para tal foram identificadas 1890 famílias e inquiridas de forma aleatória em seis distritos, através de uma ficha contendo os 14 parâmetros e a observação directa como forma de confirmar existência ou adoção dos mesmos.

Variáveis do estudo: Famílias dos centros de reassentamentos, aldeias que acolheram maior número de deslocados e os parâmetros da família modelo (MISAU). Foram realizadas questões sobre como: Tem latrina com tampa e em uso? Tem sistema de lavagem das mãos e sabão ou cinza (ex: Tip tap)? Tem rede mosquiteira em uso em cada cama/esteira? Tem sistema de tratamento e conservação de água? Tem copa para secagem de loiça? Tem suporte para pau de pilão? Tem aterro sanitário? Possui um cartão de saúde da criança menor de 5 anos e outros parâmetros nutricionais em dia? A criança come pelo menos 3 vezes por dia (produtos disponíveis localmente)? Usa método moderno de PF? Se é mãe de criança menor de 1 ano fez pelo menos 4 Consultas Pré-Natais (CPN) durante a gravidez e as consultas pós-parto dentro de prazos? As crianças com mais de 6 anos frequentam a escola? Todas as crianças com mais de 6 anos que não vão à escola concluíram a 7ª Classe? As crianças com menos de 5 anos foram registadas?

Resultados

Das 1890 famílias entrevistadas, 1134/1890 (60%) possuem uma latrina com tampa e em uso. Dez por cento(190/1890) possuem um instrumento de lavagem das mãos após as suas necessidades. Vinte e dois por cento possuem um utensílio de conservação e tratamento da água. Quarenta e dois por cento possui um aterro sanitário. Seis por cento possui um suporte para pilão. Trinta e quatro por cento possui uma copa de secagem de loiça. Quarenta e um por cento das famílias com crianças < 5 anos conseguem alimentar seus filhos 3 vezes ao dia. Vinte e sete por cento das famílias não usa métodos de planeamento familiar. Cinquenta por cento das famílias possui crianças >6 anos que vão a escola, sendo que25% das famílias é que possui crianças que completaram a 7classe. Quarenta e quatro por cento das famílias possui crianças<5 anos com registo de nascimento. Sessenta e sete por cento das famílias possui rede mosquiteira e em uso. Em 33% das famílias foi referido que as mulheres enquanto grávidas foram a pelo menos 4 CPN. A média dos parâmetros encontrados no total das 1890 famílias visitadas foi de 44%, dos 80% esperados (Figura 1).

Discussão

Estatisticamente, existe a possibilidade de que a implementação dos parâmetros seja eficaz. Embora menos da metade dos parâmetros tenham sido alcançados, pode se traduzir na possibilidade de um avanço da melhoria da saúde das famílias através da criação dos mesmos. Ainda assim, os dados reflectem que não existe garantia da evolução no alcance dos parâmetros definidos como sendo de uma família modelo.

O outro aspecto é que os parâmetros não consideram as famílias que não possuem crianças em idade escolar, pais que não tem filhos, famílias cujo agregado é de idosos, entre outros factores que podem contribuir para uma avaliação desleal entre as famílias.

A linha de base também espelha a realidade das famílias em termos de falta das condições básicas de saúde, água, alimentação e acesso à escola por parte de muitas famílias e crianças.

Conclusões

A implementação dos parâmetros da família modelo deve observar a realidade dos locais, a disponibilidade dos recursos básicos às famílias como acesso à educação, a água potável, a saúde, habitação e alimentação.

Os parâmetros da família modelo são vistos como um conjunto de práticas e comportamentos quotidianos a serem considerados a longo prazo e isto foi unanime entre as famílias visitadas. Contudo, a pobreza que se traduz na insegurança alimentar, a indisponibilidade da água potável e outros po-

derão contribuir para a ineficácia da abordagem das famílias modelo através dos vários parâmetros como o das 3 refeições ao dia, existência de recipiente de conservação e tratamento da água, sendo que, várias aldeias e centros de reassentamento não possuem água potável, e outros.
Em relação a conclusão, dados analisados e desagregados com rigor estatístico e análise multivariada estarão brevemente disponíveis, o que nos permitirá fornecer conclusões mais aprofundadas e refinadas. Os dados serão compartilhados com as autoridades locais para planificação direcionada por área geográfica, tipo de população envolvida e em indicadores individuais, a fim de se tornar uma ferramenta operacional de planejamento para os atores envolvidos e futuras pesquisas.

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Infectious and tropical diseases

COVID-19 vaccines and a perspective on Africa

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Review

COVID-19 vaccines and a perspective on Africa

Alberto Mantovani [1,2,3,*], Maria Rescigno [1,2], Guido Forni [4], Francesca Tognon [5], Giovanni Putoto [6], Jerry Ictho [7] and Peter Lochoro [8,*]

Vaccines have dramatically changed the COVID-19 pandemic. Over 30 vaccines that were developed on four main platforms are currently being used globally, but a deep dissection of the immunological mechanisms by which they operate is limited to only a few of them. Here, we review the evidence describing specific aspects of the modes of action of COVID-19 vaccines; these include innate immunity, trained innate immunity, and mucosal responses. We also discuss the use of COVID-19 vaccines in the African continent which is ridden with inequality in its access to vaccines and vaccine-related immunological research. We argue that strengthening immunology research in Africa should inform on fundamental aspects of vaccination, including the relevance of genetics, trained innate immunity, and microbiome diversity.

Highlights

Over 30 vaccines against SARS-CoV-2 are in use worldwide, but the dissection of some of the immunological mechanisms is limited to only a few.

Innate immunity activation by SARS-CoV-2 vaccines triggers adaptive immune responses, reactogenicity, and mechanisms of pathogen-agnostic protection (trained immunity).

The lipid nanoparticles (LNPs) which carry mRNA vaccines activate a complex network of innate immune cells and cytokines, but the sensors involved remain to be fully defined.

Trained innate immunity activated by LNPs, adenoviral vaccines, or unrelated vaccines such as live polio virus may be particularly relevant in African countries.

The impact of genetics, microbiome, and prevalent infectious diseases, as well as the potency, breadth, and imprinting of immune responses in African countries, remains undefined.

Mucosal vaccination eliciting strong IgA2 responses represents a holy grail because of its potential to inhibit infection and transmission.

Vaccine inequality encompasses production and access to vaccination, as well as immunological resources, and this is relevant in African countries.

Significance

An analysis of the landscape of the 30 SARS-CoV-2 vaccines in current use worldwide and their impact on innate and adaptive immunity are highly relevant; indeed, there are clear gaps in our knowledge and challenges related to low-income countries. We argue that examining vaccination

The vaccine landscape

Current mortality assessment suggests that the death of about 14.8 million people is directly or indirectly due to the coronavirus disease 2019 (COVID-19) pandemic [1]. Moreover, the impact of **long COVID** (see Glossary) and indirect effects of the pandemic are matters of major concern, for instance as regards to decreasing vaccination coverage against conventional infectious diseases in low-income countries such as Sub-Saharan Africa [2–4]. The rapid development of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines on innovative (mRNA) and conventional platforms has mitigated the impact of the pandemic and averted over 20 million deaths (19.8 million between December 2020 and December 2021) [5]. However, in spite of global health initiatives such as COVID-19 Vaccines Global Access Initiative (**COVAX**) [6] and of efforts conducted onsite by global nongovernmental organizations in the field, an equitable perspective on vaccine-related research, vaccine production, and access in low-income countries remains far from satisfactory.

As of September 2022, over 30 vaccines against the whole SARS-CoV-2 virus or the spike protein have been approved, and more than 11 billion doses have been administered (Table 1, Key table). The major platforms utilized for the development of COVID-19 vaccines include the use of inactivated virus, spike protein or peptides, adenoviruses, and mRNA (Table 1) (for reviews see refs [7–12]). Adjuvants include the traditional aluminum salts (Alum), saponin-based compounds (e.g., N57-ASI), delta inulin microcrystals, and CpG oligonucleotides. An analysis of the pros and cons of different approaches and of activity of the different vaccines in current use is beyond the scope of this review. Although the safety and efficacy of all World Health Organization (WHO)-approved vaccines have been evaluated through Emergency Use Listing Procedures[i], in a few cases only basic information on the immune mechanisms activated and the comparative efficacy of the immune responses elicited is available. Unfortunately, this is often truer for vaccines that have come into common use without approval from the WHO, US FDA, or the European Medical Agency (EMA).

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Herein we review current evidence on selected aspects of the immunology of COVID-19 vaccines, emphasizing that information is largely limited to only a few of them. The challenge represented by vaccination and vaccine research in Africa, a paradigm for low-income countries, is also discussed. Among low–middle-income countries, Africa is characterized by the lowest vaccination coverage with substantial country-to-country differences. We argue that Africa provides a context to address fundamental questions on the impact on vaccination of genetics, socioeconomic status, microbiome diversity, and trained innate immunity. Recent reviews provide a framework for this paper [7,12–14].

responses in the African continent represents a clear opportunity to investigate fundamental questions, including the impact of genetics, microbial milieu, and prevalent diseases on SARS-CoV-2 vaccine-elicited immune responses.

Vaccine-elicited immune responses

Innate immunity

Activation of innate immunity by SARS-CoV-2 vaccines is essential for triggering adaptive immune responses and is a cause of reactogenicity. Providing a framework for the discussion of specific points, Figure 1 provides a schematic view of the activation of immune responses by mRNA and adenovirus-based vaccines, antiviral effector mechanisms, and the two main immune-related adverse reactions. From another angle, vaccine-elicited **trained innate immunity** can mediate broad-spectrum antimicrobial resistance, which may be particularly relevant in the African context because of exposure to a host of infectious agents, as well as to unrelated live vaccines (discussed below). Except for mRNA vaccines, the agents listed in Table 1 rely on classic conventional adjuvants, from Alum to CpG oligonucleotides (not discussed here). The BNT162b2 and mRNA1273 mRNA vaccines (Table 1) represent a small fraction of those in use in Africa (see later) and more so in the most fragile parts of the continent. However, ongoing activities are aimed at building infrastructures for the development and production of mRNA vaccines in different African countries, across a continent which depends on external sources for 99% of its vaccine needs [15,16]. This capacity-building effort may have broad implications given the potential of mRNA technology for diseases beyond COVID-19. This scenario justifies an analysis of the interaction of mRNA vaccines with innate immunity in the African context.

Activation of innate immune responses by mRNA vaccine components

Essential components of the two currently approved mRNA vaccines are a nucleoside-modified mRNA and lipid nanoparticles (LNPs) serving as delivery vehicles. Originally, substitution of uridine with naturally occurring uridine derivatives had been shown *in vitro* and *in vivo* in mice to result in escape from recognition from RNA sensors – Toll-like receptors (TLRs) and retinoic-acid-inducible protein I (RIG-I) – reduced production of inflammatory mediators such as interferon-α (IFNα) and tumor necrosis factor (TNF), as well as increased protein translation [17]. However, LNPs used in the two approved mRNA vaccines include an ionizable lipid (iLNP); indeed, iLNP-encapsulated nucleoside-modified mRNA vaccines have been shown to elicit potent T- and B cell responses against diverse antigens [18,19]. iLNPs are more than a delivery system since they provide the required adjuvant activity by inducing, for instance, strong follicular T-helper cells and long-lived memory B cell responses to mRNA and protein vaccines against influenza virus and SARS-CoV-2 in mice [20–23] (Figure 2).

Intramuscular or intradermal injection of mRNA-iLNP vaccines (e.g., SARS-CoV-2) in mice and rhesus macaques resulted in complex leukocyte infiltrates which included neutrophils, monocytes-macrophages, dendritic cells (DCs), and natural killer (NK) cells at the site of injection and draining lymph nodes [24–26]. Neutrophils were reported to efficiently uptake iLNP but did not efficiently translate mRNA into protein [24]. Moreover, antibody depletion in mice showed that neutrophils were dispensable for eliciting the adaptive immune response [24]. Bulk and single-cell analysis of draining lymph nodes revealed that uptake and translation were largely confined to monocytes-macrophages and conventional dendritic cells (cDCs) in peripheral tissues and lymph nodes [25,26]. In mice, conventional type 1 DCs (cDC1s) and Langerhans

[1]IRCCS Humanitas Research Hospital, via Manzoni 56, 20089 Rozzano, Milan, Italy
[2]Department of Biomedical Sciences, Humanitas University, Via Rita Levi Montalcini 4, 20072 Pieve Emanuele, Milan, Italy
[3]William Harvey Research Institute, Queen Mary University, London EC1M 6BQ, UK
[4]Accademia Nazionale dei Lincei, Rome, Italy
[5]Operational Research Unit, Doctors with Africa CUAMM, Italy
[6]Head of Planning and Operational Research, Doctors with Africa CUAMM, Italy
[7]Clinical Epidemiology, Doctors with Africa CUAMM, Uganda
[8]Health Service Management, Doctors with Africa CUAMM, Uganda

*Correspondence:
alberto.mantovani@humanitasresearch.it (A. Mantovani) and
p.lochoro@cuamm.org (P. Lochoro).

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cells were essential to elicit T follicular helper (Tfh) and germinal center B cell responses to influenza virus and SARS-CoV-2 (Figure 2) [24].

iLNP injections with or without nucleoside-modified mRNA in various animal species elicited a strong cytokine response which included chemokines (e.g., CXCL1, CXCL2, CXCL10, CCL3, CCL4), cytokines (e.g., IL-1β and IL-6), and IFNs [20–22,24,27]. In mice, single-cell transcriptional profiling revealed a signature indicative of an IFN response in different lymph-node cell types as early as 1 day after injection [21]. Of note, NK cells were the major source of IFNγ in lymph nodes at early time points (1–7 days after primary immunization) as well as after secondary immunization (day 22), amplifying the activation of DCs [21]. Moreover, type 1 IFN was essential for $CD8^+$ T cell activation in lymph nodes [21]. In the context of a systems vaccinology approach in human volunteers vaccinated with BNT162b2, elevated serum concentrations of IFNγ and IFN-inducible chemokine CXCL10 were observed after secondary vaccination relative to the first, suggesting that mRNA vaccination triggers innate immunity to mount a greater response after secondary immunization [27]. In mice, gene targeting and antibody blockade of IL-6 showed that this cytokine was important for the activation of Tfh cells and induction of the germinal center B cell reaction [20]. Thus, at the injection site, draining lymph nodes, and peripheral blood, iLNPs activate a complex network of innate immune responses – including macrophages, DCs, NK cells, cytokines (e.g., IL-6 and IFNs), and chemokines – that drive the activation of adaptive T and B cell responses.

LNP sensors

The cellular sensors and mechanisms activating the innate immune response to LNP remain elusive. Early studies suggested that TLRs, the NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome, or stimulator of interferon genes (STING) recognized liposomes or LNPs [28–30]. A systematic analysis in gene-targeted mice showed that TLR2, TLR4, TLR5, TLR7, NLRP3, cyclic GMP–AMP synthase (cGAS), and STING were individually dispensable for antibody and $CD8^+$ T cell induction by BNT162b2 [21]. Targeting the melanoma differentiation-associated gene 5 (MDA5)/IFN pathway *Mavs*^{stm1Zjc} (*Mavs*$^{-/-}$ mice) resulted in reduced $CD8^+$ T cell cytotoxic responses and, to a lesser extent, decreased antibody production relative to wild-type mice [21]. Tfh cells and the germinal center B cell responses were partially reduced in MyD88-deficient – *Myd88*$^{tm1.1Defr}$ (*Myd88*$^{-/-}$) – mice compared with wild-type mice [20]. The production of IL-1β by human monocytes exposed to mRNA-liposomes was inhibited by necrosulfonamide, a gasdermin-D inhibitor, and by a pan-caspase inhibitor [22]. Moreover, mice genetically defective in type-1 IL-1 receptor chain (*Il1r*$^{-/-}$) exhibited impaired inflammatory and adaptive responses to liposome-associated mRNA or iLNP [22]. These results suggested that IL-1 played an important role in the reactogenicity and immunogenicity of mRNA vaccines [22]. Of note, fusion of LNP with cell membranes may activate an IFN response analogous to virus-like particles, suggesting that membrane perturbation *per se* might contribute to the activation of the innate immune response [31]. Moreover, iLNP has bound apolipoprotein E (ApoE) and complement cascade components, and ApoE has strongly enhanced the uptake of mRNA-LNP in DCs relative to controls, suggesting that this biomolecular component/'halo' may contribute to mRNA delivery and activation in these cells [23,32,33]. However, the mechanisms involved in sensing iLNP by cells involved in innate immunity are complex and remain incompletely defined. Data in murine models suggest that downstream of iLNP action, different sensors and pathways – including triggers of MyD88 and IFN signaling, membrane perturbation, and complement – can contribute to the activation of innate immunity, adjuvant activity, and reactogenicity in response to mRNA vaccination (Figure 2).

Trained innate immunity

In a systems vaccinology approach in human volunteers, BNT162b2 administration elicited a strong innate immune response after secondary immunization, as analyzed at the single-cell

Glossary

Breakthrough infection: SARS-CoV-2 infection occurring in vaccinated immune individuals.
COVAX: the COVID-19 Vaccines Global Access Initiative is a global alliance led by the World Health Organization, the Coalition for Epidemic Preparedness Innovations (CEPI), the Global Alliance of Vaccines and Immunization (GAVI), and UNICEF, to ensure equitable access to SARS-CoV-2 vaccines in low income countries.
Homologous or heterologous vaccination: the usage of the same or different vaccines in combination for primary, secondary, and booster vaccination.
Long COVID: colloquial term for post-COVID syndrome (PSC) or post-acute sequelae of SARS-CoV-2 (PASC), a constellation of clinical signs and symptoms which persist for weeks or months after the initial infection; it involves diverse organs and systems, including the lung, brain, and cardiovascular or neuromuscular systems.
Single- or double-dose adenoviral vaccines: Ad26.COV.2S (Jcovden) and ChAdOx1 were designed as single- or two-dose vaccines, respectively.
Trained innate immunity: exposure to microbial moieties or selected vaccines induces epigenetic modifications in myeloid precursors and mature macrophages which underlie better effector function. It is a mechanism that is responsible for pathogen-agnostic protection conferred by select vaccines, such as BCG and live polio.

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Key table

Table 1. The global landscape of SARS-CoV-2 vaccines in current use

Company	Country	Vaccine name	Produced by	Vector	Adjuvant	Doses (in millions)[a]	Refs
Vaccines based on the inactivated SARS-CoV-2 virus							
Sinovac	China	CoronaVac	Vero cells	–	Alum	2500	[94]
Sinopharm	China	BBIBP-CorV	Vero cells	–	Alum	2300	[95]
Shenzhen Kangtai	China	KCONVAC	Vero cells	–	Alum	20	[96]
Bharat Biotech	India	Covaxin	Vero cells	–	Algel-IMDG[b]	205	[97]
		Covaxin inhalable	Vero cells	–		NF[c]	[98]
Ministry of Defense	Iran	Fakhravac	Vero cells	–	NF	8	[99]
Shifa Pharmed	Iran	COVIran	Vero cells	–	Alum	20	[100]
Res Inst Safety Probl	Kazakhistan	QazCovid-in	Vero cells	–	Alum	3	[101]
Acad Sciences	Russia	CoviVac	Vero cells	–	Alum	5	[102]
Erciyes University	Turkey	Turkovac	Vero cells	–	Alum	40	[103]
Valneva	France	VLA2001	Vero cells	–	Alum	NF	[104]
Vaccines based on the spike protein or its fragments							
Vaxine	Australia	Spikogen	Insect cells	–	Advax-2[d]	NF	[105]
Medicago	Canada	Co-VLP	Tobacco cells	–	N57-As01[e]	NF	[106]
Sinopharm	China	NVSI-06-07	CHO cells	–	Alum	0.1	[107]
Anhui Zhifei Longcom	China	Zifivax	CHO cells	–	Alum	50	[108]
Biot Genetics Center	Cuba	Abdala	Yeast cells	–	Alum	35	[109]
Inst Finlay de Vacunas	Cuba	Soberana02	CHO cells	–	Alum	7	[110]
Inst Finlay de Vacunas	Cuba	Soberana Plus	CHO cells	–	Alum	7	[111]
Razi Vac Serum Inst	Iran	Razi Cov Pars	CHO cells	–	Alum	5	[112]
Bektop	Russia	EpiVacCorona	Chemical synthesis	–	Alum	5	[113]
Medigen	Taiwan	MVC-COV1901	CHO cells	–	Alum + CpG	3	[114]
Baylor College	USA	Corbevax	Yeast cells	–	Alum	NF	[115]
Novavax	USA	NVX-Cov2373	Moth cells	–	Matrix M[f]	12	[116]
Sanofi Pasteur	France	VidPrevtyn Beta[g]	Moth cells	–	AS03[h]	NF	[130]
Vaccine based on naked DNA encoding the spike protein							
Zydus Lifesciences	India	ZyCoV-D	–	High-pressure injector	CpG	NF	[117]
Vaccines based on DNA encoding the spike protein carried by adenoviruses							
CanSino Biol	China	Convidecia	–	Human adenovirus 26	–	2	[118]
		Convidecia inhalable	–	Human adenovirus 26	–	NF	[98]
Oxford-AstraZeneca	UK	ChAdOx1	–	Chimpanzees adenovirus	–		[119]
Serum Institute	India	Covishield	–	Chimpanzees adenovirus	–	2400	[120]
Gamaleya Res Inst	Russia	Sputnik V	–	Human adenoviruses 5–26	–	300	[121]
		Sputnik light	–	Human adenovirus 26	–	NF	[122]

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Table 1. (continued)

Company	Country	Vaccine name	Produced by	Vector	Adjuvant	Doses (in millions)[a]	Refs
		Sputnik inhalable	–	Human adenovirus 26	–	NF	[98]
Johnson & Johnson	USA	Jcovden[i]	–	Human adenovirus 26	–	300	[123]
Vaccines based on mRNA encoding the spike protein							
BioNTech-Pfizer	Germany/USA	BNT162b2	–	Lipid nanoparticles	–	2400	[124]
		BNT162b2 bivalent BA.1	–	Lipid nanoparticles	–	NF	[125]
		BNT162b2 bivalent BA4-5	–	Lipid nanoparticles	–	NF	[126]
Moderna	USA	mRNA-1273	–	Lipid nanoparticles	–	700	[127]
		mRNA-1273 bivalent BA1	–	Lipid nanoparticles	–	NF	[128]
		mRNA-1273 bivalent BA.4-5	–	Lipid nanoparticles	–	NF	[129]

[a]An approximate indication of the number of doses (in millions) administered worldwide, based on the processing of data from different sources as of September 2022.
[b]A TLR 7/8 ligand (IMDG) adsorbed to aluminum salts (Algel).
[c]NF, data not found.
[d]Microcrystalline polysaccharide particles engineered from delta inulin.
[e]A TLR4 ligand admixed with the 3-*O*-desacyl-4'-monophosphoryl lipid A (MPL) and the QS-21saponin.
[f]A saponin from the bark of the soapbark tree (*Quillaja saponaria*), processed into spherical particles of 40 nm.
[g]Vaccine targeting the spike protein of the Beta variant of SARS-CoV-2.
[h]Made of squalene, DL-α-tocopherol, and polysorbate 80.
[i]A single-dose vaccine.

level [27]. This response was centered on a heterogeneous population of myeloid cells and included transcription factors and components of the IFN response [27]. These results are reminiscent of the response to a conventional influenza virus vaccine [34] which has been associated with epigenetic reprogramming and enhanced resistance to unrelated viruses [34]. Such observations raise the question of whether mRNA vaccines and, in general, COVID-19 vaccines, can elicit trained innate immunity [35]. Exposure to selected pathogens and vaccines can result upon restimulation in an increased potential for effector functions via innate immune cells such as neutrophils and macrophages [35]. Also, epigenetic modifications in myeloid precursors and macrophages underlie training and pathogen agnostic protection conferred by selected vaccines such as bacillus Calmette–Guérin (BCG) [35]. There is evidence that women whose children were vaccinated with oral live polio vaccine were relatively more resistant to developing COVID-19 than a control-matched population [36,37]. Moreover, among healthcare workers, influenza virus vaccination was reported to confer protection against severe COVID-19, as assessed 14 days after vaccination [38]. Finally, in ten healthy volunteers, a single dose of an adenovirus-based SARS-CoV-2 vaccine (ChAdOx1) was associated with an increased number of circulating monocytes 3 months after vaccination relative to baseline; further, *in vitro* evidence of trained immunity for 90 days was shown via the increased production of IL-1β, IL-18, and chemokines relative to that in controls [39]. Thus, it is reasonable to speculate that trained innate immunity may actually occur in the context of SARS-CoV-2 infection, but its occurrence and actual *in vivo* relevance remain to be established, which is also a concern for African countries, as discussed later.

Adaptive immunity and the missing African data

Adaptive immune responses have been investigated in depth using state-of-the-art technology for only a relatively small number of the 30 SARS-CoV-2 vaccines in global use. Several questions specifically related to Africa remain unanswered. These include the comparative relative real-world efficacy of different vaccines, the impact on immunogenicity of infectious diseases

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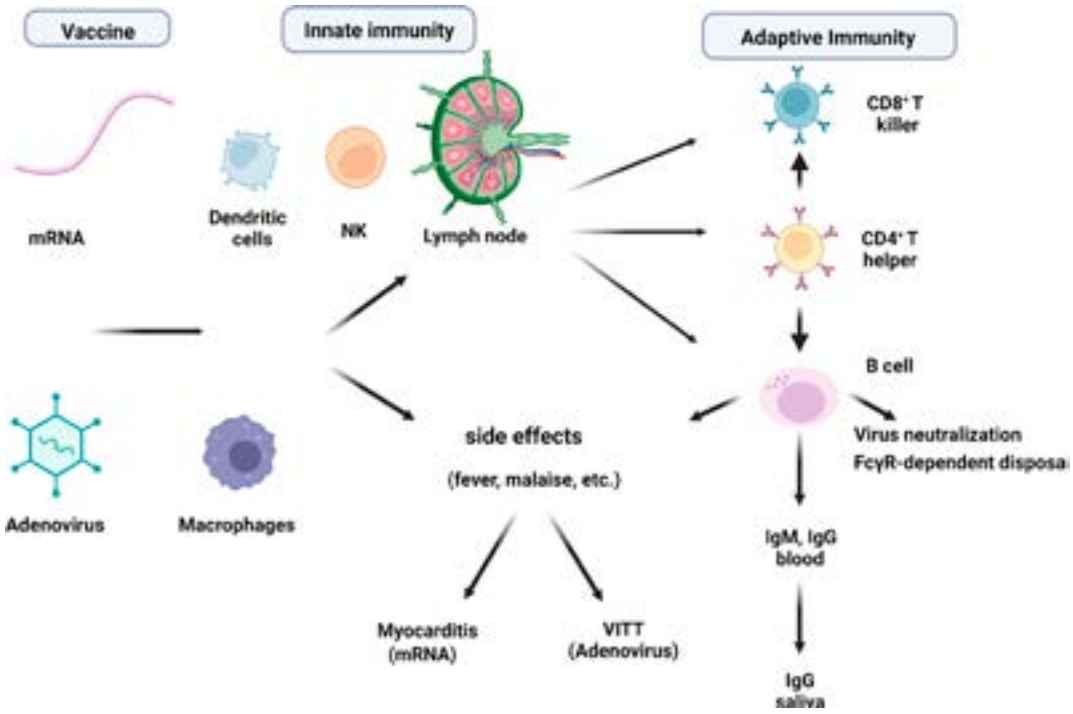

Figure 1. An overview of human immune responses following injection of mRNA and adenovirus-based vaccines. Vaccines activate a complex network of innate immunity cells and mediators which activate adaptive immune responses and mediate reactogenicity (local and systemic inflammatory responses) as indicated by studies in mice, rhesus monkeys, and humans. Saliva is characterized by the presence of blood-derived IgG and low levels of IgA. Myocarditis and vaccine-induced immune thrombocytopenia and thrombosis (VITT) are rare adverse reactions associated with mRNA and adenoviral vaccines, respectively, which are considered to be sustained by autoimmunity and inflammation [7]. This figure was modified from [7] with permission, and created with Biorender.com.

prevalent in Africa, as well as the efficacy and utility of heterologous vaccination in the African scenario. Selected relevant points are discussed here, harnessing recent reviews for a general framework [12,40,41].

Vaccine-elicited antibody and T cell responses exert differential and complementary roles in resistance to infection, severe disease, hospitalization, and death [12,40,41]. Antibodies mediate SARS-CoV-2 virus neutralization by interacting mainly with the receptor binding domain (RBD) of the spike protein and blocking the interaction with the angiotensin-converting enzyme 2 (ACE2) cellular receptor [42]. Moreover, the Fc domain of antibodies have been suggested to contribute to antiviral activity by facilitating the disposal of virus-infected cells [42–44]. In several clinical studies, humoral and cellular immune responses after vaccination with different SARS-CoV-2 vaccines resulted in long-lasting spike-protein-targeted $CD4^+$ and $CD8^+$ T cell responses [41,45–48]; these were comparable to those observed following natural infection with the virus [49,50]. $CD4^+$ and $CD8^+$ T cells mediate direct antiviral function via either the secretion of antiviral cytokines or by killing infected host cells. A rapid vaccine-induced vigorous mobilization of fully functional $CD8^+$ cytotoxic T cells was observed with different SARS-CoV-2-directed vaccines [45]. Also, as the vaccine-elicited antibody response wore off, most $CD4^+$ and $CD8^+$ T cell

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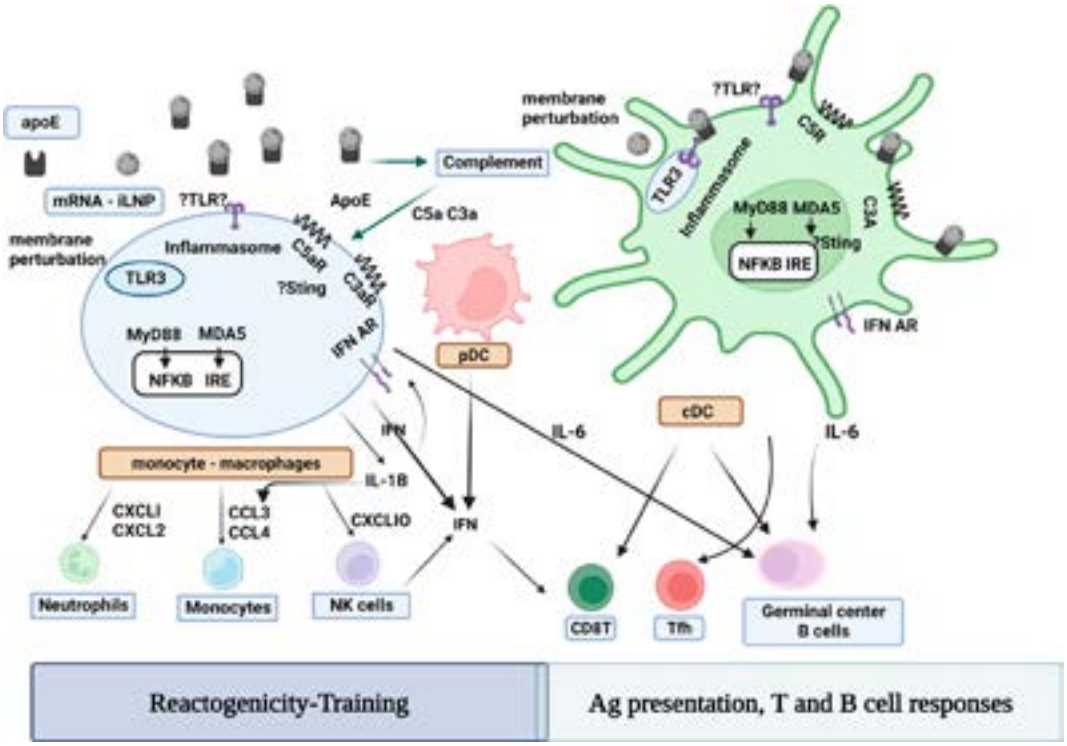

Figure 2. The complex interaction of mRNA/ionizable lipid nanoparticles (iLNPs) vaccines with innate immunity. iLNPs activate an innate immunity network which involves monocytes/macrophages, conventional dendritic cells (cDCc), plasmacytoid dendritic cells (pDCc), and natural killer (NK) cells [24–26]. Cytokines involved in the response to iLNPs include interferons (IFNs), interleukins (ILs) IL-1β, and IL-6 [20–22,24,27]. Innate immunity sensors of mRNA/iLNP complexes include members of the Toll-like receptor (TLR) family, inflammasomes, melanoma differentiation-associated gene 5 (MDA5), and stimulator of interferon genes (STING), based on studies in gene targeted mice and *in vitro* cell cultures. iLNPs are surrounded by a crown of apolipoprotein E (ApoE) and complement components (C5, C3 etc.), which may contribute to activation of myeloid cells and cDCs. iLNPs can also cause membrane perturbation. The actual relative importance and significance of innate sensors remains to be defined. Abbreviations: Ag, antigen; CCL, C-C motif chemokine ligand; CXCL, chemokine (C-X-C motif) ligand; IFN, interferon; IRE, inositol-requiring protein; MyD88, myeloid differentiation primary response 88; NFKB, nuclear factor κB. This figure was created with Biorender.com.

responses were preserved [27,41,47,49–51]. Accordingly, T cells have been credited with playing a key role in the sustained vaccine-mediated protection against hospitalization and death [12].

In early studies of vaccination campaigns in high-income countries, in subjects who had been infected by SARS-CoV-2, a single injection of an mRNA vaccine elicited a strong antibody response similar to a two-vaccination regimen (e.g., [52,53]). These results led to a single-injection policy in ex-COVID-19 subjects in many European countries, with a substantial saving in vaccine doses at a time of limited vaccine availability [54]. However, vaccination coverage in many Sub-Saharan African countries is limited to a single injection[i]. Thus, whether exposure to SARS-CoV-2 or other microbial agents mitigates the limitations of suboptimal vaccination in Africa remains to be defined.

In high-income countries (e.g., the EU and North America) the intensity and duration of vaccine-induced antibody responses have been reported to be markedly affected by age, concomitant

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disease, and/or immunosuppressive therapy [27,55–58]. The available information relates to diseases and conditions prevalent in such countries (e.g., cancer, transplantation, and/or autoimmunity). However, there is a significant lack of knowledge related to how infectious diseases such as malaria and tuberculosis that are prevalent in sub-Saharan Africa affect vaccine immunogenicity.

Major histocompatibility complex (MHC) alleles have been associated with immunogenicity of the adenoviral ChAdOx1 vaccine in a UK cohort [59]. Extending genetic analysis to other geographical contexts and vaccines, including Africa, may shed new light on how genetics impact on the variability of vaccine-elicited immune responses.

The capacity of adjourned vaccines to generate antibodies to both conserved and new epitopes of the spike protein of Omicron variants may be hampered by the 'original antigenic sin' (imprinting), a phenomenon that limits the capacity of a vaccine-imprinted immune system to respond to new variants of a previous antigen, since the reactivation of memory B cells surpasses in speed and size the *de novo* activation of new naive B cells directed towards the new epitopes [60–63]. It has been reported that immune imprinting from a previous infection with SARS-CoV-2 variants, or by vaccinations, markedly shapes the ability of the immune system to respond against Omicron variants [60–63] with a negative effect on antibodies and B and T cell immunity [61]. Although epidemiological evidence in a large cohort in Qatar revealed that previous infection with non-Omicron variants strengthened Omicron-induced protection against the BA-4 and BA-4 prevailing Omicron variants [64], imprinting remains a matter of concern. The occurrence and significance of imprinting in the particular African context remains to be ascertained.

Recent studies have compared in depth T and B cell responses after mRNA, protein (Novavax), and adenovirus vaccines, the latter of which have been widely used in African countries [47,48]. Substantial differences were observed in the strength, clonal distribution, and RBD-specific memory B cell numbers obtained with different regimens of **homologous or heterologous vaccination**, either with two doses of mRNA vaccines, **single- or double-dose adenoviral vaccines** (Ad26.COV.2S and ChAdOx1), or a ChAdOx1/mRNA combination [48]. For instance, two doses (primary and secondary) of mRNA vaccines or heterologous ChAdOx1/mRNA vaccination elicited higher serum antibody titers in 49 individuals than single- or double-dose adenoviral vaccines [48]. Of note, although less potent than mRNA vaccines, ChAdOx1 elicited a subset of memory B cells producing neutralizing antibodies against SARS-CoV-2 variants of concern with distinct properties than those elicited by mRNA vaccines in terms of potency and breadth [48]. These results raise the issue of the potential utility of heterologous vaccination, but the mechanisms responsible for these intriguing observations remain elusive. Considering other types of immunogens, meta-analyses comparing the intensity of the immune response induced by seven COVID-19 vaccines, as measured as neutralizing antibody titers, showed that vaccines based on inactivated viruses elicited less intense and more transient responses than the current vaccines [65]. Similar results were observed in a longitudinal study of antibody responses to seven vaccines (BNT162b2 mRNA, mRNA-1273, Gam-COVID-Vac, Coronavac, ChAdOx1-S, Ad5-nCoV, and Ad26.COV2) in four countries (Mexico, Brazil, Italy, and Argentina), with lower antibody titers detected after immunization with inactivated virus than with the other vaccines [66]. Recently, in the context of a systematic effort, antibodies to the fusion peptide and the stem region of spike were detected only in convalescent individuals and in vaccinated individuals with the inactivated virus, but not with mRNA or adenovirus-based vaccines [67]. This observation is intriguing because mRNA and adenoviral vaccines are generally more potent immunogens [65,66]. These results suggest there may be important differences in the ability of different vaccines – including the adenovirus and whole-virus-based ones in wide use in sub-Saharan Africa – in eliciting

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antibodies to broadly conserved neutralizing epitopes. This is relevant because the breadth of the immune response is a key determinant of resistance to emerging new variants. In general, this also calls for an in-depth comparative dissection of the quality and efficiency of adaptive immune responses elicited by vaccines used in the African continent compared with mRNA and protein vaccines used in high-income countries; indeed, this type of analysis may shed new light on general issues related to vaccine immunogenicity, and genetics, as well as microbial and disease contexts.

Mucosal vaccination

SARS-CoV-2 infection occurs on mucosal surfaces of the nose and throat [12–14]. Mucosal humoral immunity is due mainly to secretory IgA and IgM, which play an important role in neutralizing respiratory viruses by blocking their adhesion to epithelial cells [68,69]. Intramuscular SARS-CoV-2 vaccines do not elicit a mucosal secretory IgA2 response; however, a few vaccine-induced serum IgG and IgA antibodies can reach mucosal surfaces and limit SARS-CoV-2 entry [70]. In saliva and at mucosal surfaces, the titers of vaccine-induced anti-SARS-CoV-2 IgG and IgA are of several orders of magnitude lower than those in sera [70–72]. In patients with a history of COVID-19, higher titers of secretory IgA were detected in saliva than in previously uninfected subjects [72,73]. Furthermore, transudate serum IgA consists of the IgA1 type and is thus more susceptible to bacterial proteases; this is relevant because the presence of commensals may degrade such antibodies. As soon as the elicited immune response decreases, serum antibody titers reaching mucosal surfaces decrease [72], as does protection against infection [12]; by contrast, protection against severe disease that is associated with serum antibodies and T cells persists for over 6 months, as assessed by clinical trials and real-world studies [12,51,74,75].

In preclinical mouse models, intranasal vaccination or boosters with mRNA- or adenovirus-based vaccines against SARS-CoV-2 spike has resulted in mucosal immune responses and protection [76–78]. Even though mucosal vaccines have been approved in some countries (Table 1), there is little evidence as to their clinical effectiveness and the actual induction and duration of elicited mucosal responses. The recent disappointing results obtained with the mucosal formulation of the ChAdOx1 vaccine further underlines the difficulty of eliciting a substantial mucosal response in humans [79]. The four COVID-19 intranasal vaccines approved in China, India, Iran, and Russia (Table 1) are a mucosal formulation of viral-vectored vaccines. These vaccines have been reported only to boost serum antibodies titers [74,75]. Effective mucosal vaccination with its benefits in terms of resistance to infection, reduction of transmission and social acceptability remain the holy grail in the fight against COVID-19. However, in the Sub-Saharan African context, mucosal vaccines may have additional advantages concerning cost and sustainability, as well as facilitated delivery.

A perspective on Africa

Implementing COVID-19 vaccination in Africa poses specific hurdles and challenges in relation to the socioeconomic context, the characteristics of the pandemic, and the available vaccine armamentarium, in addition to the immune response-related questions discussed above (Box 1). Poverty, concurrent debilitating diseases, and weak healthcare systems have raised major concerns about the impact of the pandemic on sub-Saharan Africa. Apparently, these fears were not borne out by the actual impact of the pandemic. Here, COVID-19 is frequently perceived as a disease of elderly white men and not a priority in Africa [80]. As discussed above, trained innate immunity induced by exposure to infectious agents – including other coronaviruses, widespread usage of live vaccines such as BCG and oral polio [35–37], and differences in the microbiome compared to other continents [81] – may have contributed to the relative resistance of African continent to disease, although this is largely speculative. But what is the real COVID-19 picture in Africa (Box 1)? As of 10 August 2022, official data from Africa Communicable Disease Control (ACDC) reported a

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Box 1. COVID-19 vaccination in Africa in a nutshell

- Reported COVID-19 death rate in the African region is 165 per million inhabitants (in Americas and Europe it is approximately 2500), but it may actually be ten times higher.
- Infection fatality rate is 2.7% for young people and 1.7% for older people.
- Seroprevalence is ~65%.
- Trained innate immunity, conferred by microbial exposure and live vaccines (BCG, polio), and/or young age, likely account for the relative resistance of populations in the continent.
- Ten vaccines have been used, with adenovirus-based vaccines accounting for >46%.
- Average vaccination coverage is 22% (73% in high-income countries) with profound variations. Estimates for recall and booster doses are much lower.

total of 12 003 567 cases and 255 180 deaths in the African continent, the majority from the Republic of South Africa [80]. These represent around 2% and 3.9% of all cases and deaths from COVID-19 worldwide, respectively. The reported death rate in the WHO African region is 165 per million compared to over 2500 for the Americas and Europe, and close to 1000 globally [3,82]. Thus, in spite of poverty, debilitating diseases and fragile healthcare systems, Africa has been seemingly characterized by lower infection and mortality rates compared to other regions, the so-called 'COVID-19 African paradox' [80,83–86]. However, the actual total death rate estimated by the Institute of Health Metrics and Evaluation (IHME) is about ten times higher than 165 per million [3]. In fact, new emerging studies indicate that the impact of COVID-19 in Africa is substantial. For example, a recent synthesis of 151 seroprevalence surveys in Africa published between January 2020 and December 2021 revealed that exposure to SARS-CoV-2 moved from 3% in June 2020 to 65% by September 2021 [82,83]. The infection fatality rate in low-income countries, including African ones, appears to be 2.7 times higher for the young and 1.7 times for the elderly [85]. In Zambia, a survey carried out at the morgue of a tertiary hospital in Lusaka reported that around 90% of more than 1000 deceased individuals tested positive for SARS-CoV-2 during the peak waves caused by the Beta and Delta variants [86]. Moreover, in Africa and other low-income countries, perhaps more than elsewhere, COVID-19 has had an indirect negative impact on health, as shown by the disruption of routine immunization programs and increases in deaths from tuberculosis or malaria [3,85]. The pandemic has also had a significant impact on children's wellbeing in terms of health, and multiple material deprivations (for example, education, housing, nutrition, sanitation, and water) [3,85]. After remaining relatively unchanged since 2015, the prevalence of undernourishment jumped from 8% in 2019 to around 9.3% in 2020 and continued to rise in 2021 to around 9.8% [87]. Thus, although the young age of the African population and the microbiome–immune system interactions may have contributed to rendering populations in African countries somewhat more resistant to COVID-19 (e.g., [35–37,81]), the actual impact of the pandemic in this continent should not be underestimated (see also Box 2).

Box 2. SARS-CoV-2 vaccines and long COVID

Post-acute sequelae of SARS-CoV-2 (PASC) or long COVID is a major matter of concern because of its impact on individuals and society. Immune responses to the virus or unrelated viruses and autoimmunity are key components of the pathogenesis of PASC [2]. The impact of vaccination on the development of PASC has been investigated in a limited number of studies. In a large cohort of subjects, with low (<10%) female representation, vaccinated with a single dose of the adenoviral Ad26.CoV2.S or two doses of an mRNA vaccine, only limited protection against PASC after **breakthrough infection** was observed [91]. In a longitudinal study covering Omicron in a hospital population, substantial (approximately 70%) dose-dependent protection was observed [92]. Similar results were obtained in a general population study in Israel [93]. Therefore, these results suggest that optimal vaccination with mRNA vaccines provides substantial protection against long COVID. The duration of protection, its significance in the involvement of different organs, and the impact of vaccines other than the mRNA ones, remain to be defined. The occurrence and relevance of long COVID in the African context has not been assessed. In the perspective of vaccination coverage in Africa, it is noteworthy that a single dose of adenoviral vaccine conferred very limited protection against long COVID [91].

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As of December 2022, while almost 80% of people in high-income countries are vaccinated, only 32% of people in Africa have received at least one vaccine dose, far below the 70% vaccination coverage target of WHO[iii] (Figure 3). More than 60% of the doses arrived in the African continent through COVAX, 12% through the African Vaccine Acquisition Trust (AVAT) initiative launched by the African Union, and for the remaining percentage through bilateral agreements with industry or high-income countries[iii]. Doses received by vaccine type are shown in Figure 4. COVID-19 vaccination programs started in March 2021 in most

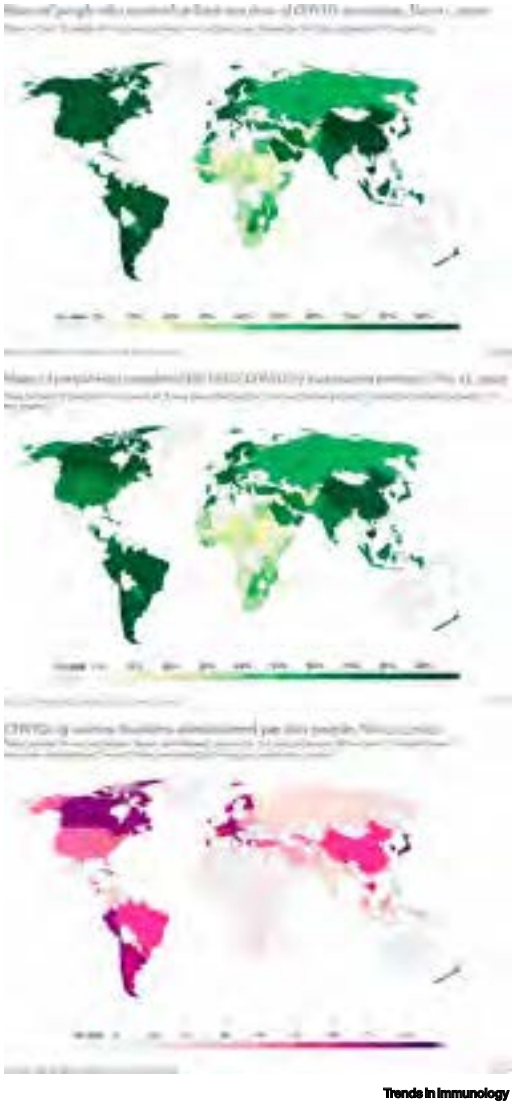

Figure 3. A global view of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine coverage. Upper panel, one dose; middle panel, two doses; lower panel, three doses (source accessed in November 2022[iv]).

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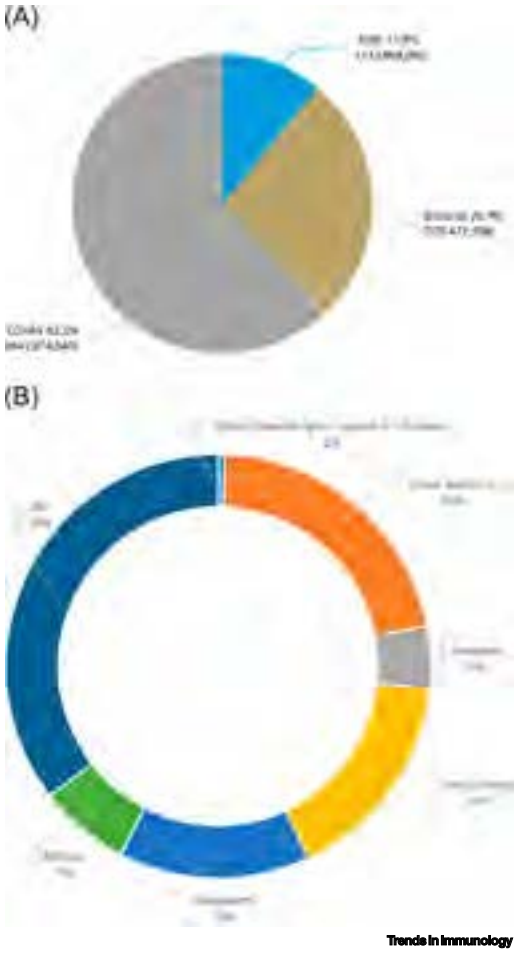

Figure 4. Sources and types of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines used in Africa. Panel A refers to sources and panel B refers to types of vaccines. Data source for the panels: Official Regional Collaborating Centre and Member State Reports[v]. In panel A, the percentage and, in parentheses, the total number of vaccine doses obtained through the COVID-19 Vaccines Global Access Initiative (COVAX), the African Vaccine Acquisition Trust (AVAT), and bilateral agreements are presented. In panel B the percentages of different vaccines used in Africa are presented. Abbreviation: J&J, Johnson and Johnson.

African countries [80], nearly half a year after vaccination had started in higher-income countries, targeting mainly healthcare workers and individuals at higher risk of infection (e.g., [55,56]). While vaccine hoarding by rich countries was an initial cause of delay for deployment of vaccines in African countries [88], currently, country health system capacity challenges and related factors are responsible for poor uptake and coverage, even at a time when global availability has improved [80].

Key constraints include limited training of healthcare workers, inadequate funding, weak planning, poor infrastructure for storage and distribution, public hesitancy, and low acceptance [80], the latter ranging from 15% in Cameroon to 86% in Rwanda [84]. Whereas vaccines may have a high financial cost for many African countries, 60% of the funds needed for successful vaccination

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campaigns is spent on operational costs such as storage, distribution, training of health personnel, personal protective equipment, and other vaccine commodities [80]. Global vaccine availability is becoming less of a problem, but vaccine absorption is now an issue of concern because of these systemic challenges. Moreover, because of the short expiry of vaccines supplied to Africa, seven African countries have been reported to have destroyed about 450 000 doses of COVID-19 vaccine that had passed the expiration date [84].

Countries such as Rwanda and Morocco – which have instituted strong risk communication and community engagement, and have invested in strengthening local health systems capable of reaching more isolated populations – have shown good results with COVID-19 vaccination. However, countries such as Eritrea, South Sudan, and Burundi are still lagging behind [89]. Thus, the landscape of COVID-19 vaccination coverage in Sub-Saharan Africa is diverse, but overall remains dismal; equitable access is an unfulfilled dream.

Concluding remarks

Despite the unprecedented development of effective COVID-19 vaccines, substantial knowledge gaps remain (see Outstanding questions), and more so from the perspective of African countries. These include the impact and significance of trained innate immunity in different geographical contexts, the influence of the microbiome and infectious disease diversity on adaptive immune responses, fundamental mechanisms of immunological memory, as well as the potential of heterologous vaccination in different genetic and socioeconomical contexts. The successful development of effective mucosal vaccines remains a challenge and may have a broad impact, more so in disadvantaged contexts, such as in Africa.

Vaccine inequality encompasses not only production capacity and access to vaccination, but also vaccine-related immunological research. Strengthening the sequencing capacity of SARS-CoV-2 variants in Africa has had a major positive impact in terms of surveillance and understanding dispersal dynamics on the continent [90]. Capacity-building efforts in Africa were initiated by the International Union of Immunological Societies (IUIS) and by the African Federation of Immunological Societies (FAIS)[vi] to strengthen immunology in Africa. Immunological research in Africa may contribute to shedding light on fundamental aspects of SARS-CoV-2 vaccination, including genetics, microbiome, and disease influence on responses, as well as mechanisms and relevance of innate trained immunity.

Outstanding questions

What are the fundamental mechanisms of immunological memory, and can we move from 'wait and see' to predict duration of SARS-CoV-2 vaccination?

What is the hierarchy and significance of innate immunity sensors triggering response to iLNP?

What is the relevance of innate trained immunity for protection against COVID-19 in low-income African countries and for adaptive immune responses to be defined?

What is the real-life relevance of imprinting, particularly in Africa, in association with a distinct microbial milieu?

Can effective SARS-CoV-2 mucosal vaccines be developed?

What is the relevance of genetics, microbiome, pathogen- and vaccine-elicited innate trained immunity, and socioeconomic context on vaccine-elicited immune responses in Africa?

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Declaration of interests

No interests are declared.

Resources

[i] www.who.int/teams/regulation-prequalification/eul/covid-19
[ii] https://ourworldindata.org/coronavirus
[iii] https://ourworldindata.org/
[iv] https://ourworldindata.org/coronavirus
[v] https://africacdc.org/covid-19-vaccination
[vi] https://iuis.org/activities/the-fais-legacy-project/

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Authors
Parotto E., Lamberti-Castronuovo A., Censi V., Valente M., Atzori A., Ragazzoni L.

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EDITED BY
Shusen Sun,
Western New England University,
United States

REVIEWED BY
Raffaele Campisi,
Azienda Ospedaliera Universitaria
Policlinico G. Rodolico-San
Marco, Italy
Claudia Carmassi,
University of Pisa, Italy

*CORRESPONDENCE
Emanuela Parotto
✉ emanuela.parotto@gmail.com

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Exploring Italian healthcare facilities response to COVID-19 pandemic: Lessons learned from the Italian Response to COVID-19 initiative

Emanuela Parotto[1]*, Alessandro Lamberti-Castronuovo[2,3], Veronica Censi[4], Martina Valente[2,3], Andrea Atzori[4] and Luca Ragazzoni[2,3]

[1]Dipartimento di Chirurgia DIDAS, Unità Operativa Complessa (UOC) Istituto Anestesia e Rianimazione, Azienda Ospedale Università, Padova, Italy, [2]CRIMEDIM - Center for Research and Training in Disaster Medicine, Humanitarian Aid and Global Health, Università del Piemonte Orientale, Novara, Italy, [3]Department for Sustainable Development and Ecological Transition, Università del Piemonte Orientale, Vercelli, Italy, [4]Collegio Universitario Aspiranti Medici Missionari (CUAMM)-Doctors With Africa, Padova, Italy

The COVID-19 pandemic exerted an extraordinary pressure on the Italian healthcare system (Sistema Sanitario Nazionale, SSN), determining an unprecedented health crisis. In this context, a multidisciplinary non-governmental initiative called Italian Response to COVID-19 (IRC-19) was implemented from June 2020 to August 2021 to support the Italian health system through multiple activities aimed to mitigate the effects of the pandemic. The objective of this study was to shed light on the role of NGOs in supporting the SSN during the first pandemic wave by specifically exploring: (1) the main challenges experienced by Italian hospitals and out-of-hospital care facilities and (2) the nature and extent of the IRC-19 interventions specifically implemented to support healthcare facilities, to find out if and how such interventions met healthcare facilities' perceived needs at the beginning of the pandemic. We conducted a cross-sectional study using an interviewer administered 32-item questionnaire among 14 Italian healthcare facilities involved in the IRC-19 initiative. Health facilities' main challenges concerned three main areas: healthcare workers, patients, and facilities' structural changes. The IRC-19 initiative contributed to support both hospital and out-of-hospital healthcare facilities by implementing interventions for staff and patients' safety and flow management and interventions focused on the humanization of care. The support from the third sector emerged as an added value that strengthened the Italian response to the COVID-19 pandemic. This is in line with the Health—Emergency and Disaster Risk Management (H-EDRM) precepts, that call for a multisectoral and multidisciplinary collaboration for an effective disaster management.

KEYWORDS

COVID-19 pandemic, Italian's healthcare system, health crisis, response, lessons learned, third sector, H-EDRM

1. Introduction

The SARS-CoV-2 outbreak and the related COVID-19 pandemic have been the worst public health challenge in recent Italian history, placing extraordinary pressure on the country's healthcare and long-term care systems, and on the economy as a whole (1–5). COVID-19 emerged in Italy with major clusters located in northern Italy, mainly around the cities of Codogno, Bergamo and Cremona in the Lombardy region, and around the cities of Vo' and Padua in Veneto region (6) (Figure 1). Subsequently, cases spread across the country with a more sustained transmission in neighboring regions (1). Two months after the beginning of the first COVID-19 wave, the estimated excess deaths in Lombardy, the hardest hit region in the country, reached a peak of more than 23,000 deaths. This is equivalent to an excess mortality of +118% compared to the average mortality rate of the period 1st January-−30th April 2015–2019 (7). In the context of a rapidly evolving pandemic situation, the Italian Health System (Servizio Sanitario Nazionale, SSN) struggled to deal with the surge of COVID-19 patients. The most immediate challenge that the SSN faced during the first wave was the rapid saturation of hospital Intensive Care Units (ICU) capacity (8). The consequences of the spread of the virus were felt also in out-of-hospital facilities, such as nursing homes and community hospitals. Nursing homes represented particularly fragile environments in which protection strategies and training came at a later stage compared to hospitals. Personal Protective Equipment (PPE) and swab tests were in short supply for hospital staff and were even more scarce in long-term-care institutions (9). This resulted in a very rapid spread of the virus: between February, 1st and April, 14th, 2020, ∼40% of deaths in the nursing homes were associated with COVID-19 (9).

Italy developed an array of strategies to contain and mitigate the epidemic. These strategies included case-detection and contact-tracing, isolation and quarantine, physical distancing and mobility restrictions and a massive expansion of health care infrastructure and equipment (8, 10–13). Unfortunately, due to the novel aspects of the COVID-19 pandemic and to the sudden surge of patients, the SSN was unable to mount a unified response to the health crisis. Many Non-Governmental Organizations (NGOs) were mobilized to strengthen Italian healthcare facilities (14–16) and to support vulnerable populations (17, 18). The Italian NGO CUAMM—Doctors with Africa (hereinafter referred to as CUAMM) launched the Italian Response to COVID-19 (IRC-19) initiative, thanks to the support of the United States Agency for International Development (USAID) and the Center for Research and Training in Disaster Medicine, Humanitarian Aid, and Global Health (CRIMEDIM) at the University of Eastern Piedmont (Università del Piemonte Orientale, UPO), Novara, Italy (19) (Figure 2). This initiative had a duration of 14 months (June 2020–August 2021) and aimed at supporting

FIGURE 1
COVID-19 Italian major clusters at the beginning of the first pandemic wave.

the Italian health system through multiple activities across the territory for the prevention and mitigation of the effects of the COVID-19 pandemic (Figure 2). Within the IRC-19 initiative, four main fields of activity were defined: (1) supporting both hospital and out-of-hospital care facilities that had previously contacted the NGO asking for specific interventions to face the first pandemic wave; (2) promoting training initiatives with a focus on Global Health and Disaster Medicine topics; (3) increasing communities' awareness on pandemic-related issues; (4) providing assistance to vulnerable communities, e.g., homeless individuals (Appendix A in Supplementary material).

The objective of this study was to shed light on the role of NGOs in supporting SSN during the first pandemic wave by specifically exploring: (1) the main challenges experienced by Italian hospitals and out-of-hospital care facilities and (2) the nature and extent of the IRC-19 interventions specifically implemented to support healthcare facilities, in order to find out if and how such interventions met the healthcare facilities' perceived needs at the beginning of the pandemic.

2. Methods

We conducted a cross-sectional study using an interviewer-administered 32-item questionnaire (Appendix B in Supplementary material) among 14 Italian healthcare facilities from 5 different Italian regions (Lombardia, Trentino Alto-Adige, Veneto, Emilia-Romagna, Marche) involved in the IRC-19 initiative. The questionnaire was administered online from April 1st to May 31st, 2021, *via* the video conferencing

Parotto et al. 10.3389/fpubh.2022.1016649

FIGURE 2
Italian Response to COVID-19 (IRC-19) initiative: map of interventions performed.

tool Zoom. Two researchers conducted the interviews to collect responses to the questionnaire: one researcher actively asked the questions, and the other took notes throughout the interviews. All interviews were conducted in Italian and targeted people in managerial positions within the healthcare facilities. The average interview time was 30 min. Scientific literature was consulted (20–22) to develop the questionnaire. Such questionnaire (Appendix B in Supplementary material) predominantly relied on the World Health Organization (WHO) Emergency and Disaster Risk Management framework (H-EDRM) (23) and the United States Centers for Disease Control and Prevention (CDC) comprehensive hospital preparedness checklist for COVID-19 (24). The recommendations provided by the H-EDRM and the items selected from the CDC checklist were integrated in order to develop a guide aimed to explore the challenges experienced by the healthcare facilities related to healthcare workers, patients and structural/logistic features. Four different sections were distinguished: (a) general information about the healthcare facility; (b) basic characteristics of the facility; (c) main challenges experienced by the facility at the beginning of the first COVID-19 pandemic wave; (d) interventions implemented through the IRC-19 initiative. Data was collected in each healthcare facility in the period from June 1st, 2020, to April 1st, 2021. Each section included multiple choice questions that were integrated with additional comments provided by participants. Count, frequency, percentage, and mean/median scores were used to report descriptive statistics. The limited sample size and heterogeneity among healthcare centers did not allow to assess any statistical inference. Qualitative thematic analysis was used to analyze the open-ended answers provided by participants to supplement multiple choice questions (25). The qualitative analysis was performed following the Consolidated Criteria for Reporting Qualitative Research (COREQ) (26). Both descriptive statistical and qualitative results were reported as integrated with each other.

Stakeholders were contacted *via* email and information on the study objective, methodology and ethical implications was reported in the email. Written informed consent was obtained by all participants. The study was conducted according to the Declaration of Helsinki guidelines and approved by the Ethics Committee of the A.O.U. "Maggiore della Carità" in Novara (Study Number 015.059).

3. Results

3.1. Characteristics of the healthcare facilities

The 14 healthcare facilities that took part in this study belonged to the following categories: nursing homes ($N = 5$); community hospital ($N = 1$); community for people with addiction problems ($N = 1$); tertiary hospital wards ($N = 5$); field hospital ($N = 1$). Community hospitals are intended as short-term hospitalization facilities aimed to support patients who require low clinical intensity health interventions and who need continuous nursing health care/surveillance that is not available at home. The number of beds for each healthcare facility ranged from 38 to 1,220. The number of hospital admissions per year, reported per hospital ward, ranged from 3,600 to 40,000 (Table 1). The interviewed people were nurses ($N = 7$) and medical doctors ($N = 7$). All of them had managerial roles.

3.2. Main challenges experienced by healthcare facilities

The challenges that Italian healthcare facilities faced during the first COVID-19 wave can be categorized in three main areas: (1) maintaining and supporting healthcare workforce (safety, training, and wellbeing), (2) providing care to patients, and (3) improving the infrastructure of the healthcare facilities (digitization and structural changes) (Table 2; Figure 3).

The challenges that the sudden surge of COVID-19 patients determined in each of the above mentioned sectors (healthcare workforce, patients, and healthcare facilities' infrastructure) are interdependent among each other. As an example, the surge in COVID-19 patients created challenges with HCWs' safety, training, and wellbeing (Figure 3). It also led to specific structural changes in the health facilities to expand existing treatment areas. The subsequent reorganization of spaces within healthcare facilities allowed to implement infection prevention and control measures and a safe management of patients, consequently leading to a redistribution of HCWs themselves within the healthcare facilities.

Most of the respondents (93%) considered safety of HCWs a primary concern. Issues in PPE availability and the lack of hand wash points were reported by 64% and 71% of the facilities, respectively: *"At the beginning of the first pandemic wave we didn't have facial masks, not even surgical ones" (Nursing home, Trentino Alto-Adige); "At the beginning of the first pandemic wave we experienced a shortage of PPE. When we had the first positive patient in our facility, we didn't have adequate PPE to protect ourselves and other patients. Subsequently, the situation improved, but at first the supply was sufficient only for COVID-19 wards and not for all health professionals and patients" (Community hospital, Marche).* Adequate training of HCWs concerning the proper use of PPE and the managing of COVID-19 patients was considered a priority by all respondents in order to ensure safety of the health professionals: *"After receiving the proper training about the virus, we were able to overcome our fears" (Nursing home, Veneto).* Moreover, 86% of the participants underlined the importance of ensuring the

TABLE 1 Healthcare facilities involved in the study.

Region	Province	Health facilities involved	Patients admission capacity	
			Number of beds	Number of hospital admissions/year (2019)
Lombardia	Cremona, CR	Emergency department	-	40,000
	Monza—Brianza, MB	Emergency department	-	40,000
	Milano, MI	Obstetric ward	114	5,300
	Brescia, BS	Pediatric emergency department	-	3,600
	Lecco, LC	Pediatric ward	18	-
Trentino	Trento, TN	Nursing home	38	-
	Trento, TN	Nursing home	60	-
Veneto	Belluno, BL	Nursing home	63	-
Emilia Romagna	Ravenna, RA	Community for people with addiction problems	1,200	-
	Parma, PR	Pediatric emergency department	-	20,000
Marche	Macerata, MC	Community hospital	40	-
	Ancona, AN	Nursing home	54	-
	Ancona, AN	Nursing home	40	-
	Ancona, AN	Field hospital	150	-

TABLE 2 Main challenges reported from different Italian healthcare facilities during the first COVID-19 pandemic wave (PPE, Personal Protective Equipment).

Areas of interest	Main challenges experienced	Specific needs	Number of health facilities ($N_{total} = 14$)	Percentage (%)
Healthcare workers	Safety	PPE supply	9	64
		Hygiene measures	10	71
		Reorganization of spaces	12	86
	Training	Training courses	14	100
	Wellbeing	Psychological wellbeing	12	86
Patients	Safety	Reorganization of spaces	12	86
	Humanization of care	Digitization and reorganization	12	86
Health care facilities	Structural changes	Reorganization of spaces	12	86
	Digitization	Wi-Fi implementation	7	50
		Personal computer purchase	6	43
		Tablets purchase	8	57
		Smartphones purchase	2	14

separation between dirty and clean areas. Alongside physical safety, a vast majority of respondents (86%) reported the need to manage severe psychological stress and to protect health workers' wellbeing as a major priority. The psychological stress was due to the spread of an unknown and severe disease with a high number of victims and to the need of working in unfamiliar environments with new protocols: *"We were worn out and devastated. We have had a lot of deaths among our patients" (Nursing home, Trentino Alto –Adige); "The beginning of the pandemic felt almost like being swept away by an avalanche...At the beginning of the pandemic our pediatric unit was transformed into an adult COVID-19 unit. This change was extremely stressful for our healthcare workers, not used to managing adult patients" (Pediatric Hospital ward, Lombardia); "We were overwhelmed by the emergency and the massive influx of patients... We cried in the wards, in the offices... but we didn't have the time to organize psychological support for our workers" (Hospital, Lombardia).* Protection of patients' safety emerged as a critical challenge

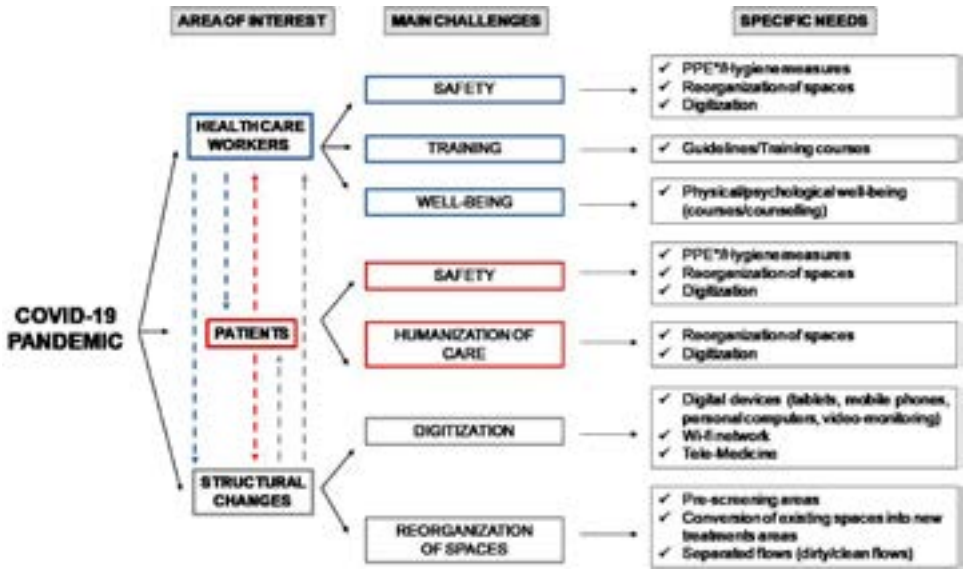

FIGURE 3
Main challenges experienced by both hospitals and out-of-hospital care facilities during the first pandemic wave. The three main areas of interest (healthcare workers, patients and structural changes) showed interdependence among each other. The interdependence is illustrated in the figure with dashed lines. *PPE, Personal Protective Equipment.

in 86% of the health facilities considered. Many participants considered the reorganization of pre-existing spaces through the purchase of specific furnishings (62%) and the installation of automated doors (38%) as fundamental. This was done in order to ensure the separation between dirty and clean areas: *"It was very difficult to guarantee the different dirty/clean paths due to the structural characteristics of our building" (Nursing home, Trentino Alto –Adige)*; *"In our facility we had tight spaces … it was difficult to guarantee community life in safe conditions to our guests" (Nursing home, Veneto)*. In addition, many respondents (69%) underlined the need to develop new structures aimed to guarantee an adequate treatment area both for COVID-19 and non-COVID-19 patients. In order to ensure the best possible treatment to patients, many respondents (86%) considered providing humanized care despite the strict isolation measures imposed by the emergency as necessary (*"our structure is built to foster community life", Nursing home, Trentino Alto–Adige)*. The quick implementation of digital services was considered a major need at the beginning of the first pandemic wave. Many participants regarded the implementation of the Wi-Fi system (50%) and the purchase of digital devices (personal computers, 43%; tablets, 57% and mobile phones, 14%) as fundamental. These initiatives served to improve working conditions and the humanization of care.

3.3. IRC-19 interventions

The interventions implemented within the IRC-19 initiative can be grouped in three main sectors: (1) interventions for patients and staff safety; (2) for the positive/negative flow management of patients/HCWs; (3) for the humanization of care (Table 3).

IRC-19 interventions for patients and staff safety aimed at creating a safer environment for both HCWs and patients, reducing the risk of COVID-19 infection while ensuring the performance of the services and activities (*"Feeling taken into consideration made us stronger and more confident in dealing with the pandemic", Nursing home, Trentino Alto-Adige)*. The interventions performed included assembling temporary infrastructures (29%), purchasing new furniture (43%) and new lockers for HCWs (21%), renovating existing structures with the creation of new spaces (57%), installing new automated doors (21%) and hand wash-points (43%), creating warehouses for the storage of PPE (7%). The IRC-19 initiative contributed to ensuring occupational health and safety strengthening HCWs' training with the realization of two free modular training packages called JUST IN TIME and FIT4CARE, performed in 64% of the health facilities enrolled in this study: *"FIT4CARE course was much appreciated…concerning the issue of health*

TABLE 3 IRC-19 interventions group according to five Italian regions involved in the study (PPE, Personal Protective Equipment).

Region	Safety (health care workers/patients)	Flow management	Humanization of care
Lombardia	• ***Safety*** - Wash points for hands hygiene - Changing rooms for health care workers - Waiting room - External canopy - Workroom with a personal computer station - Radiolucent stretchers, mattresses, washable cushions - Movable dividers to ensure privacy for patients - Maternal and fetal multi-parametric monitors - Video surveillance system in patients' room - Breast pumps - Neonatal heating mats	• ***Structural changes*** - Refurbishment and integration of horizontal and vertical external signs for the access-exit routes - Movable dividers - Automatic doors	• ***Digitization*** - Tablets - Smartphones
Trentino Alto—Adige	• ***Safety*** - Wooden prefabricated where health care workers can wear uniforms and PPE • ***Training*** - JUST IN TIME course • ***Wellbeing*** - FIT4CARE course	• ***Structural changes*** - Automated doors	• ***Structural changes*** - Wooden prefabricated house to schedule visits with relatives - Glazed windows areas to allow interactions between residents and to schedule visits with relatives
Veneto			• ***Structural changes*** - Gazebo to guarantee outdoor activities for residents and meeting with relatives
Emilia—Romagna	• ***Safety*** - Personal computers, tablets, speaker phone, wide-angle webcam, wireless keyboard/mouse to implement information system technology • ***Training*** - JUST IN TIME course • ***Wellbeing*** - FIT4CARE course	• ***Structural changes*** - Plasterboard - Doors - Tents	• ***Digitization*** - Multi-media units to allow telemedicine and virtual meetings between patients and their relatives - Wi-Fi system
Marche	• ***Safety*** - Wash-points for hands hygiene - PPE storage cabinet - Lockers for health care workers with double compartments (clean/dirty) - Wi-Fi to allow data transmission and video calls - Personal computers, tablets, printers, to implement information system technology - Sanitizable chairs - Furniture for the storage of contaminated waste • ***Training*** - JUST IN TIME course • ***Wellbeing*** - FIT4CARE course	• ***Structural changes*** - Automated doors, movable dividers - Cabinet for storage of sanitizing materials - Microwave oven to allow the heating of infusion liquids and drugs - Freezers that allow to eliminate pre-packaged ice packs that occupy large volumes of space - Thermometers that allow to monitor the temperature for the storage of drugs - Furnishing accessories (chairs, tables)	• ***Structural changes*** - Furnished room to allow communication between healthcare workers and relatives • ***Digitization*** - Tablets to allow video calls - Smart TV for living room and for patients isolated in their rooms • ***Others*** - Sanitizable toys for occupational therapy for patients suffering from cognitive impairment

10.3389/fpubh.2022.1016649

professional well-being we didn't receive support from our hospital" (Pediatric ward, Emilia—Romagna).

The IRC-19 interventions for the positive/negative flow management of patients/HCWs aimed at managing the flows of patients, residents, visitors and HCWs entering and leaving the facilities and preventing the spread and contamination of the virus. This was possible thanks to the improvement and re-organization of the entry-exit routes of the facilities (21%), and the purchase of specific furnishings such as movable dividers to guarantee patients' privacy or to perform medical visits in safety (36%).

Many IRC-19 interventions were aimed at ensuring humanized care despite the isolation measures. The interventions performed ranged from the implementation of the Wi-Fi network (50%) to the purchase of mobile phones and tablets (64%): *"Thanks to the IRC-19 initiative we implemented a tele-surveillance system for COVID-19 patients during labor and after delivery" (Obstetric ward, Lombardia)*; *"We received tablets that allowed our COVID-19 patients to communicate with their relatives and to see their newborns in case they were admitted to Neonatal Intensive Care Unit after the delivery" (Obstetric ward, Lombardia).* Moreover, prefabricated buildings (36%) were constructed, where family visits were allowed: "*The family house given by this project represents an important additional value for our institute and our community. It has gathered admiration and positive comments among public opinion and in the media. It gave us the opportunity to react and to leave no one behind" (Nursing home, Trentino Alto-Adige); "Thanks to this project we had the possibility to re-organize our spaces for meetings and social interaction for our residents...Thanks to this project we will be able to open our institute to the community" (Nursing home, Veneto).*

Notably, these interventions promoted the use of telemedicine both for patients and HCWs: *"Thanks to these interventions we have managed to maintain the psychological well-being of our guests. We have managed to carry out the activities that are essential for our community. During the pandemic period we have not observed an increase in dropout rates among our guests" (Community for people with addiction problems, Emilia Romagna).*

4. Discussion

The main needs experienced by different Italian healthcare facilities concerned three main areas: HCWs (safety, training, and wellbeing), patients (safety and humanization of care) and structural changes (reorganization of spaces and digitization). Specific strategies were implemented to meet such needs. Despite the different specificities, it should be noticed that the three main groups mutually interacted (Figure 3), suggesting that they have to be considered all together in planning successful pandemic responses. With regard to the IRC-19 interventions, it is possible to identify three main target areas: interventions targeting staff and patients' safety, interventions targeting patients/health professionals flow management and interventions aimed to ensure humanization of care (Table 3). The entirety of the IRC-19 interventions supported the healthcare facilities involved in this study by promptly addressing the main needs experienced by the healthcare facilities during the first pandemic wave.

The shortage and improper use of PPE, that was mainly seen in out-of-hospital facilities, represented one of the major challenges encountered. This confirms the results of previous studies targeting nursing homes that highlighted not only the shortage of PPE during the first pandemic wave but also the late implementation of response strategies at this level compared to hospitals (27). The need to reshape health services delivery by improving primary and community care provision was already suggested in recent publications as a fundamental strategy to face health pandemic challenges and render communities more resilient (28). Strengthening primary and community care services might contribute to reducing the surge of avoidable hospitalizations for Ambulatory Care Sensitive conditions (ACSCs) that persist in the long term after disasters, as it was shown in a recent literature review (29). Furthermore, the respondents considered adequate training of HCWs as fundamental to guarantee safety and protection and to face the impact of the pandemic, reflecting findings reported in previous studies (30). Concerning HCWs' wellbeing, a relevant challenge identified in this study was the significant psychological stress to which the staff was exposed during the first pandemic wave. Scientific literature has previously documented the negative impact on HCWs' psychological health during the pandemic (24, 25). This is mainly attributable to the increased workload together with the shortage of adequate PPE and the absence of an evidence-based treatment (24, 25). The lack of adequate training (30, 31), the fear of contagion (32) and the management of quickly deteriorating patients (32–34) are additional factors mentioned in the literature.

The COVID-19 pandemic has altered the way patients and families endure illness and death and has emphasized the importance of being culturally prepared to face suffering and death to such a large extent (35–38). In this study, the lack of a "humanized care" was mainly felt in nursing homes and community hospitals, where patients' relational aspects with the community and the outside world are of paramount importance. Similarly, obstetric and pediatric units underlined the need to protect relationships between mothers and children despite the restriction measures.

With regard to the health facilities' structural changes described in this study, several measures were reported as fundamental to guarantee adequate infection prevention and control: (1) the ability for hospitals to retrofit or reallocate parts of their facilities in order to ensure separate emergency

entrances for contagious patients, (2) having patients' pre-screening and treatment areas; (3) having separation between patients, visitors, and staff, based on their level of contagion. These are all measures that need to be considered when defining health facilities' preparedness strategies (39).

In addition to structural changes, the implementation of digitization was reported as a relevant measure both to facilitate relationships between HCWs/patients/caregivers and to allow remote medical consultations. The adoption of telemedicine emerged as a global theme during the COVID-19 pandemic (35–37). In this regard, the Italian Ministry of Health, together with the Ministry for Technology Innovation and Digitization and the WHO, launched an open call to implement telemedicine and monitoring system technologies (40) in the health facilities. However, many Italian hospitals lack adequate infrastructure for effective telemedicine platforms, due to supply-chain breakdown and insufficient internet capabilities (41). The IRC-19 initiative contributed to address these needs providing support with the implementation of digital technologies.

The first IRC-19 intervention area was aimed to guarantee staff and patients safety through structural changes and training strategies. Structural changes included the creation of specific prefabricated buildings, the purchase of specific furniture and devices (automated doors, lockers, wash points for hand hygiene, warehouse for PPE storage) and the renovation of existing structures with the creation of new spaces and the installation of temporary infrastructures. The measures taken were considered as essential by most of the participants in order to establish an adequate Infection Prevention and Control (IPC) system within the healthcare facilities affected by the pandemic crisis.

Training strategies were developed as online teaching learning sessions (OTL) and included the JUST IN TIME and the FIT4CARE courses. The JUST IN TIME course focused on disasters and COVID-19 management principles and offered take-home messages to support healthcare workers struggling with the lack of knowledge and the absence of evidence-based treatments. The FIT4CARE course was aimed to improve healthcare professionals' wellbeing offering feasible and easy-to-apply tools provided by experts in Nutrition, Fitness training and Psychology. It facilitated healthcare workforce in facing the intense physical and mental fatigue experienced during the first pandemic wave.

The second IRC-19 intervention area focused on the appropriate flow-management within the healthcare facilities. It included the purchase of specific furniture (movable dividers and automated doors), the installation of new buildings (gazebos and tents) and the delineation of different clean/dirty pathways. Reorganizing spaces efficiently was considered as a fundamental intervention in most of the healthcare facilities involved in this project due to the fact that it helped to create a safer environment reducing the risk of the contagion and the spread of the virus.

The third IRC-19 intervention concerned the need to ensure humanized care with a patient-centered approach despite social distancing and restrictive safety measures. The possibility to guarantee an appropriate relationship between patients and HCWs and between patients and their families was an important need experienced both in hospital wards and in community hospitals/nursing homes. In hospitals, interventions to guarantee the humanization of care were mainly requested in maternal and obstetric units. The installation of a Wi-Fi monitoring and of a video/audio system for maternal and fetal surveillance in each patient room allowed health professionals to constantly interact with patients during labor and after delivery, reducing movement across different areas. The purchase of tablets ensured the communication in the post-partum period between mothers and their newborns or relatives in case of women with prolonged hospital stay or newborns admitted in Neonatal Intensive Care Unit. The purchase of breast pumps and heating mats were aimed at protecting and maintaining the relationship between mothers and newborns in the COVID-19 maternal unit. In nursing homes maintaining human relations was considered fundamental for the protection of patients' health. The installation of new buildings (e.g., wooden houses and a gazebo with lighting and heating systems) allowed to schedule visits of family members in accordance with safety procedures. Moreover, the implementation of digitization systems (Wi-Fi, personal computers, webcam) helped guests to maintain some contact with their relatives and allowed telemedicine consultations.

The digitization measures adopted thanks to the support of the IRC-19 initiative played an important role in assisting healthcare facilities to face multiple pandemic challenges. The implementation of digital technologies was perceived as fundamental to ensure the continuity of care through remote medical consultations and to support the relationships between patients and family members in spite of the containment measures. Moreover, the possibility to provide medical consultations remotely reduced the risk of contagion both for healthcare professionals and patients contributing to creating a safer environment and to reducing the fear of contagion.

In conclusion, the IRC-19 initiative supported Italian health care facilities in facing the main challenges encountered during the first pandemic wave, stepping in to fill some unmet needs when the SSN was overwhelmed. Recent studies showed that NGOs globally played a significant role when national governments alone couldn't manage to fulfill the needs of the population (42–44), but scientific publications concerning this topic were missing at the time of writing this manuscript. The findings of this study confirmed the results of previous publications that have emphasized the importance of NGOs' role in supporting countries when emergencies and disasters occur (45, 46). The solid working experience with vulnerable and marginalized people in low resource settings, the closer connection with the communities and the adoption of more

flexible bureaucratic processes were identified among the main factors that allow these organizations to respond more quickly to crises (43).

These reflections are closely related to the main foundations reported by the H-EDRM framework (23). The effective management of the challenges that the COVID-19 pandemic posed to the Italian health system required multisectoral and multidisciplinary collaboration to be solved. Recent findings shown that the interconnection of different sectors (e.g., PHC, hospital and third sector) with a decentralized distribution of services to primary and community care was key for overcoming challenges posed by the COVID-19 pandemic (30). Within the context of multisectoral collaboration, strong relationships between healthcare facilities and the third sector represented an irreplaceable strategy to face the pandemic disaster during the first wave.

4.1. Limitations

The main limitations concerned the small sample size and the heterogeneity of the healthcare facilities involved. The small sample size didn't allow to assess any statistical inference concerning quantitative data. Nevertheless, the number of participants interviewed followed the principle of qualitative data saturation in accordance to the Consolidated Criteria for Reporting Qualitative Research (COREQ) (26). The heterogeneity of the sample encompassed both the different patients' admission capacity and the different typology of healthcare facilities involved. Although the absence of an homogeneous population entailed some important limitations, it offered a broader set of perspectives to evaluate the impact of COVID-19 pandemic on the Italian health system.

In addition, we considered health care facilities supported by the same non-governmental project. Hence, other strategies in support of the SSN (i.e., other non-governmental organizations, private sector, and private-public partnerships) were not considered. Further studies are needed to expand the sample and to prove the involvement of the third sector in the health management of disasters.

5. Conclusions

The COVID-19 pandemic has exerted extraordinary pressure on the entire SSN, both on hospitals and out-of-hospital healthcare facilities. The crisis of the first pandemic wave made it difficult for the SSN to homogeneously guarantee an immediate and effective support to all the challenges experienced by the different Italian health care facilities. In this complex context, the IRC-19 initiative represented an instrument to fill this gap, allowing to support and strengthen both hospitals in the frontline against the virus as well as out-of-hospital healthcare facilities that were nevertheless severely hit. The support from the third sector emerged as an added value that strengthened the Italian response to the COVID-19 pandemic disaster.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

EP designed the study and drafted the manuscript. EP and VC conducted the data collection. AL-C, MV, VC, AA, and LR completed and revised the drafted manuscript. All authors have approved the final version of the manuscript for submission.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.1016649/full#supplementary-material

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HIV-HCV Incidence in Low-Wage Agricultural Migrant Workers Living in Ghettos in Apulia Region, Italy: A Multicenter Cross Sectional Study

PAPER

Authors
Totaro V., Patti G., Segala F.V., Laforgia R., Raho L., Falanga C., Schiavone M., Frallonardo L., Panico G.G., Spada V., De Santis L., Pellegrino C., Papagni R., D'Argenio A., Novara R., Marotta C., Laforgia N., Bavaro D.F., Putoto G., Saracino A., Di Gennaro F.

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HIV-HCV Incidence in Low-Wage Agricultural Migrant Workers Living in Ghettos in Apulia Region, Italy: A Multicenter Cross Sectional Study

Valentina Totaro [1,†], Giulia Patti [1,†], Francesco Vladimiro Segala [1,†], Renato Laforgia [2], Lucia Raho [2], Carmine Falanga [3], Marcella Schiavone [2], Luísa Frallonardo [1], Gianfranco Giorgio Panico [1], Vito Spada [1], Laura De Santis [1], Carmen Pellegrino [1], Roberta Papagni [1], Angelo D'Argenio [1], Roberta Novara [1], Claudia Marotta [4], Nicole Laforgia [2], Davide Fiore Bavaro [1], Giovanni Putoto [4], Annalisa Saracino [1] and Francesco Di Gennaro [1,4,*]

[1] Clinic of Infectious Diseases, Department of Precision and Regenerative Medicine and Ionian Area (DiMePRe-J), University of Bari Aldo Moro, 70124 Bari, Italy
[2] Doctors with Africa CUAMM, 70123 Bari, Italy
[3] ANLAIDS Sezione Lombardia, 20124 Milan, Italy
[4] Operational Research Unit, Doctors with Africa CUAMM, 35121 Padua, Italy
* Correspondence: francesco.digennaro1@uniba.it
† These authors contributed equally to this work.

Abstract: Migrant populations are more susceptible to viral hepatitis and HIV due to the epidemiology from their country of origin or their social vulnerability when they arrive in Europe. The aims of the study are to explore the incidence of HIV and HCV in low-wage agricultural migrant workers and their knowledge, attitude, and practice with regard to HIV and HCV, as well as their sexual behaviour and risk factors. As part of the mobile clinic services, we performed a screening campaign for HIV-HCV involving migrants living in three Apulian establishments. Results: Between January 2020 and April 2021, 309 migrants (n. 272, 88% male, mean age 28.5 years) were enrolled in the study. Most of the migrants interviewed (n = 297, 96%) reported a stopover in Libya during their trip to Italy. Only 0.9% (n. 3) of migrants reported having been tested for HCV, while 30.7% (n. 95) reported being tested for HIV. Furthermore, screening tests found four migrants (1.3%) to be HIV positive and nine (2.9%) to be HCV positive. The median knowledge score was 1 (IQR 0-3; maximum score: 6 points) for HCV and 3 (IQR 1-4; maximum score: 7 points) for HIV and low use of condoms was 5% (n. 16), while more than 95% show an attitude score of 5 (IQR 5-6; maximum score:6 points) on HIV-HCV education campaigns. In a multivariate analysis, being male (OR = 1.72; 95% CI 1.28–1.92), being single (OR = 1.63; 95% CI 1.20–2.03), being of low educational status (OR = 2.09; 95% CI 1.29–2.21), living in shantytowns for >12 months (OR = 1.95; 95% CI 1.25–2.55), and originating from the African continent (OR = 1.43; 95% CI 1.28–2.01) are significant predictors of poor knowledge on HCV. Our data show low knowledge, especially of HCV, confirming migrants as a population with a higher risk of infection. To develop education programmes, integrated care and screening among migrants could be an effective strategy, considering the high attitude toward these items shown in our study.

Keywords: migrant; health status; HIV; HCV; ghettos; Italy

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1. Introduction

Despite progress in controlling the spread of infectious diseases, HIV and HCV still represent a major global health problem. In fact, in 2021, there were an estimated 38.4 million HIV-positive individuals worldwide, two thirds of whom lived in the WHO (World Health Organisation) African Region; 1.5 million people contracted HIV, and 650,000 people died from HIV-related causes [1]. Approximately 1.5 million new cases of the hepatitis C virus are reported each year, with an estimated 58 million people worldwide, 3.2 million of

whom are children and adolescents, carrying a chronic infection. According to the WHO, 290,000 people died from hepatitis C in 2019, primarily from cirrhosis and hepatocellular carcinoma (primary liver cancer). The highest burden of HCV disease is in the Eastern Mediterranean and European regions, the South-East Asia region, the Western Pacific region, and the African region [2]. Europe is a major migrant destination, with most migrants from HIV and HCV endemic countries entering the continent through Italy [3]. Based on UNHCR arrival registration data, about 400,000 migrants have arrived in Italy in recent years. There have already been about 70,000 sea arrivals since January 2022 [4]. Once in Italy, these individuals sadly often have a low income, most frequently due to casual day-to-day work, broken family ties, and no fixed address [5]. In Italy, there are 500,000 migrants employed in agriculture. Many of them reside in shantytowns, incorrectly referred to as "ghettos", which are remote from urban centres with poor hygienic conditions and lack access to water, electricity, or health services. The majority of them are from low and middle income countries such as those of sub-Saharan Africa, Eastern Europe and Asia. Their surroundings are miserable. Agricultural workers are a class of exploited employees since there are no laws or protections for them as workers, and their pay is inadequate for the kind of job they do and the hours they work. It is estimated that there are 50–70 shantytowns that host 100,000 migrant laborers [6]. The health of refugees and migrants is influenced by the conditions in their countries of origin, while traveling, and in their host communities. Despite the existence of a universal health care system and legislation providing for the health of migrants, they have limited to no access to basic medical care. These and other sub-optimal health determinants, such as education, income, and housing, compounded by linguistic, cultural, and legal barriers, are causes of poor health outcomes and the spread of infectious disease [7,8]. The majority of migrants are unaware of their HBV, HCV, and HIV status, although they come from endemic countries [5]. Consequently, certain migrant subgroups are more susceptible to viral hepatitis and HIV due to their prior exposure to risk factors owing to the conditions of social marginality in which they live in Italy and Europe; they are also more likely to go undiagnosed than the general population of their host country and they are more likely not to be supported by the healthcare system due to complex social factors, language barriers, social vulnerability or other barriers to their inclusion in the health system [9–11]. These subgroups should thus be informed, screened, and provided with specialised treatment. The primary objectives of the study were to define the incidence of HIV and HCV among migrant agricultural workers, as well as to determine their knowledge, attitudes, behaviors, and risk factors for HIV and HCV.

2. Materials and Methods

2.1. Study Setting, Design and Population

According to a regional programme and local and regional institutions, a cross-sectional, multicenter HIV-HCV screening was conducted from 10 January 2020, to 20 April 2021 in three ghettos in Apulia with HIV/HCV saliva testing. We formed a multidisciplinary team consisting of at least one specialist physician in infectious diseases, a medical resident in infectious diseases from the University of Bari, nurses, a cultural mediator, and a number of volunteers from Doctors with Africa CUAMM, which has been working in the ghettos since 2015 and also provides logistical support.

We included in these three Apulian establishments in our study:

1. The Ghetto Pista in Borgo Mezzanone, in the province of Manfredonia, with an estimated 2500 migrant workers, from Africa and Asian;
2. "Casa Sankara" and "Arena", establishments organized by the Apulia region for the agricultural worker population, which is predominantly from African nations;
3. The Gran Ghetto, located in Rignano Garganico, where an estimated 1000 migrants from African countries lived.

The eligible population comprised all individuals present in these establishments during the study period. In this research, no exclusion criteria were utilized.

Questionnaires

The development of the questionnaire was informed by a literature review and administered through a face-to-face interview conducted by a medical resident in infectious diseases and a nurse, with the support of a cultural and linguistic mediator. It was made of questions divided into four sections: (I) socio-demographic information (age, marital status, education, occupation typology of work contract, documentation to remain in Italy); (II) sexual habits (condom use, smoking habits, etc.); (III) information on HIV-HCV status (previous test if performed); and (IV) survey KAP (knowledge, attitude, and practice), with a 5-point Likert-style scale on HIV and HCV. To guarantee the confidentiality of the data, before to conducting the interview, informed consent was obtained, and the objectives and methods of the study were explained. After obtaining informed consent, an OraQuick rapid antibody test for HIV-1 and HIV-2 and an OraQuick anti-HCV test were performed. The collected data were entered into a dedicated online platform (Kobotool), and a quality control check of the data entry was performed before data analysis.

2.2. Statistical Analysis

A descriptive analysis was performed to define the distribution of the characteristics of the sample, and an $\chi 2$ test (with Fisher's correction if fewer than five cases were present in a cell) was applied for categorical variables. An analysis of determinants of knowledge on HCV was conducted through the construction of multiple logistic regression models. The variable "knowledge on HCV" was collapsed into two levels: a high level of knowledge on HCV was attributed to respondents who provided correct responses to at least three of the six questions included in the knowledge section of the questionnaire, while a low level of knowledge on HCV was defined as those who provided only two correct answers out of six.

Covariates included in the models were: type of educational status (<8 ys vs. >8ys); participants' sex; participants' age; marital status; continent of origin (Asia vs. Africa), whether they had a family doctor, type of work (regular vs. irregular), previous HIV test, previous HCV test, comorbidity, and main area of work (surgical, clinical, non-clinical). Multiple logistic regression models were built. Each variable was examined by univariate analysis using the appropriate statistical test (Student's *t*-test or $\chi 2$ test) and was included in the model when the *p*-value was <0.25. Subsequently, multivariate logistic regression with backward elimination of any variable that did not contribute to the model on the grounds of the likelihood ratio test (cut-off, $p = 0.05$) was performed. Adjusted odds ratios and 95% confidence intervals were calculated. All statistical calculations were performed using Stata v.15.0 (Stata Corp., College Station, TX, USA)

3. Results

Between 10 January 2020, and 20 April 2021, 309 migrants (n = 272, 88% male, mean age 28.5 years, IQR 18-61), residents of the ghettos of the Apulian region (n = 69 in Gran Ghetto, n = 175 in Ghetto Pista, and n = 65 in Casa Sankara), were enrolled in the study. Most of the migrants interviewed (n = 297, 96%) reported a stopover in Libya during their trip to Italy, 77% came from African countries, with an average length of stay in Italy of about 55 months, and a stay in the ghetto of more than 18 months. Only 38% (n =117) had a regular work permit; 29% (n = 89) were family doctors, with roughly 70% (n = 211) having completed more than 8 years of school. Furthermore, previous HIV and HCV tests had been carried out in 30.7% of cases (no. 95) for HIV and in only 0.9% of cases (no. 3) had testing been undertaken for HCV. Other sociodemographic information collected is reported in Table 1.

Table 1. Baseline sociodemographic characteristics of 309 agricultural migrant workers who participated in the KAP (knowledge, attitude and practices) survey and screening for HIV-HCV.

Variables	Frequency (n)	Percentage (%)
	Tot 309	
Gran Ghetto	69	22.3
Ghetto Pista	175	55.6
Casa Sankara	65	22.1
Male	272	88
Age (years) Mean (SD)	28.5	
18–30	166	53.7
31–45	124	40.1
>45	19	6.2
Marital status		
Single	201	65
Married	108	35
Educational status		
<8	98	31.7
>8	211	68.3
BMI		
>30	3	1
25–29.9	15	4.8
18.24.9	180	58.2
<18.5	101	36
Religion		
Muslim	256	82
Christian	54	18
African Continent	239	77.4
Asian Continent	70	22.6
Screening results		
HIV Positivity	4	1.3
HCV positivity	9	2.9
How long in Italy (mean, months)	58.3 (2–150)	-
How long in the ghetto (months)	19.3 (3–109)	-
Length of the travel (from country to Italy	12.2 (7–22)	-
Stopover in Lybia		
Yes	297	96
Do you have a regular contract for work		
yes	117	38
Do you have a family doctor		
Yes	89	29
Previous HIV test?		

Table 1. *Cont.*

Variables	Frequency (n)	Percentage (%)
	Tot 309	
yes	95	30.7
Previous HCV test?		
yes	3	0.9
Comorbidity?		
yes	49	15.8

Knowledge of HIV and HCV is shown in Table 2. The median knowledge score was 1 (IQR 0-3; maximum score: 6 points) for HCV and 3 (IQR 1-4; maximum score: 7 points) for HIV. Five percent (N.15) of the population under examination strongly agree and 10% (N.31) agree that HIV can be transmitted through kissing a person living with HIV. Approximately 50% (195/309) of the population strongly agree that HCV can be transmitted through kissing a person living with HCV, while only 20% (n. 61) agree that HCV is transmitted through unprotected sex, while about forty-one per cent (n. 127) believe HCV causes liver cancer. With regard to HIV, 69% (n. 212) of the population under examination strongly agree/or agree that HIV is transmitted by contamination with infected blood, tattooing, and syringe use, and only 16% (n. 50) believe that, if untreated, HIV could be transmitted from mother to child during birth or pregnancy. The full series of questions and responses are shown in Table 2.

Table 2. HIV-HCV Knowledge.

Questions	Strongly Disagree		Disagree		Neither Agree Nor Disagree		Agree		Strongly Agree	
	HIV	**HCV**	**HIV**	**HCV**	**HIV**	**HCV**	**HIV**	**HCV**	**HIV**	**HCV**
HIV/HCV can be transmitted through kissing a person living with HIV/HCV	77(25)	25(8)	108(35)	37(12)	77(25)	93(30)	31(10)	108(35)	15(5)	46(15)
HIV/HCV is transmitted through unprotected sex	46(15)	90(29)	68(22)	87(28)	31(10)	71(23)	124(40)	46(15)	71(23)	15(5)
With HIV treatment people can live a good quality of life and no longer be infectious/There is a HCV treatment that allows a definitive cure	46(15)	46(15)	77(25)	93(30)	31(10)	124(40)	93(30)	31(10)	62(20)	15(5)
HIV/HCV, if not treated, is transmitted from mother to child during birth	25(8)	62(20)	25(8)	109(35)	31(10)	46(15)	167(54)	71(23)	62(20)	22(7)
HIV/HCV is transmitted by contamination with infected blood, tattooing, syringe use	19(6)	108(35)	31(10)	68(22)	31(10)	71(23)	169(55)	49(16)	59(19)	43(14)
HCV causes liver cancer	65(21)		59 (19)		59(19)		62(20)		65 (21)	
With HIV treatment people can live a good quality of life and no longer be infectious.	31(10)		74(24)		53(17)		86(28)		56(18)	
Median Knowledge score	HIV 3 (IQR 1-4; maximum score: 7 points) HCV 1 (IQR 0-3; maximum score: 6 points)									

With regard to the attitudes towards HIV and HCV, 55% (n. 170) of the population under examination agree and 37% (n. 114) strongly agree with receiving HIV treatment in case of infection; 60% (n. 185) of the population under examination agree and 34% (n. 105) strongly agree with taking HCV treatment. Our study's total population (100%, n. 309) supports education and screening campaigns (considering that 85% (n. 263) agree and 15% (n. 46) strongly agree with HIV education campaigns; and 80% (n. 247) agree and 20% (n. 62) strongly agree with HCV education campaigns; 77% (n. 238) agree and 23%

(n. 71) strongly agree for HIV screening campaigns. Only a very small percentage would avoid relationships with infected people. Table 3 shows all of the questions and responses concerning attitudes towards HIV/.

Table 3. Attitude about HIV and HCV.

Questions	Strongly Disagree		Disagree,		Neither Agree Nor Disagree		Agree		Strongly Agree	
	HIV	HCV	HIV	HCV	HIV	HCV	HIV	HCV	HIV	HCV
I would take HIV/HCV treatment	0 (0)	0(0)	0(0)	3(1)	25(8)	15(5)	170(55)	185(60)	114(37)	105(34)
Will not maintain friendship if a friend with HIV/HCV infection	154(50)	127(41)	124(40)	136(44)	12(4)	31(10)	15(5)	15(5)	3(1)	0(0)
Will not host an individual living with HIV/HCV at home	139(45)	124(40)	71(23)	124(40)	77(25)	46(15)	31(10)	9(3)	21(7)	2(6)
I would be in favour of education compains on HIV/HCV	0(0)	0(0)	0(0)	0(0)	3(1)	0(0)	263(85)	247(80)	46(15)	62(20)
I would be in favour of HIV/HCV screening compains	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	238(77)	263(85)	71(23)	46(15)
Attitude median score	5 (IQR 5-6; maximum score:5 points) on both HIV-HCV education compains									

In practice, only 5% of men (n. 15) always have sex with a condom, and 50% (n. 155) do not recommend the use of condoms during sex. On the other hand, almost 100% of never-used syringes were already used, as showed in Table 4.

Table 4. HIV and HCV Practices.

Questions	Strongly Disagree	Disagree	Neither Agree nor Disagree	Agree	Strongly Agree
I always have sex with a condom	179(58)	37(12)	77(25)	6(2)	9(3)
I never used siringes already used	3(1)	3(1)	6(2)	226(73)	71(23)
I recommend the use of condoms to my friends during sex.	62(20)	93(30)	93(30)	15(5)	15(5)
Sex under influence of drugs or alcohol	185(60)	99(32)	15(5)	6(2)	3(1)
In the last 3 months did you have a dangerous sexual intercourse ?	77(25)	15(5)	124(40)	62(20)	31(10)

In a multivariate analysis, shown in Table 5, being male (OR = 1.72; 95% CI 1.28–1.92), being single (OR = 1.63; 95% CI 1.20–2.03), being of low educational status (OR = 2.09; 95% CI 1.29–2.21), living in the ghettos for >12 months (OR = 1.95; 95% CI 1.25–2.55), and having an African origin (OR = 1.43; 95% CI 1.28–2.01) are significant predictors of poor knowledge of HCV. On the contrary, having regular work (OR = 0.64; 95% CI 0.39–0.83), having a family doctor (OR = 0.24, 95%CI 0.18–0.73), and having performed a previous HIV/HCV test (OR = 0.59; 95% CI 0.10–0.90) are indicative of a low knowledge of HCV.

Table 5. Factors associated with a low knowledge of HCV.

Characteristics	Univariate Analysis OR	Multivariate Analysis Adj-O.R.
Age (1 ys)	1.02 (0.98–1.04)	-
Male	1.51 (1.42–2.02)	1.72 (1.28–1.92)
Educational status < 8	1.80 (1.50–2.00)	2.09 (1.28–2.21)
Single	1.14 (1.08–1.78)	1.63 (1.20–2.03)
BMI > 25	0.34 (0.10–1.10)	1.24 (0.69–1.45)

Table 5. *Cont.*

Characteristics	Univariate Analysis OR	Multivariate Analysis Adj-O.R.
>12 months in the ghetto	1.85 (1.35–2.45)	1.95 (1.25–2.55)
African continent	1.21 (1.13–1.70)	1.43 (1.28–2.01)
have regoular contract for work	0.51 (0.41–1.10)	0.64 (0.39–0.83)
family doctor	0.25 (0.10–0.40)	0.24 (0.18–0.73)
Previous HIV/HCV test performed	0.34 (0.10–1.10)	0.59 (0.10–0.90)

4. Discussion

In this study, we investigated the incidence, knowledge, attitude, and practices about HIV and HCV among migrant agricultural labourers residing in the Apulian ghettos. We found low levels of knowledge, notably regarding HCV, a favourable attitude toward these infections, and poor practices. The majority of migrants interviewed originated from Asia and Africa. Nearly every immigrant who joined was male and young (under 40 years of age), and many of them stated that they had been in the ghetto for roughly a year and a half out of their four years in Italy. A total of 117 migrants (38%) reported having regular employment contracts, whereas only 89 (29%) had a primary care physician. Ninety-five of the questioned migrants (30.7%) had previously been tested for HIV, whereas only three (0.9%) had been tested for HCV. Considering the modes of transmission, the level of knowledge of these diseases is low, particularly for HCV (approximately 30% of the examined population is aware of the mode of transmission, compared to 70% for HIV), and despite only four migrants testing positive, the vast majority did not use condoms during sexual encounters.

In our study, the incidence of HIV infection was 1.3% more than HIV incidence in Italy (0.6%) [12]. In the last decade, Apulia has reported approximately 161 HIV cases per year. In 2020, the incidence was 1.8 cases per 100,000 residents, while in 2019, it was 4.2 cases per 100,000 residents, likely because of the underdiagnosis and/or undernotification related to the COVID-19 pandemic. The highest incidence was found in the 30–39 age group [12], which is about the same age as the participants in our study, who were almost all under 40 years old.

In our country, the percentage of subjects infected with HCV reported by the main studies is about 2% of the general population [13]. In January 2020, it was estimated that there were approximately 30,000 people (an incidence of 0.76%) in the Apulian region with chronic active HCV infection who had not yet been treated with antiviral therapy [14]. The incidence among migrants in our study was higher (2.9%); this reflects evidence in the literature that highlights a higher HCV incidence among migrants than in that of the general population [15]. According to the European Centre for Disease Prevention and Control (ECDC), the risk of HIV infection and associated co-infections, such as HBV, HCV, and tuberculosis, is higher for migrants in the European Union and European Economic Area (EU/EEA). Indeed, in the West, migrants still represent half of all diagnosed individuals (over 47%); in Italy, the number of new diagnoses among migrants comprises about one-third of all new diagnoses in 2017 [16]. Migrant men who have sex with men, heterosexual migrant and ethnic minority men who engage in high-risk behaviors, and migrant women have all been identified as being among the groups most at risk for HIV. Higher HIV incidence among some migrant groups compared to the general population is linked to epidemiological patterns in countries of origin and also to higher exposure in countries of destination due to vulnerability and poor living conditions [17]. Several experiences have demonstrated that there are inequalities in access to healthcare services between migrants and the general population, as well as an increased risk of poor health status among migrants [18]. In addition, individuals may be excluded from the general health-care system due to a language barrier and conditions related to their poor living conditions as a result of their difficulty in finding a work or a regular contract, which impedes their

inclusion in the social and health systems [11,19]. In our survey, only 89 migrants (29%) reported having a family doctor and thus primary access to care. According to the 2017 WHO Global Hepatitis Report, only 20% of HCV infected people are aware of their infection globally [20]. With regard to HIV, the Joint United Nations Programme on HIV/AIDS (UNAIDS)reports that 85% of all people living with HIV knew their status in 2021. In 2021, about 5.9 million people did not know that they were living with HIV [21]. Migrants are less likely to know if they are infected because the health care in their home countries isn't good enough or because they live in remote areas in the country that they move to. However, not knowing about these diseases makes it harder to diagnose and treat them [11,22]. In addition, among the questioned migrants, nearly no one had been tested for HCV. Multiple studies have found a high frequency of this illness among migrants and stressed the susceptibility of travelers in their destination countries and throughout their migration path. Migrants who landed in western Sicily between 2015 and 2017 were provided early testing for the Hepatitis B virus (HBV), Hepatitis C virus (HCV), and human immunodeficiency virus (HIV). The acceptance percentage of 95.9% (2,751 migrants) reflected the favourable attitude revealed in our study. The rate of HCV was 0.9%, but the incidence of HIV was a staggering 2.2%. In particular, HIV infection was more prevalent among women who stayed in Libya for an extended period and were subjected to physical and/or sexual assault, highlighting one of the many reasons why migrants have a higher risk of contracting HIV and other illnesses [23]. Other studies reported a high prevalence of HIV among sub-Saharan African adults who interacted with the native population. Significant numbers were socially, legally, and economically disadvantaged, as seen by their unauthorised status, financial difficulties, and lack of secure housing [24,25], highlighting how living on the margins of society in poor living conditions increases the risk of disease and negative outcomes.

Therefore, it follows that travelling to Europe and living in a marginalised condition in Europe are two situations when there is a greater risk of contracting these infections.

In our study, the majority of migrants (96%) shared a stopover in Libya, and their journey from their country of origin to Italy lasted approximately one year on average. Most of the migrants who tested positive for HBV, HCV, or HIV in southern Italy between March 2019 and February 2020 and were sent to the Fondazione ARCA to register and apply for refugee status or a temporary residential permit were also ones who made the stopover in Libya. In this study, HCV and HIV infections were only found in migrants who had lived in Italy for more than 6–12 months. This could mean that the migrants probably got the infections after they moved to Italy and also that Libya, as suggested by several international organizations, is an indirect factor of violence [3]. Similarly, the migrants we screened have been in Italy for some time (about 4.8 years) and have been living in the ghetto for about 1.6 years on average; their travel from their country of origin to Italy lasted about 1 year on average. This emphasises the significance of ensuring access to prevention for migrant communities.

In line with our results, other surveys found low knowledge of therapy and a good attitude. In spite of having less knowledge regarding the effectiveness of therapy, migrants who took part in a French study were generally well-informed about HIV, but substantially less about hepatitis. Most of the participants did not know that the liver was the affected organ, or that the disease was transmittable by blood. This lack of information may be due to the fact that hepatitis is not considered a "plague" like HIV. Migrants' acceptability of HIV and hepatitis testing was high [26], and other studies in migrants have suggested a high level of acceptability for screening for infectious diseases [27]. According to a German study, there are particular gaps in knowledge of HIV among younger, more recent migrants, those without regular access to the health care system, and those with a lower socio-economic status and a Muslim religion. Less than half of participants reported always using condoms with non-steady sexual partners [28]. The literature identifies a variety of social, economic, cultural, and legal issues that make immigrants and members of ethnic

minorities more vulnerable to HIV infection. High-risk behaviours and limited access to healthcare are linked to increased susceptibility.

In addition, migrant men who have sex with men are an "invisible" group in HIV discussions. This invisibility is thought to contribute to their higher vulnerability to HIV infection. According to UK studies, men from sub-Saharan Africa report high levels of risky sexual behavior, yet they consider HIV prevention initiatives to be largely focused on women and children [29,30].

Dias et al. studied the role of mobility in the assumption of sexual risks and the acquisition of HIV among sub-Saharan African migrants living in two European cities. In this study, the overall percentage of those who had sex without condoms in the study sample was high (68.1%), confirming high levels of risky sexual behaviour among migrant populations. The specific risk factors associated with sex without condoms included being female, being over 30, traveling, having had the last sexual encounter with a regular partner, never having been tested for HIV, and having a non-reactive test result in the study. More than half of the travelers reported concurrency, i.e., having a regular partner in the host country while having other sexual partners abroad [31]. In addition to the high incidence of these infections among the migrant population and the gaps in linkage to care, there are several other reasons why this subgroup must be screened for viral hepatitis and HIV. Regarding HCV infection, it is known that chronic viral hepatitis has a protracted asymptomatic course during which infected persons are ignorant of their infection, up until the severe illness stage [32,33]. Each year, approximately 1.3 million deaths are caused by viral hepatitis, primarily due to chronic liver disease and its consequences [33]. Oral direct-acting antiviral (DAA) therapy for 8 to 12 weeks can easily eradicate HCV infection while lowering the risk of developing hepatocellular carcinoma and the progression to liver cirrhosis [34,35]. Considering that most of the mortality and medical costs were attributable to advanced liver disease, the early diagnosis and treatment of HCV are a very important issue for promoting public health.

Consequently, these categories must be addressed if viral hepatitis is to be eradicated in the European Economic Area or worldwide [11,36]. The World Health Organization has developed a set of goals for hepatitis elimination which include a 65% reduction in HCV-related deaths and a 90% reduction in HCV incidence by 2030 [37].

Furthermore, late HIV diagnosis is associated with an increased risk of morbidity and mortality, and may reduce the response to treatment; moreover, those who are diagnosed late are likely to utilise more healthcare resources; finally, late presentation increases the probability of transmission. Late presenters have a lower perceived risk of infection, are not routinely offered HIV testing, and are frequently from marginalised groups [38,39].

Twenty years of research demonstrate that HIV therapy is very efficient in preventing HIV transmission and that HIV-positive individuals with undetectable viral loads cannot transfer the virus sexually [40].

With the increased availability of antiretroviral medication (ART), worldwide and regional policies and guidelines emphasise the individual and public health advantages of HIV testing. In addition, they emphasise the need for early HIV detection and the link between testing and treatment, care, and support. However, not all nations, including those that recognise the heightened HIV risk of migratory communities, have clear HIV testing guidelines for these people [41]. There is evidence in the literature that HIV-HCV testing strategies in migrant populations are effective, including in terms of cost, identifying strategic advantages in rapid counselling and rapid testing [42,43], which could also be extended to education and prevention programmes for other sexually transmitted diseases.

We recognize that there are some limitations in our study: first of all, the small sample may not be representative of the entire ghetto population, but the difficulty of reaching this population nevertheless makes the data very interesting. Furthermore, the questionnaire used for the survey is not a validated questionnaire [44,45], but is in any case the result of a literature review.

5. Conclusions

Our findings show that agricultural migrant workers have a higher incidence of both HIV and HCV than the native population, as well as a lack of knowledge about both viruses, particularly HCV. We do not know whether the higher incidence of infection stems from the epidemiology of the countries of origin or whether infections contracted in Italy are also related to poor living conditions. The high willingness to participate in awareness-raising and screening programmes shown by migrants is a key element to being able to implement educational, screening, and prevention programs, and enable a greater diffusion of correct lifestyles. Of course, correct lifestyles cannot be detached from the environment in which people live. If this population lives in shanty towns/ghettos far from inhabited centers, isolated without water or sanitation (not by choice, but because they are exploited by the agromafia phenomenon), it is difficult to talk about lifestyles. It is unthinkable that people in Europe will be living in such exploitative conditions in 2023. It is urgent that a coordinated action between NGOs, politicians, universities, and volunteers is essential to highlight the issue of ghettos and their extremely poor living conditions and to take the most effective action possible to get those living in them out, as well as to ensure that such settlements no longer exist in a world that wants to truly call itself civilised.

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PAPER

Authors
Trifirò S., Cavallin F., Mangi S., Mhaluka L., Maffoni S., Taddei S., Putoto G., Torelli G.F.

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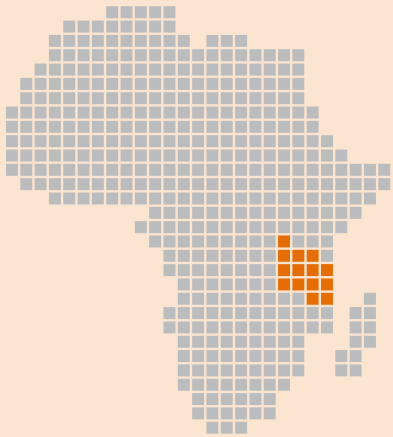

Hypertension in people living with HIV on combined antiretroviral therapy in rural Tanzania

Silvia Trifirò[1,2], Francesco Cavallin[3], Sabina Mangi[4], Lawrence Mhaluka[4], Silvia Maffoni[1,5], Stefano Taddei[6], Giovanni Putoto[7], Giovanni F Torelli[8,9]

1. Doctors with Africa CUAMM, Iringa, Tanzania.
2. Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy.
3. Independent statistician, Solagna, Italy.
4. Tosamaganga Council Designated Hospital, Iringa, Tanzania.
5. University of Pavia, Italy.
6. University of Pisa, Italy.
7. Doctors with Africa CUAMM, Padua, Italy.
8. Doctors with Africa CUAMM, Dar Es Salaam, Tanzania.
9. Policlinico Umberto I, Rome, Italy.

Abstract

Exposure to anti-retroviral therapy in HIV infection has been associated with hypertension, but whether and to what extent HIV-related factors and anti-retroviral treatment contribute to hypertension is not well defined; in addition, data are particularly scarce in Sub-Saharan Africa.

Aim of the study was to investigate prevalence and awareness of hypertension in a cohort of people living with HIV (PLWHIV) on anti-retroviral therapy in rural Tanzania, and to identify possible predictors of hypertension.

A cross-sectional study on hypertension in PLWHIV was conducted at Tosamaganga District Hospital, Iringa Region, Tanzania. Subjects on anti-retroviral therapy, age 26-80 years and with monthly attendance to the HIV clinic, were considered eligible.

A total number of 242 patients were included in the analysis. Sixty-two subjects (26%) had hypertension, the majority (77%) of them not aware of the condition and/or not on treatment. Older age, higher BMI and lower baseline T-CD4 count were predictors of hypertension at multivariate analysis. The results of the study suggest that hypertension screening should become part of ordinary care of PLWHIV in Tanzania, particularly in subjects with more severe immunosuppression. Leveraging already existing HIV services could be an option to prevent the burden of non-AIDS complication and related deaths.

Keywords: HIV; Hypertension; sub-Saharan Africa.

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Introduction

HIV infection is one of the major global public health concerns, with around 38 million people estimated to be HIV positive in 2018, of whom around two thirds living and aging in Sub-Saharan Africa (SSA) [1]. The increasing use of combined anti-retroviral therapy (cART) has shifted the course of the infection to a chronic condition, substantially increasing the survival of people living with HIV (PLWHIV) and posing the new challenge of non-AIDS-related chronic diseases, such as cardiovascular diseases (CVDs) and other chronic non communicable diseases (NCDs) [2-4]. These conditions generally occur due to aging and to the nutrition transition that SSA countries are facing, together with demographic, urban and economic development, leading to a shift of the nutritional status from predominant undernourishment to higher rates of overweight and obesity [5].

Overall, these factors represent additional and long-term burdens for fragile health care services in low-resource settings, historically oriented toward reproductive health and acute communicable diseases [6].

Corresponding author:
Giovanni F Torelli,
Doctors with Africa CUAMM, Dar es Salaam, Tanzania.
E-mail: g.torelli@cuamm.org

PLWHIV have been demonstrated to be at high risk of CVDs [7-9], and hypertension represents an important cardiovascular risk factor in these patients [1]. HIV and cART are associated with CVDs in several pathophysiological pathways. HIV infection per se has been demonstrated to accelerate inflammatory processes known to promote atherosclerosis and hypertension, such as endothelial dysfunction and thrombosis [11]. Exposure to cART has been associated with hypertension [12] and patients receiving cART, especially those based on protease-inhibitors (PI), seem more prone to develop overweight, obesity and metabolic derangements, providing a metabolic profile at increased risk of hypertension [13]. In addition, well-known risk factors for hypertension, such as smoking, alcohol intake and physical inactivity, are frequently reported in PLWHIV [14]. On the whole, PLWHIV on cART seem a category at higher risk for hypertension, when compared both to the general population and to cART naïve subjects [14]. However, epidemiological data regarding hypertension among PLWHIV in SSA are scarce [15]. Furthermore, whether and to what extent HIV-related factors and cART contribute to hypertension is not well-defined, with contradictory and often inconsistent data. Besides, vertical international programs on HIV and AIDS do not always focus on NCDs in low-resources setting.

The aim of this study was to investigate prevalence and awareness of hypertension in a cohort of PLWHIV on cART in rural Tanzania, and to identify possible predictors of hypertension among clinically relevant factors.

Materials and methods

Study design

This was a retrospective cross-sectional study on hypertension in PLWHIV attending the local HIV clinic at Tosamaganga Hospital, Tanzania from November 2017 to February 2018. The study was conducted according to Helsinki Declaration principles, and approved by the Hospital Management Team, who waived the need for patient written consents, given the retrospective nature of the study and the use of anonymized data.

Setting

The study was conducted at the HIV clinic of Tosamaganga Hospital in the Iringa District Centre, Tanzania. Tosamaganga Hospital is a district designated hospital located in a rural area in South-western Tanzania and serves approximately 260,000 people. Tosamaganga Hospital has a capacity of 164 beds and an outpatient area that includes general ambulatory services and the HIV clinic. HIV prevalence rates varies largely across the country and, while a relatively low HIV prevalence is observed in some areas of Northern Tanzania, particularly high rates of infection are reported in the South, up to 11.3% in Iringa region.

Institutional background

Doctors with Africa CUAMM (Collegio Universitario Aspiranti Medici Missionari) is an Italian Non-Governmental Organization (NGO) which has been supporting health service delivery in Africa for 70 years [16]. CUAMM started working in Tanzania in 1968, in support of not-for-profit facilities in Njombe region, and has now widened its activities to 6 regions, currently working in 105 health centers and two hospitals across the country. CUAMM has been supporting Tosamaganga Hospital since 1988.

Patients

PLWHIV attending the HIV clinic for clinical follow up and for monthly dispensation of cART from November 2017 to February 2018 were retrospectively evaluated for inclusion in the study. PLWHIV, aged between 26 and 80 years were eligible for inclusion. Exclusion criteria were pregnancy, lactation or unavailability of variables of interest.

Variables

Demographical data, social information and past medical history were retrieved from hospital records. Biometric data, blood pressure and capillary blood glucose were also collected from recorded data. Hypertension was defined as a clinical diagnosis with blood pressure (BP) ≥ 140/90 mmHg, as defined by WHO [17]. Blood pressure was taken using a manual sphygmomanometer. Height was taken with a portable stadiometer, in centimetres. Weight was taken with an analogic weighting scale. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m^2) and categorized using the standardized definition of the WHO: <18.5 kg/m^2 as underweight, 18.5–24.9 kg/m^2 as normal weight, 25.0–29.9 kg/m^2 as overweight; and >30 kg/m^2 as obesity [18]. Waist circumference measurements were done with a tape at the approximate midpoint between the lower margin of the last palpable rib and the top of the iliac crest as per WHO guidelines. Central obesity was defined as waist cir-

cumference > 88 cm for females, >102 cm for males [19]. Diabetes was diagnosed with fasting glucose ≥ 126 mg/dl and/or random blood glucose ≥ 200 mg/dl, as per WHO definitions [20].

Statistical analysis

Continuous variables were summarized as median and interquartile range, and categorical variables as number and percentage. Association between categorical variables was evaluated using Fisher's test or Chi Square test. Association between binary variables and continuous variables was evaluated using Mann-Whitney test. A logistic regression model was estimated to identify the independent predictors of hypertension among clinically relevant factors. Some variables of interest were not included in the model due to small occurrence (diabetes, cardiac disease and family history for hypertension), while duration of HIV infection and duration of cART were not included due to high collinearity with age.

Initial model included age, BMI, waist circumference, WHO stage and T-CD4 cells count at diagnosis. Model selection was performed by minimizing the Akaike information criterion (AIC): waist circumference and WHO stage at diagnosis were removed from the model due to inflation of AIC. Model performance was evaluated with internal validation (c-index) and calibration (calibration-in-the-large and calibration slope) using bootstrap methods and showed moderate validation (c-index 0.738) and good calibration (calibration-in-the-large -0.018 and calibration slope 1.015).

All tests were 2-sided and a p-value less than 0.05 was considered statistically significant. Data analysis was performed using and R 3.5 (R Foundation for Statistical Computing, Vienna, Austria) [21].

Results

A total number of 360 patients attended the HIV clinic November 2017 to February 2018. One hundred eighteen patients were excluded from the analysis (six did not meet age criteria and 112 had no information on blood pressure).

Finally, 242 patients (median age 43 years, IQR 38-50; 98 males and 146 females) were included in the analysis. Patients' characteristics are shown in Table 1.

Sixty-two patients (25.6%) had hypertension and 48 of them (77%) were not aware of the condition and/or were not on treatment. Ten subjects (4.2%) had diabetes. Thirty-five patients (14.8%) were overweight, 10 (4.2%) were obese and 19 patients (7.9%) had central obesity.

Hypertension was associated with older age ($p<0.0001$), previous history of cardiac disease ($p=0.0002$), diabetes ($p=0.004$), family history for hypertension ($p=0.003$), higher BMI ($p=0.002$) and larger waist circumference ($p=0.003$) (Table 1).

Table 1: Patient characteristics

Variables	All patients	No hypertension	Hypertension	p-value
N of subjects	242	180	62	-
Age, years [a]	43 (38-50)	42 (37-50)	49 (42-57)	<0.0001
Male: Female (%)	96:146 (40:60)	70:110 (39:61)	26:36 (42:58)	0.78
Education level: None Primary Secondary or above	 25 (10.3) 198 (81.8) 19 (7.9)	 16 (8.9) 151 (83.9) 13 (7.2)	 9 (14.5) 47 (75.8) 6 (9.7)	0.34
Farmers	222 (91.7)	164 (91.1)	58 (93.5)	0.74
Personal insurance holders	17 (7.0)	9 (5.0)	8 (12.9)	0.07
Tobacco smoking: No Former Current	 204 (84.2) 14 (5.8) 24 (10.0)	 153 (85.0) 9 (5.0) 18 (10.0)	 51 (82.2) 5 (8.1) 6 (9.7)	0.67
Alcohol intake: No Former Current	 144 (59.5) 55 (22.7) 43 (17.8)	 109 (60.6) 38 (21.1) 33 (18.3)	 35 (56.5) 17 (27.4) 10 (16.1)	0.59
History of stroke	3 (1.2)	1 (0.6)	2 (3.2)	0.10
History of cardiac disease	8 (3.3)	1 (0.6)	7 (11.3)	0.0002
Fasting BG, mg/dl [a]	92 (83-99)	91 (82-98)	93 (86-106)	0.07
Random BG, mg/dl [a]	91 (85-99)	90 (84-98)	95 (88-99)	0.14
Diabetes [b]	10 (4.2)	3 (1.7)	7 (11.3)	0.004
Family history of hypertension	17 (7.0)	7 (3.9)	10 (16.1)	0.003
BMI, kg/m^2 [ac]	21.6 (19.8-24.3)	21.3 (19.6-23.8)	23.3 (20.5-27.0)	0.002
BMI categories, kg/m^2 [c] < 18.5 18.5-24.9 25.0-29.9 >30	 26 (11.0) 166 (70.0) 35 (14.8) 10 (4.2)	 19 (10.7) 135 (76.3) 20 (11.3) 3 (1.7)	 7 (11.7) 31 (51.7) 15 (25.0) 7 (11.7)	0.0002
Waist circumference, cm [ad]	78 (73-85)	78 (73-83)	83 (75-94)	0.003
Central obesity	19 (7.9)	9 (5.0)	10 (16.1)	0.01

Legend: Data expressed as No. (%) or [a] median (IQR). Fasting and random blood glucose (BG) were available in 158 and 86 patients, respectively. Data not available in [b]3, [c]5, [d]8 patients.

Median known duration of HIV infection was 6 years (IQR 3-9 years) and median duration of cART was 5 years (IQR 2-8). Information on HIV infection and cART history is reported in Table 2. Overall, cART was started at median 76 days (IQR 20-278) after HIV diagnosis.

All the patients were on cART. The majority of patients were receiving a first line regimen (79.2%) and the most common cART combination was not PI-based (91.9%) vs PI-based (17.1%). The single tablet, co-formulated combination of tenofovir disoproxil fumarate (TDF), lamivu-

dine (3TC) and efavirenz (EFV) was the most common regimen (60%), followed by the single tablet containing TDF, emtricitabine (FTC) and EFV (14%). Lopinavir/ritonavir (LPV/r) was the most prescribed PI (6.2%).
Median T-CD4 cells count increased from 213 cells/µl (IQR 113-314) at diagnosis (baseline T-CD4 cells count) to 518 cells/µl (IQR 382-730) at the last visit (p<0.0001). Hypertension was associated with more advanced WHO clinical stage at diagnosis (p=0.04), longer duration of HIV infection (p=0.04) and longer exposure to cART (p=0.009) (Table 2). Hypertension was also associated with lower baseline T-CD4 cells count (p=0.01) but neither with T-CD4 cells count at last visit (p=0.53) nor with PI use (Table 2).

Table 2: HIV infection and cART history

Variables	All patients	No hypertension	Hypertension	p-value
N of patients	242	180	62	-
Known duration of HIV infection, years [ab]	6 (3-9)	6 (3-9)	8 (3-10)	0.04
WHO clinical stage at diagnosis: [c]				0.04
I	44 (21.1)	40 (25.8)	4 (7.5)	
II	41 (19.7)	30 (19.4)	11 (20.8)	
III	92 (44.3)	63 (40.6)	29 (54.7)	
IV	31 (14.9)	22 (14.2)	9 (17.0)	
T-CD4, cells/µl [a]				
At diagnosis [d]	213 (113-314)	219 (123-329)	153 (65-279)	0.01
At last visit [e]	518 (382-730)	509 (382-745)	546 (378-663)	0.53
cART start after diagnosis, days [af]	76 (20-278)	79 (21-294)	54 (15-212)	0.43
Duration of cART, years [ag]	5 (2-8)	4 (2-8)	7 (3-9)	0.009
Number of cART lines, [h]				0.58
1 line	187 (79.2)	142 (81.1)	45 (73.8)	
2 lines	34 (14.4)	23 (13.1)	11 (18.0)	
3 lines	12 (5.1)	8 (4.6)	4 (6.6)	
4 lines	3 (1.3)	2 (1.1)	1 (1.6)	
cART [h]				0.99
Not PI-based	217 (91.9)	161 (92.0)	56 (91.8)	
PI-based	19 (0.1)	14 (8.0)	5 (8.2)	

Legend: Data expressed as No. (%) or [a] median (IQR). Data not available in [b]7, [c]34, [d]28, [e]25, [f]11, [g]9, [h]6 patients.

Multivariable analysis of hypertension was performed using a logistic regression model. Older age (OR 1.06, 95% CI 1.02 to 1.10) and higher BMI (OR 1.15, 95% CI 1.06 to 1.25) were associated with increased odds of hypertension, while higher T-CD4 cells count at diagnosis (OR 0.73, 95% CI 0.56 to 0.92) was associated with decreased odds of hypertension (Table 3).

Table 3: Multivariable analysis of hypertension

Variables	p-value	OR (95% CI)
Age, years	0.001	1.06 (1.02 to 1.10)
BMI, kg/m^2	0.002	1.15 (1.06 to 1.25)
T-CD4 at diagnosis, x100 cells/µl	0.01	0.73 (0.56 to 0.92)

Discussion

Our findings showed a considerable prevalence of hypertension, with high rate of unawareness, in a cohort of PLWHIV on cART in rural Tanzania. Hypertension prevalence in our study was high and comparable to available data in SSA ranging from 16% to 30% according to the study region [22-26]. The rate of hypertension unawareness was similar to data in literature as well, underlying the high burden of asymptomatic and untreated hypertension in PLWHIV in Tanzania.

Older age, higher BMI and lower baseline T-CD4 cells count were associated with increased likelihood of hypertension at multivariable analysis. Longer duration of HIV infection and longer exposure to cART might also be associated with hypertension, but multicollinearity of these parameters with age prevented any definitive conclusions. Well-known traditional cardiovascular risk factors such as older age and higher BMI were identified as independent risk factors for hypertension, same as observed in HIV-negative people.

Furthermore, lower baseline T-CD4 cells count, were found associated with hypertension, in agreement with findings of some previous studies [27-30]. On the whole, low-grade chronic inflammation, deriving both from overweight with excess in visceral adipose tissue and long-standing HIV infection, could take part in the inflammatory processes that lead to hypertension, as reported in literature [31]. The specific mechanism of interaction between HIV infection and hypertension seems chronic immune activation, which is recognized to be pro-inflammatory and pro-atherosclerotic and the basis of T-CD4 depletion. Thus, T-CD4 depletion could represent the epiphenomenon of chronic processes that lead to both to immunosuppression and hypertension [32].
This hypothesis is contradictory with some other studies reported in literature [33-34] but similar findings from large multinational cohorts of PLWHIV on cART corroborate the hypothesis that low T-CD4 cells count are a HIV-related predictor of hypertension [35].

Our findings support an inverse relationship between baseline T-CD4 cells count and hypertension [27-30], and suggest a possible association between blood pressure and duration of HIV infection and length of cART exposure. Older patients and/or patients with overweight, long standing HIV infection or low T-CD4 levels should be particularly targeted for frequent blood pressure monitoring and the identification of other cardiovascular risk factors to encourage lifestyle modification and early treatment.
The study has some limitations. First, it is a single-center study in rural Sub-Saharan Africa, thus the generalizability of the findings is limited to similar settings. Second, the retrospective data collection limits the possibility of analysing follow-up data. Furthermore, the majority of subjects were exposed to a single cART (tenofovir, efavirenz and lamivudine), which is not frequently associated to cardio-metabolic risk, and none of them was cART naïve, thus limiting any comparisons of effects of cART per se or alternative cART not in use in Tosamaganga on blood pressure. Finally, the scarce availability of diagnostic resources at Tosamaganga Hospital could have hampered the possibility to diagnose other NCDs, such as cardiovascular diseases, diabetes, kidney diseases and dyslipidemias, and its relationship with HIV infection and immunosuppression.

Our findings could aid governmental and international health care actors in the assessment of services requiring support and implementation at regional level in Tanzania, such as active screening for hypertension and dedicated treatment programs among PLWHIV living in Iringa region. This is even more important when considering the significantly higher prevalence of HIV infection in Iringa region as compared to national data.
Aging and exposure to cART are likely to configure among PLWHIV chronic health care needs than overlap to the ones of general population, and leveraging HIV clinics for NCDs could be an option to face the double burden of NCDs and HIV in Tanzania [36]. Ordinary HIV follow-up could be an opportunity for screening, counseling and managing hypertension and the other non-infectious comorbidities found in our cohort of PLWHIV on cART, such as overweight. An adequate management of weight and eating habits could therefore prevent or contribute at reducing the increase in BP in these subjects, thus reducing the cardio-metabolic burden and related complications.
On the whole, we believe in a comprehensive approach to the chronic care of HIV subjects on cART. Vertical projects aiming exclusively at HIV care may miss critical aspects to improve overall health of PLWHIV on cART in Tanzania, such as hypertension and excessive body weight.

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Priority age targets for COVID-19 vaccination in Ethiopia under limited vaccine supply

PAPER

Authors
Galli M., Zardini A., Gamshie W.N., Santini S., Tsegaye A., Trentini F., Marziano V., Guzzetta G., Manica M., Manenti F., Ajelli M., Poletti P., Merler S. D'Andrea V., Putoto G.

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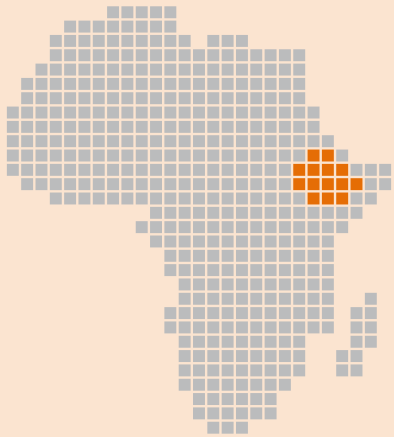

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Priority age targets for COVID-19 vaccination in Ethiopia under limited vaccine supply

Margherita Galli[1,2,9], Agnese Zardini[1,9], Worku Nigussa Gamshie[3], Stefano Santini[4], Ademe Tsegaye[5], Filippo Trentini[1,6], Valentina Marziano[1], Giorgio Guzzetta[1,7], Mattia Manica[1,7], Valeria d'Andrea[1], Giovanni Putoto[4], Fabio Manenti[4], Marco Ajelli[8,10], Piero Poletti[1,7,10]✉ & Stefano Merler[1,7,10]

The worldwide inequitable access to vaccination claims for a re-assessment of policies that could minimize the COVID-19 burden in low-income countries. Nine months after the launch of the national vaccination program in March 2021, only 3.4% of the Ethiopian population received two doses of COVID-19 vaccine. We used a SARS-CoV-2 transmission model to estimate the level of immunity accrued before the launch of vaccination in the Southwest Shewa Zone (SWSZ) and to evaluate the impact of alternative age priority vaccination targets in a context of limited vaccine supply. The model was informed with available epidemiological evidence and detailed contact data collected across different geographical settings (urban, rural, or remote). We found that, during the first year of the pandemic, the mean proportion of critical cases occurred in SWSZ attributable to infectors under 30 years of age would range between 24.9 and 48.0%, depending on the geographical setting. During the Delta wave, the contribution of this age group in causing critical cases was estimated to increase on average to 66.7–70.6%. Our findings suggest that, when considering the vaccine product available at the time (ChAdOx1 nCoV-19; 65% efficacy against infection after 2 doses), prioritizing the elderly for vaccination remained the best strategy to minimize the disease burden caused by Delta, irrespectively of the number of available doses. Vaccination of all individuals aged ≥ 50 years would have averted 40 (95%PI: 18–60), 90 (95%PI: 61–111), and 62 (95%PI: 21–108) critical cases per 100,000 residents in urban, rural, and remote areas, respectively. Vaccination of all individuals aged ≥ 30 years would have averted an average of 86–152 critical cases per 100,000 individuals, depending on the setting considered. Despite infections among children and young adults likely caused 70% of critical cases during the Delta wave in SWSZ, most vulnerable ages should remain a key priority target for vaccination against COVID-19.

Two years into the pandemic, the reported burden of the coronavirus disease 2019 (COVID-19) has been relatively low throughout Africa as compared to high-income countries[1,2]. In Africa, approximately 40% of people are aged less than 15 years, compared to a global mean of 25%[3], and severe outcomes of COVID-19 are strongly associated with age[4–6]. However, the impact of COVID-19 in low-income countries may have been vastly underestimated due to lacking testing capacity[7–9]. For instance, a recent post-mortem study in Zambia revealed that, contrary to expectations, deaths possibly ascribable to COVID-19 were common among patients of a referral hospital, with about 20% deceased individuals resulting infected with SARS-CoV-2 compared to less than 10% tested before death[10].

The identification of appropriate strategies to minimize COVID-19 burden in sub-Saharan settings remains an open challenge. Unprecedented social distancing measures have been applied worldwide to mitigate the COVID-19 pandemic[11–15]. However, the implementation of drastic restrictions for long time periods would have

[1]Center for Health Emergencies, Bruno Kessler Foundation, Trento, Italy. [2]Department of Mathematics, Computer Science and Physics, University of Udine, Udine, Italy. [3]Doctors with Africa CUAMM, Woliso, Ethiopia. [4]Doctors with Africa CUAMM, Padova, Italy. [5]Doctors with Africa CUAMM, Addis Ababa, Ethiopia. [6]Dondena Centre for Research on Social Dynamics and Public Policy, Bocconi University, Milan, Italy. [7]Epilab-JRU, FEM-FBK Joint Research Unit, Trento, Italy. [8]Laboratory for Computational Epidemiology and Public Health, Department of Epidemiology and Biostatistics, Indiana University School of Public Health, Bloomington, IN, USA. [9]These authors contributed equally: Margherita Galli and Agnese Zardini. [10]These authors jointly supervised this work: Marco Ajelli, Piero Poletti and Stefano Merler. ✉email: poletti@fbk.eu

disproportionate effects on the already vulnerable economies of low-income countries[11,13,14]. Mass immunization programs still represent the main public health strategy to reduce COVID-19 burden. While high-income countries have rapidly progressed in the deployment of multiple vaccine doses, at the end of 2021, only 15% of the total African population was vaccinated with at least one dose[2].

Ethiopia represents an illustrative case study for the limited access to vaccination experienced by sub-Saharan countries during 2021. In this country, the national vaccination campaign was launched on March 13, 2021[16], prioritizing healthcare workers at first, and then the elderly and patients with chronic diseases[17]. On November 16, 2021, the vaccination campaign was expanded to all individuals aged 12 years or more. By the end of 2021, Ethiopia had received a total of 14.6 million doses[18], a vaccine supply that would suffice for covering at most 6% of the country's population with the recommended two-doses schedule. However, only 3.4% of the citizens were fully vaccinated by the end of 2021[19] and even at the end of 2022, only 34% of the population had completed a primary vaccination course[20]. Besides the low availability of vaccines, the high vaccine hesitancy found among both healthcare workers[21–24] and the general community[25–27], in addition to logistic difficulties, likely contributed to the slow deployment of COVID-19 vaccination in Ethiopia.

In this study, we assess the potential impact of different vaccination policies in reducing the burden caused by the Delta variant of SARS-CoV-2 across different geographical settings of the Southwest Shewa Zone (SWSZ) of Ethiopia in the context of limited vaccine supply. Alternative priority targets for vaccination are evaluated by considering different scenarios regarding the available number of vaccine doses and by taking into account the immunity acquired by natural infection before the launch of the national vaccination campaign. To do this, we developed and simulated a transmission model for SARS-CoV-2 informed with data on age-specific mixing patterns recently collected across different areas of the SWSZ, characterized by heterogeneous population density, age structure, and access to primary care[12]. The effect of different immunization strategies is evaluated in terms of the number of infections and critical cases that could have been averted after the rollout of vaccination based on ChAdOx1 nCoV-19, representing the vaccine predominately adopted during 2021 in Ethiopia. Obtained results could be instrumental to identify the optimal strategies for the deployment of vaccines in geographical contexts characterized by an initially limited vaccine supply.

Methods

The SARS-CoV-2 transmission dynamics is simulated by using a deterministic age-structured SIR (Susceptible-Infectious-Recovered) model. Susceptibility to SARS-CoV-2 infection is assumed to vary with age according to estimates made available by Hu et al.[28]. Specifically, taking the age group of 20–59 years as the reference, the authors estimated the relative susceptibility for individuals aged 0–19 years at 0.59 (95%CI: 0.35–0.92) and at 1.75 (95%CI: 1.07–2.81) for the individuals aged 60 years or more. A homogeneous susceptibility across ages is explored for sensitivity analysis. An average generation time of 6.6 days and homogenous infectiousness across different ages are assumed[29,30].

The adopted approach leverages on contact data collected in four districts of the SWSZ of the Oromia Region (Ethiopia), representing the main geographical area served by the St. Luke Hospital of Woliso Town, the referral hospital of the Zone[12]. These districts count 449,460 inhabitants, corresponding to 40.8% of the total population of the SWSZ. Age-specific contact matrices were recently estimated for three types of geographical contexts: rural villages, dispersed subsistence farming settlements, and urban neighborhoods of Woliso Town[12]. The model is run separately for each geographical context, assuming a constant population size over time, and accounting for the age structure characterizing the settings under study (Table 1)[12].

The developed model keeps track of the contribution of infectors of different ages in causing secondary infections and critical cases across the different geographical contexts. Critical disease cases are defined as positive individuals who would either require intensive care or result in a fatal outcome. Age-specific risks of developing critical disease after SARS-CoV-2 infection are considered[5].

The contribution of different ages in causing secondary infections and critical cases is explored by considering two pandemic phases. As for the first phase, lasting until the launch of the national vaccination program in March 2021, we consider the emergence of SARS-CoV-2 in a fully naïve population of individuals and analyze the epidemic dynamics under the dominance of the ancestral strain of SARS-CoV-2 and in the absence of vaccination. A school closure mandate is also assumed for the entire period as this represented a persistent restriction

Age group	Overall	Urban neighborhoods	Rural villages	Remote settlements
0–9 years	130,360	17,207	86,864	26,289
10–19 years	115,563	16,170	78,745	20,648
20–29 years	70,470	12,231	47,897	10,342
30–39 years	63,885	10,573	43,838	9474
40–49 years	35,578	4699	25,166	5713
50–59 years	16,587	2004	11,365	3218
60+ years	17,017	1797	11,568	3652
Total	449,460 (100%)	64,681 (14.4%)	305,443 (68.0%)	79,336 (17.7%)

Table 1. Age structure of the population residing in the three geographical contexts. Data refers to the population living in the four districts of the SWSZ where contact data were collected[12].

adopted by the government to counter the spread of COVID-19 during the first pandemic wave[12,31]. The spread of infection is simulated by considering an initial reproduction number R of 1.62 (95%CI: 1.55–1.70), as estimated from the exponential growth of cases reported in Ethiopia from May to mid-June 2020[12]. This corresponds to assuming for the ancestral strain a basic reproduction number (R_0) around 3, which is in line with the estimate of $R_0 = 2.55$ provided for Ethiopia by Iyaniwura et al.[32] as well as with estimates available from other countries[33–36]. We carried out a sensitivity analysis where we considered an $R_0 = 2.55$[32], corresponding to an R of 1.40 in the presence of school closure. The transmission dynamics during this pandemic phase is simulated until a given setting-specific proportion of the population gets infected. Such proportion is defined according to the levels of serological prevalence estimated for March 2021 in the Jimma Zone of Ethiopia: 31% in rural and remote sites and 45% in urban areas[37]. Different seroprevalence values are considered for sensitivity analysis to account for the uncertainty surrounding the circulation of the infection before March 2021 and the potential waning of naturally acquired immunity. Lower levels of protection may also reflect the potential ability of the circulating SARS-CoV-2 variants to escape natural immunity. The model ability in capturing the observed epidemiological patterns is assessed by comparing the age distribution of the cumulative number of simulated infections with the one associated with SARS-CoV-2 positive individuals ascertained with real-time reverse transcription polymerase chain reaction (RT-PCR) between March and September 2020 in the Oromia Region[38]. To assess the robustness of the estimated age distribution with respect to the assumed immunity levels, we investigate how the model performances would change considering the levels of serological prevalence estimated for the Jimma Zone in December 2020 (18% in rural and remote sites and 32% in urban areas)[37].

The second pandemic phase that we consider mirrors the SARS-CoV-2 transmission dynamics after the launch of the national vaccination program in March 2021, when students were regularly receiving in-person education[31]. To account for the replacement of the ancestral lineages by the Delta variant of SARS-CoV-2 likely occurred in mid 2021[39], we calibrate the transmission rate parameter in such a way to obtain an $R_0 = 6$ in absence of interventions and population immunity, based on published estimates[40–44]; alternative values of R_0 are explored for sensitivity analysis. Model estimates of the natural immunity acquired by different age groups during the first pandemic phase are used to initialize the immunological status of the population in this second phase. We set the maximum duration of the simulations at 2 years to guarantee the modeling of the entire course of the Delta epidemics.

The impact of different vaccination strategies on the burden of COVID-19 is assessed in terms of the potential attack rate of infection and the cumulative incidence of critical cases expected after March 2021, in the absence of restrictions on the individuals' contacts. The comparison of alternative vaccination priority groups is carried out by assuming that the considered vaccination target is achieved before the upsurge of cases caused by the emergence of the Delta variant, neglecting the transient dynamic characterizing the rollout of the vaccination.

Five illustrative scenarios are analyzed. First, we consider a scenario where the number of administered vaccines is negligible, and we evaluate the impact of pre-existing immunity levels in shaping the contribution of different ages to the disease spread. Given the low vaccine uptake recorded in Ethiopia, this scenario may reflect what might have occurred in the months following the launch of vaccination because of Delta expansion in the population. Second, we investigate the potential benefit of the vaccination campaign conducted in Ethiopia until the end of 2021, when only 3.4% of Ethiopian citizens were fully vaccinated[19]. Specifically, we assume that the administered doses were distributed to individuals aged 50 years or older (thereby achieving a coverage of 33% in this age group), since they represent the main initial priority target (together with healthcare workers) defined by the Ethiopian vaccination program[17]. In the third scenario, we still consider that a limited number of doses is available, and we compare a vaccination program targeting 100% of individuals aged 50 years or older, with an alternative scenario where the same number of vaccine doses is offered to all ages eligible for vaccination (≥ 10 years of age). Fourth, we assume that all individuals aged 50 years or more are fully vaccinated and we project the potential impact of expanding vaccination to other age groups. In this case, we compare the impact of administering the vaccine only to individuals aged 30–49 years with an alternative scenario where the same number of doses is uniformly distributed to all eligible ages (10–49 years). Different coverage levels (from 0 to 100%) among individuals aged 30–49 years are considered. Finally, to provide a comprehensive view of the potential benefits of vaccination, we consider different combinations of coverage levels attained among subjects aged 50 years or more and individuals aged between 10 and 49 years, irrespectively of the number of doses and logistic efforts required to achieve the considered targets.

In the model, vaccinated individuals are assumed to receive two doses of vaccine which significantly reduce their risk of infection and of developing severe outcomes[45–51]. Since ChAdOx1 nCoV-19 was the dominant vaccine employed in Ethiopia during 2021[52], the vaccine efficacy against infection and critical diseases is set at 65% and 71.5%, respectively[45,48–51,53]. In a sensitivity analysis, different values for the vaccine efficacy are considered to reflect the use of alternative vaccine products, the administration of only one dose of the vaccine, and a lower vaccine effectiveness against the Delta variant caused by the progressive waning of vaccine-induced protection[54]. The infectiousness of SARS-CoV-2 breakthrough infections (i.e., infections occurring among vaccinees) is assumed to be reduced by 50%[46]; equal infectiousness is considered as sensitivity analysis.

Epidemiological transitions are modeled by the following system of ordinary differential equations:

$$\begin{cases} \dot{S}_a = -r_a S_a \sum_{\tilde{a}} \lambda_{a,\tilde{a}} \\ \dot{S}^v_a = -(1 - VE^{inf}) r_a S^v_a \sum_{\tilde{a}} \lambda_{a,\tilde{a}} \\ \dot{I}_{a,\tilde{a}} = r_a \lambda_{a,\tilde{a}} S_a - \gamma I_{a,\tilde{a}} \\ \dot{I}^v_{a,\tilde{a}} = (1 - VE^{inf}) r_a \lambda_{a,\tilde{a}} S^v_a - \gamma I^v_{a,\tilde{a}} \\ \dot{R}_{a,\tilde{a}} = \gamma I_{a,\tilde{a}} \\ \dot{R}^v_{a,\tilde{a}} = \gamma I^v_{a,\tilde{a}} \end{cases}$$

where a defines the age of the individuals, S_a represents susceptible individuals of age a who have never been vaccinated, S^v_a represents vaccinated individuals of age a who experienced a reduced force of infection, VE^{inf} is the vaccine efficacy against the infection, $I_{a,\tilde{a}}$ and $I^v_{a,\tilde{a}}$ represent the unvaccinated and vaccinated individuals of age a infected by subjects of age $\tilde{a}$, $R_{a,\tilde{a}}$ and $R^v_{a,\tilde{a}}$ represent the corresponding number of individuals who recovered from these two classes, r_a is the relative susceptibility in the age class a, $1/\gamma$ is the average duration of the infectivity period. Finally, $\lambda_{a,\tilde{a}}$ represents the contribution of age $\tilde{a}$ to the force of infection experienced by susceptible individuals of age a, which is defined as follows:

$$\lambda_{a,\tilde{a}} = \beta M_{a,\tilde{a}} \left(\frac{\sum_s I_{\tilde{a},s}}{N_{\tilde{a}}} + \delta \frac{\sum_s I^v_{\tilde{a},s}}{N_{\tilde{a}}} \right)$$

where $M_{a,\tilde{a}}$ represents the average number of daily contacts that an individual of age class a has with persons of age group $\tilde{a}$, β is a scaling factor shaping the SARS-CoV-2 transmission rate, $N_{\tilde{a}}$ is the total population in the age class $\tilde{a}$, and δ is the relative infectiousness of vaccinated cases, hereafter assumed to be 0.5.

The number of critical cases $C_{a,\tilde{a}}$ among infectees of age a attributable to the age group of infectors $\tilde{a}$ is computed by applying the estimated risk of developing critical disease for age a, ρ_a[5] to the simulated cumulative number of infections caused by infectors of age $\tilde{a}$ in age group a, $i_{a,\tilde{a}}$, and accounting for the reduction of critical disease risk, VE^{crit}, in breakthrough infections $i^v_{a,\tilde{a}}$:

$$C_{a,\tilde{a}} = \rho_a \left(i_{a,\tilde{a}} + \left(1 - VE^{crit}\right) i^v_{a,\tilde{a}} \right)$$

Results are presented in terms of mean values and 95% Prediction Intervals (PI) computed over 1000 model realizations using different samples of the model input distributions. For the sake of brevity, some results are provided as the range between the minimum and maximum values of the mean estimates obtained across the different geographical contexts. Model simulations were implemented in C programming language and all subsequent analyses and graphics were obtained with the statistical software R (version 4.1.2).

Ethics approval and consent to participate. The analysis relies only on secondary data published in[12,37,38]. Human participants were not involved in this study.

Results

SARS-CoV-2 transmission in the pre-vaccination period. The age distribution of the infections estimated with the model under the assumption of a fully susceptible population and by considering the school closure mandate well compares with the one associated with SARS-CoV-2 infections ascertained via PCR in the Oromia Region between March and September 2020[38] (Fig. 1A). Similar results are also obtained with a model mimicking the achievement of immunity levels estimated for the Jimma Zone in December 2020[38] (see Supplementary Fig. S3). Results obtained on the spread of SARS-CoV-2 before the start of COVID-19 vaccination (March 2021) suggest a marked variability across the different geographical contexts in the expected proportion of individuals over 50 years of age who acquired natural immunity: from 47.6% (95%PI: 37.5–59.9%) in rural areas to 64.6% (95%PI: 48.4–78.9%) in the remote settlements (Fig. 1B). Our estimates of serological profiles also show a relatively higher immunity among individuals under 50 years of age in urban neighborhoods compared to other settings.

According to our simulations, the highest fraction of SARS-CoV-2 infections during the first pandemic year was caused by infectors aged less than 30 years, with the mean estimates ranging from 46.1 to 58.7% across all the considered geographical contexts (Fig. 2C). The mean fraction of critical cases attributable to infectors younger than 30 years was in the range of 24.9–48.0% depending on the geographical context considered. However, a non-negligible fraction of transmission was found to be assortative, i.e., characterized by a similar age between the infectors and their secondary cases (Fig. 2A). Specifically, we estimate that, in remote settlements, 48.7% of infections over 60 years of age might have occurred because of social interactions occurred within this age group. In this setting, individuals aged 50 years or more might have caused half of all critical cases (50.9% in all ages vs 15.9–18.9% in the urban and rural areas, see Fig. 2C). This may be explained by the older population structure characterizing less urbanized populations (see Fig. 2C and Table 1), and the higher number of community contacts reported by the elderly with individuals of similar age (see Supplementary Figs. S1 and S2).

SARS-CoV-2 transmission at vaccination launch. To mimic the COVID-19 epidemiology during the emergence of the Delta variant, we simulate the SARS-CoV-2 transmission under the assumption that the vaccine uptake achieved in the entire population was negligible. However, pre-existing levels of natural immunity as estimated for March 2021 are considered and an increased viral transmissibility is assumed to reflect the transmission advantage of the Delta variant compared to pre-circulating strains[41]. We estimate that at the launch of the vaccination campaign, the effective reproduction number was 2.96 (95%PI: 1.84–4.42), 3.91 (95%PI: 3.51–

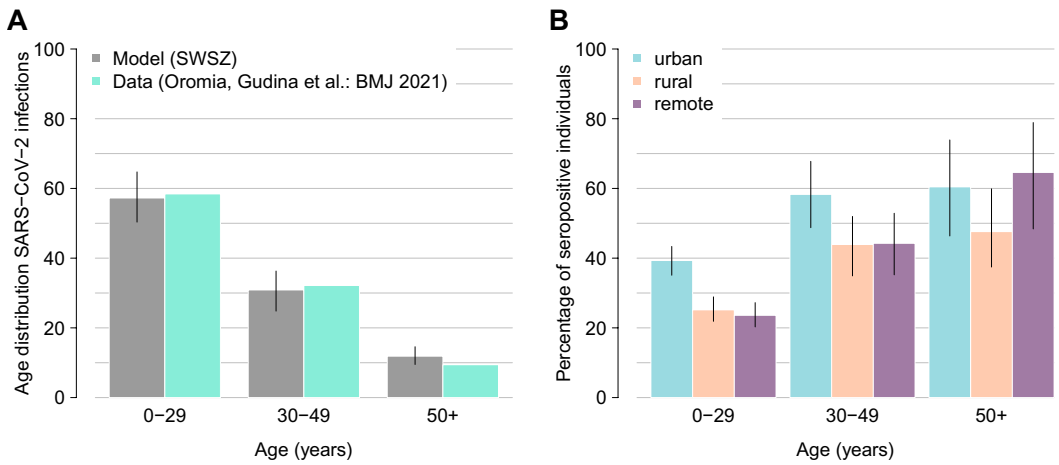

Figure 1. **(A)** Comparison between the age distribution of all confirmed cases reported between March and September 2020 in the Oromia Region[38] and the age distribution of the cumulative infections as obtained with a model mimicking the school closure and the achievement of immunity levels estimated for the Jimma Zone in March 2021[37]. Aggregated model estimates for the entire SWSZ are obtained by considering the proportion of population living in remote settlements, rural villages, and urban neighborhoods of the SWSZ, their age structure, and the age-specific infection attack rate expected across the different social contexts before March 2021[12]. (**B**) Model estimates of the age-specific percentage of the population immune to SARS-CoV-2 after natural infection at the beginning of the vaccination campaign (March 2021) in urban, rural, and remote areas of the SWSZ. Colored bars represent average estimates; solid lines represent the 95% PI of model estimates.

4.37), and 3.80 (95%PI: 2.48–5.88) in urban, rural, and remote settings, respectively (see Supplementary Fig. S4). Our results suggest that the natural immunity acquired in the first pandemic phase and the reopening of teaching activities would have reshaped the contribution of different ages in the spread of COVID-19 (Fig. 2B,C). Specifically, we find that, after March 2021, the mean contribution of individuals under 30 years of age in causing new infections and critical cases might have increased to 84.5–87.3% and 66.7–70.6%, respectively. Accordingly, we estimate a mean decrease in the contribution of the elderly in generating SARS-CoV-2 secondary infections in the range of 2.0–3.5% and critical cases in the range of 7.2–13.5% depending on the geographical setting.

Our estimates suggest that, as the fraction of vaccinated individuals has remained negligible until December 2021, the cumulative incidence of critical cases expected during the Delta wave might have reached 134 (95%PI: 91–174), 223 (95%PI: 180–259), 173 (95%PI: 118–234) per 100,000 residents in the urban, rural, and remote settings, respectively.

Epidemiological outcome considering different vaccine uptake and priority targets. We evaluate the potential benefit of the low vaccination uptake achieved in Ethiopia at the end of 2021, when only 3.4% of Ethiopian citizens were fully vaccinated[19], by assuming that all the administered doses were distributed throughout the population over 50 years (thereby achieving a coverage of 33% in this age group). We estimate that the number of averted critical cases would be 14 (95%PI: 6–21), 30 (95%PI: 20–37), and 20 (95%PI: 7–36) per 100,000 residents in urban, rural, and remote areas, respectively, corresponding to 10.0–13.5% of expected critical cases in absence of vaccination. These estimates are based on the assumption that all individuals were vaccinated before being infected with SARS-CoV-2 and therefore correspond to an upper limit of the efficacy of the vaccination program by the end of 2021.

Moreover, we compare the impact of two alternative vaccination strategies in a context of limited vaccine supply: prioritizing individuals older than 50 years or distributing the available vaccines throughout the population over 10 years. Our findings suggest that the best strategy to reduce the potential burden of critical disease is to prioritize vaccination of older individuals (Fig. 3). Specifically, we find that the vaccination of 100% of individuals aged 50 years or more has the potential of averting 40 (95%PI: 18–60), 90 (95%PI: 61–111), and 62 (95%PI: 21–108) critical cases per 100,000 residents in urban, rural, and remote areas, respectively (Fig. 3D). If the same number of vaccine doses would be uniformly administered to individuals over 10 years, the mean number of averted critical cases is expected to be in the range of 11–22 per 100,000 residents, depending on the geographical context considered. As concerns the reduction in the number of infections, the two alternative vaccination strategies are substantially equivalent, with differences in the expected mean attack rates ranging from 0.5 to 1.1% across the three geographical contexts (Fig. 3B).

We then explore the scenario where vaccination is expanded to younger age groups after all individuals over 50 years of age are fully vaccinated. We find that the best vaccination policy to further reduce the burden of critical cases remains prioritizing the older segments of the population (i.e., people aged between 30 and 49 years, see Fig. 4B). Compared to a scenario with no vaccination, administering the vaccine to all individuals

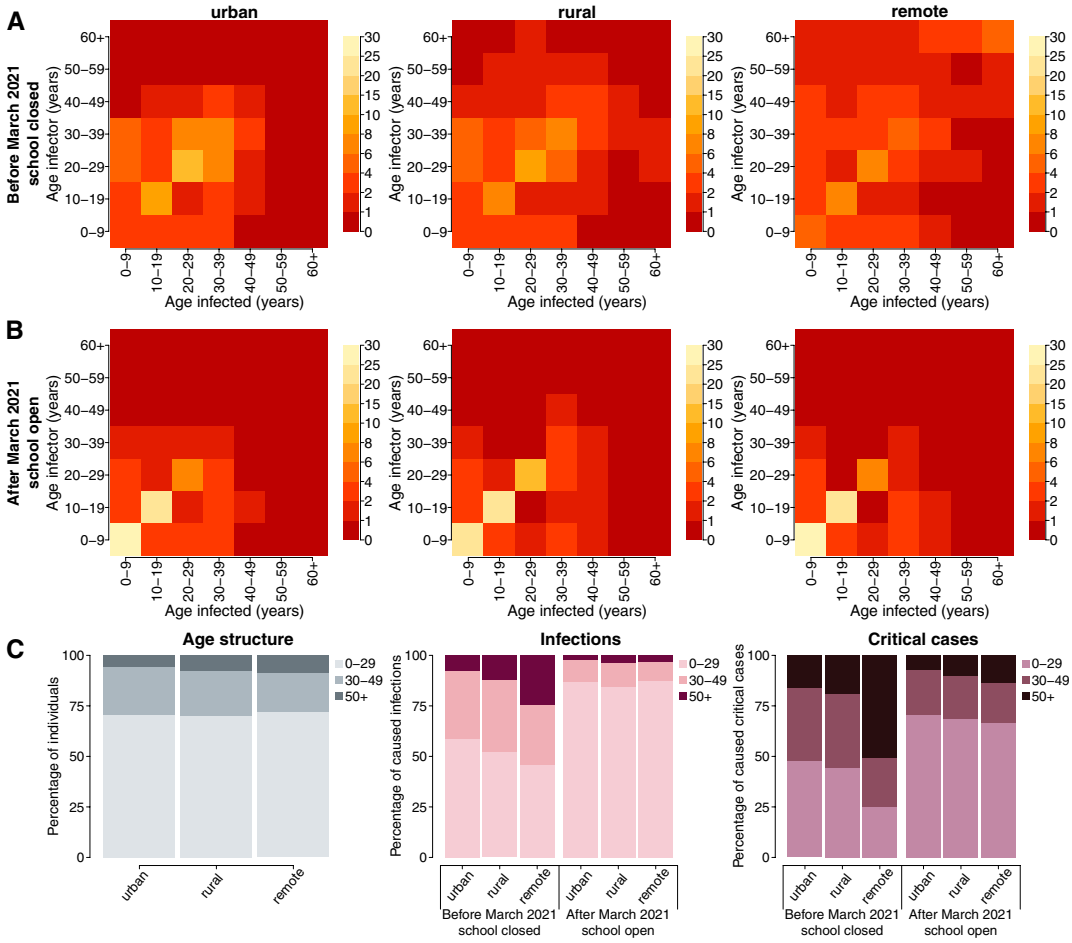

Figure 2. **(A,B)** Percentage of SARS-CoV-2 infections caused by contacts between susceptible individuals in the age group a (x axis) and infected individuals in the age group $\widetilde{a}$ (y axis), as estimated by the model before and after March 2021 in urban neighborhoods, rural villages, and remote settlements. **(C)** Age distribution of the population residing in the three geographical contexts and bar plots of the overall proportion of infections and critical cases caused by infectors aged 0–29, 30–49, 50+ years.

aged 30 years or more would avert 86 (95%PI: 56–113), 152 (95%PI: 120–181), 114 (95%PI: 68–164) critical cases per 100,000 residents in urban, rural, and remote areas, respectively. This policy is estimated to halve the cumulative incidence of critical disease otherwise expected if only individuals older than 50 years get the vaccine (range of mean estimates: 48–71 vs 93–133 per 100,000 residents). Our estimates suggest that the most effective strategy to reduce the infection attack rate is to uniformly distribute the available vaccines among individuals aged 10–49 years. However, the percentage of infections averted under this policy is limited to less than 10% across all considered contexts (Fig. 4A).

To illustrate the full potential of COVID-19 vaccination, we finally estimate the infection attack rate and the cumulative incidence of critical cases under different combinations of vaccination coverage in the elderly (≥ 50 years of age) and in individuals aged 10–49 years, irrespectively of possible limits in the vaccine supply and logistic constraints (Fig. 5). Obtained results confirm that the most effective strategy to reduce the number of SARS-CoV-2 infections is the vaccination of younger subjects. We find that the vaccination of the entire population over 10 years with two doses of ChAdOx1 nCoV-19 would reduce the reproduction number to 2.17–2.81 (see Supplementary Fig. S4), therefore suggesting that further efforts would have been required to interrupt the SARS-CoV-2 circulation in Ethiopia. This may be due to several factors, including the low effectiveness of 2 doses of ChAdOx1 nCoV-19 against infection with the Delta variant, the high viral transmissibility of Delta, and the high fraction of individuals younger than 10 years, which represent between one fourth and one third of the total population residing in the three geographical contexts (Table 1).

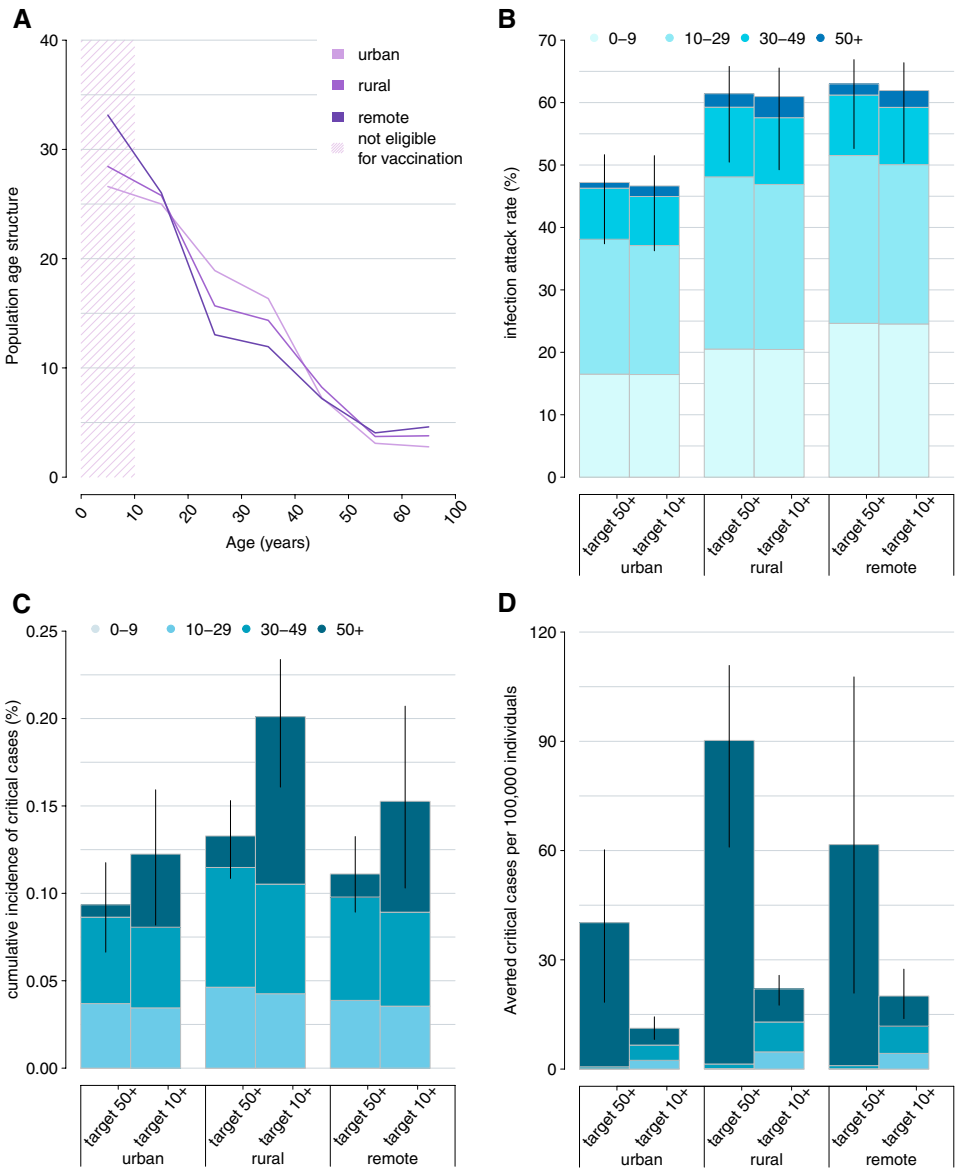

Figure 3. **(A)** Population age structure in urban, rural, and remote settings of the SWSZ. The shaded area highlights the age segments of the population who are not yet eligible for COVID-19 vaccination. (**B**–**D**) Infection attack rate, cumulative incidence of critical cases, and averted critical cases per 100,000 residents as estimated for different geographical contexts (urban, rural, and remote) under the assumption that either all the individuals aged 50 years or older are vaccinated or that the same number of vaccine doses is uniformly distributed throughout the population over 10 years. Therefore, an equal number of people is assumed to be vaccinated in the two scenarios. Bars represent average estimates, stratified by the age group of infected individuals (0–9, 10–29, 30–49, 50+ years); solid lines represent the 95% PI of model estimates.

When assuming that all individuals aged 50 years or more are vaccinated, the lowest cumulative incidence of critical cases is estimated to occur in urban neighborhoods, where 93 (95%PI: 66–118) subjects per 100,000 residents are estimated to be exposed to COVID-19 critical disease (Fig. 5B). To reduce the number of critical

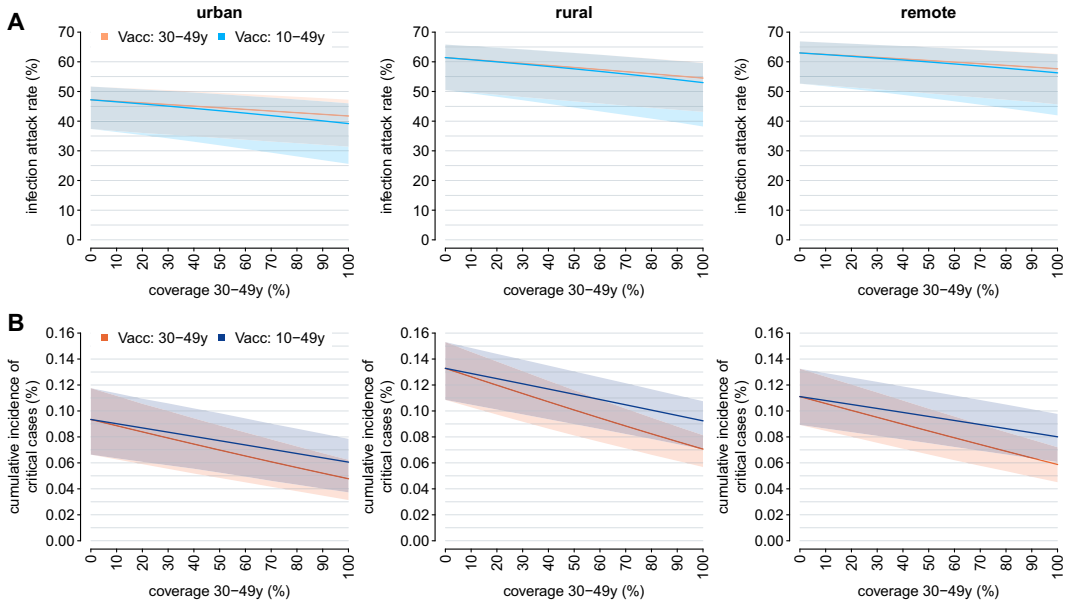

Figure 4. Estimated infection attack rate (**A**) and cumulative incidence of critical cases (**B**) in urban, rural, and remote areas, as obtained under the assumption that all individuals above 50 years are vaccinated with two doses and by considering different scenarios for the number of additional doses that would be available. In each panel, two strategies are compared: in the first, a further vaccination effort is simulated to reach a specific coverage level in subjects aged 30–49 years (orange); in the second, the same number of doses is used to uniformly vaccinate individuals aged 10–49 years (blue). Solid lines represent the mean model estimates; shaded areas represent the 95% PI.

cases in rural areas under such an incidence level, the strategy minimizing the number of administered doses requires the vaccination of all individuals aged 50 years or more and the vaccination of at least 30% of younger individuals. In remote settlements, the same achievement would require the vaccination of at least 90% individuals over 50 years of age and a vaccination coverage of 20% in younger ages.

To reduce the cumulative incidence of critical disease under 50 cases per 100,000 individuals in less urbanized areas, a 90% vaccination coverage over 50 years of age should be complemented with more than 70–80% coverage among younger eligible subjects. In urban neighborhoods, the same result would require 90% coverage among the elderly and 50% coverage in younger individuals. If a maximum uptake level of 80% would be achieved in the elderly, to obtain similar results the vaccination of at least 60%, 90%, and 80% of the population under 50 years of age is needed in urban, rural, and remote areas, respectively.

The ranking of different vaccination strategies highlighted under our baseline assumptions is confirmed in a wide spectrum of sensitivity analyses accounting for (i) a different efficacy of the vaccine (see Supplementary Fig. S5), (ii) the uncertainty in the immunity levels acquired during the first pandemic phase (see Supplementary Fig. S6), (iii) the uncertainty in the reproduction number due to possible changes in the transmission determined by social distancing measures and in the increased transmissibility estimated for Delta compared to pre-circulating lineages (see Supplementary Fig. S7), (iv) equal infectiousness of breakthrough infections and infections among unvaccinated individuals (see Supplementary Fig. S8), (v) a homogeneous susceptibility by age (see Supplementary Fig. S9), and (vi) the estimate of the basic reproduction number of the ancestral lineages provided for Ethiopia by Iyaniwura et al.[32] (see Supplementary Fig. S10).

Discussion

A limited vaccine supply should be considered when exploring the impact of vaccination strategies against COVID-19 in low-income countries[2,19]. In this study, we evaluated different age priority targets for vaccination in Ethiopia, considering changes in the disease spread determined by natural immunity acquired during the first year of the pandemic. To this aim, we simulated SARS-COV-2 spread before the launch of the national immunization campaign and assessed the potential disease burden caused by the Delta variant under different vaccination scenarios across urban, rural, and remote areas of the Southwest Shewa Zone.

Obtained results suggest that, before March 2021, infected individuals aged 50 years or more might have been responsible on average for 50.9%, 18.9%, and 15.9% of all critical cases occurred in remote, rural, and urban settings, respectively. Nonetheless, we found that a pivotal role in the spread of SARS-CoV-2 was played by subjects under 30 years, who might have been responsible for about half of the infections in all the considered areas.

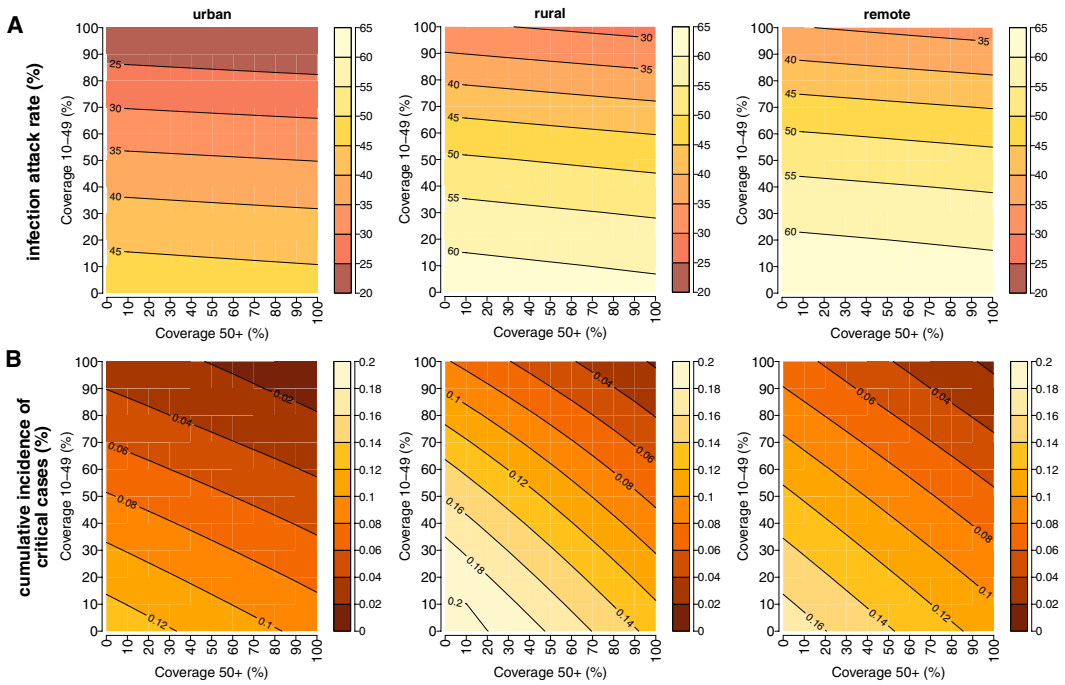

Figure 5. Infection attack rate (**A**) and cumulative incidence of critical cases (**B**) as estimated for urban, rural, and remote areas for different combinations of vaccination coverage in individuals aged 50 years or more and in individuals aged 10-49 years.

Vaccination coverage against COVID-19 has remained extremely low in Ethiopia throughout 2021[2,19]. As COVID-19 deaths ascertained in this country until December 2021 suggest a mortality rate around 5.9 per 100,000 residents[55], our estimates of the incidence of critical cases in the absence of vaccination highlight that COVID-19 deaths may have been poorly detected in sub-Saharan settings. This is in line with a post-mortem surveillance suggesting 91.4% underreporting of COVID-19 deaths in Zambia[10]. We found that less urbanized areas might have been exposed to a higher burden of COVID-19 cases during the Delta epidemic wave due to older populations or a lower circulation of the infection during the first pandemic year. Additionally, the natural immunity acquired in the first pandemic phase and the reopening of schools significantly increased the proportion of critical cases caused by younger infectors. Nonetheless, our estimates highlight that prioritizing older age segments of the population for vaccination remains the most effective strategy to minimize the burden of critical illness in the Southwest Shewa Zone of Ethiopia. This conclusion emerges irrespectively of the overall number of available doses and despite the high infection rates experienced by the elderly during the first year of the pandemic and the large contribution played by young individuals in the spread of the disease afterwards. Our findings therefore confirm the results obtained across different countries in early 2021[46,56,57].

Presented results should be interpreted considering the following limitations. The comparison of alternative vaccination priority groups was carried out by assuming that the vaccine is instantaneously administered to all individuals in the target ages, therefore neglecting the time required for the rollout of the vaccination. To better highlight the overall potential of vaccination, we simulated its impact from March 2021, when the national vaccination program was officially launched. Due to the circulation of SARS-CoV-2 after this date and the waning of immunity acquired from natural infection, initial conditions considered to compare the different vaccination strategies do not reflect the current epidemiological conditions in the Southwest Shewa Zone. Nonetheless, the resulting priority ages were found to be robust under alternative modeling assumptions on the immunity level acquired in the first pandemic year and on the vaccine efficacy. Another limitation of this study is that we did not consider the waning of immunity. This model assumption may result in an underestimation of the disease burden expected after the launch of the COVID-19 vaccination. No data specific for the Southwest Shewa Zone were available that could allow the estimation of region-specific reproduction numbers; therefore, we used estimates from nationally aggregated data, which may be biased by overrepresentation of cases in Addis Ababa, where infection dynamics may be different from the rest of the country. It is also worth mentioning that school closure was the only intervention we considered when estimating the age-specific immunity profile before the vaccination launch. This means that variations in the social distancing measures adopted during the first pandemic year were not considered. These include an initial suspension of nonessential productive activities in early 2020[12] and the progressive re-opening of schools from November 2020[31,58]. However, the carried-out analysis

shows that our model was sufficiently robust to reproduce the age distribution of SARS-CoV-2 infections identified in the considered region during the first wave of COVID-19. Moreover, the impact of different COVID-19 prioritization strategies was simulated under the hypothetical scenario of an unmitigated COVID-19 epidemic, without considering any restriction or intervention. Therefore, our estimates of the expected number of infections and critical cases after March 2021 should be considered as illustrative worst-case scenarios to compare the performance of alternative vaccination strategies. The lack of available estimates on the infection-fatality ratio and infection-hospitalization ratio for the Delta variant in African countries did not allow us to quantify the reduction in the number of hospitalizations and years of life lost to COVID-19 determined by vaccination. We did not consider possible heterogeneities in infectiousness by age and symptomatic status. The spatial spread of COVID-19 was not considered in this work. Data on mixing patterns show that more than 97% of contacts occurred within the neighborhood of residence[12]. The low interconnectivity may suggest a slow spatial spread of the infection, especially in remote areas; however, this should not affect the total burden of disease if SARS-CoV-2 reached almost all populated areas (as suggested by the high number of infections reported in all regions of Ethiopia[19]). We therefore expect our conclusions to be robust with respect to the lack of spatial structure in the model. Finally, because of the lack of direct data from Africa, the relative susceptibility, the age-specific risks of developing critical disease, and the potential increased transmissibility and immune escape associated with the Delta variant were assumed from evidence gathered in other countries[5,28,41].

Conclusions

Despite infections among children and young adults likely caused 70% of critical cases during the Delta wave in SWSZ, most vulnerable ages should remain a key priority target for vaccination against COVID-19. Considering the potential emergence of novel variants of SARS-CoV-2 in the future, our estimates suggest that in Ethiopia older individuals residing in less urbanized settlements should be prioritized for vaccination. Future non-pharmaceutical interventions should focus on reducing potential infectious interactions between the elderly and individuals under 30 years of age, representing their most likely infectors.

Data availability

The datasets analyzed during the current study are available in the following published papers[12,37,38].

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Author contributions

P.P., M.A., and S.M. conceived the study. A.Z. and M.G. wrote the code and performed the analysis. A.Z., M.G., and P.P. wrote the first draft of the manuscript. P.P., M.A., and S.M. supervised the study. All authors contributed

to interpret the results, read, reviewed, and approved the final version and the submission of the manuscript. The corresponding author had final responsibility for the decision to submit for publication.

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Correspondence and requests for materials should be addressed to P.P.

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Effectiveness of provider-initiated versus client-initiated HIV testing by different health facility departments in Northern Tanzania

PAPER

Authors
Ramadhani A., Rinke de Wit T.F., Martelli G., Costigan K., Katambi P., Mllacha P., Pozniak A., Maokola W., Mfinanga S., Hermans S.

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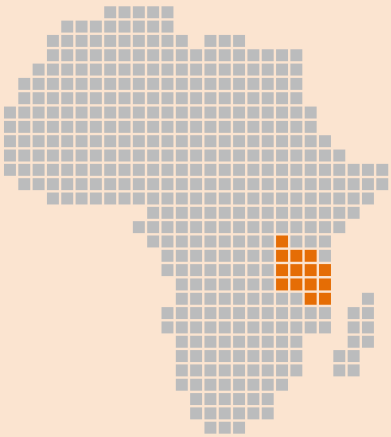

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Effectiveness of provider-initiated versus client-initiated HIV testing by different health facility departments in Northern Tanzania

Ramadhani Abdul[1*], Tobias F. Rinke de Wit[1], Giulia Martelli[3], Kathleen Costigan[2], Patrobas Katambi[4], Peter Mllacha[5], Anton Pozniak[6], Werner Maokola[7], Sayoki Mfinanga[8,9,10] and Sabine Hermans[1]

Abstract

Background HIV prevalence in Tanzania is still high at 4.7% among adults. Regular HIV testing is consistently advocated in the country to increase the level of awareness of HIV status, thus contributing to national HIV prevention. We report findings from three years of implementation of an HIV Test and Treat project utilizing provider-initiated and client-initiated testing and counselling (PITC and CITC). This study compared the effectiveness of PITC versus CITC in HIV case detection by the different departments of health facilities.

Method This retrospective cross-sectional study used health facility-based HIV testing data collected from adults aged 18 years and above between June 2017 – July 2019 in the Shinyanga region, Tanzania. Chi-square and logistic regression analysis were used to assess determinants of yield (HIV positivity).

Results A total of 24,802 HIV tests were performed of which 15,814 (63.8%) were by PITC and 8,987 (36.2%) by CITC. Overall HIV positivity was 5.7%, higher among CITC at 6.6% than PITC at 5.2%. TB and IPD departments had the highest HIV positivity 11.8% and 7.8% respectively. Factors associated with a positive test were testing at a department in the facility compared to CITC, first-time test, and being or having been married compared to being single.

Conclusion Success in identifying HIV + patients was highest among people visiting the clinic for HIV testing (CITC) and first-time testers. With PITC, HIV + patient detection differed between departments, suggesting divergent risk profiles of respective clients and/or divergent HIV alertness of staff. This underscores the importance of increased targeting for PITC to identify HIV + patients.

Keywords Provider initiated testing and counselling(PITC), Client initiated Counselling and Testing(CITC), HIV testing, Tanzania

*Correspondence:
Ramadhani Abdul
r.abdul@aighd.org; rabdul.swaibu@gmail.com
[1]Amsterdam UMC, Department University of Amsterdam, Department of Global Health, Amsterdam Institute for Global Health and Development, Amsterdam, the Netherlands
[2]Bugisi Health Centre, Shinyanga, Tanzania
[3]Infectious Diseases Unit, AUSL Romagna, Morgagni Pierantoni Hospital Forlí, Doctors with Africa CUAMM IT, Forlí, Italy
[4]Ngokolo Health Centre, Shinyanga, Tanzania
[5]Shinyanga Regional Referal Hospital, Shinyanga, Tanzania
[6]Chelsea and Westminster Hospital NHS Foundation Trust and LSHTM, London, UK
[7]National Aids Control Program(NACP), Dodoma, Tanzania
[8]National Institute for Medical Research(NIMR)-Muhimbili centre, Dar es Salaam, Tanzania
[9]Alliance for Africa Health Research, Nairobi, Kenya
[10]School of Public Health, Department of Epidemiology and Statistics, Muhimbili University of Health and Allied Science, Dar es Salaam, Tanzania

Introduction

Despite progress made, the prevalence of HIV in Tanzania remains high. The latest 2020 UNAIDS estimates the prevalence in adults aged 15–49 at 4.5(4.2–4.6)%, about 88(85–96)% of people living with HIV know their HIV status, and the proportion on ART is estimated at 86(83–93)% [1, 2]. In 2016–2018 a population-based survey estimated the first 90 of the 90-90-90 goals, awareness of HIV status among those estimated to be HIV-positive, at 60.6% [3]. Since then, Tanzania has adopted multiple approaches to increase HIV case detection, which includes Provider-initiated Testing and Counselling (PITC), whereby health providers recommend HIV testing services (HTS) to all clients seeking health services [4]. Despite the Tanzania National Guideline recommending providers to offer PITC [5], its general implementation is still low [6]. Although PITC alone is unlikely to yield the desired testing coverage on its own [7], its contribution is considered important [8, 9], and suboptimal use would be a missed opportunity to diagnose and link HIV patients into care [10, 11]. Continuing evaluation is essential to understand how PITC is implemented, the characteristics of people accessing the services, and the corresponding HIV testing yields across the facility.

This study aims at assessing the effectiveness of PITC in HIV case detection by the different departments of health facilities (tuberculosis, outpatient, and inpatient department) and comparing this with Client Initiated Testing and Counselling (CITC), in which the client reports at the facility to get tested for HIV. Specifically, the study aimed to (a) describe the testing and sociodemographic characteristics of people coming forward for testing in each of the facilities, overall and by testing strategy (PITC and CITC); (b) determine the testing yield by testing strategy (PITC vs. CITC), overall and stratified by the facility, (c) calculate PITC yield in different departments within the facility and (d) analyse factors associated with finding HIV positive patients.

Method

Study setting and design

This retrospective cross-sectional study used routine facility-based historical data on HIV testing from testing registers of three facilities: Shinyanga Regional Referal Hospital (SRRH) and Ngokolo Health Centre (Ngokolo HC) in the municipal district, and Bugisi Health Centre (Bugisi HC) in a rural district of Shinyanga region, between June 2017 and July 2019. Bugisi HC and Ngokolo HC are private, faith-based facilities. SRRH is a public regional referral facility.

This study was nested within the Shinyanga & Simiyu Test and Treat study, which assesses the feasibility of universal access to HIV Test and Treat by implementing a differentiated HIV care model in North-Western Tanzania [12]. SRRH was only added as a project facility in 2020 and therefore did not receive staff support during the study period. As part of the study, several testing approaches were implemented: community-based testing and facility-based testing [13]. For this paper, we only report on facility-based testing.

Facility-based HIV testing approaches

Two testing approaches were investigated. First, CITC, whereby a client voluntarily attends the facility for HTS at a dedicated CITC department within the facility. As per national guidelines, repeat testing was not done if a client returned within three months. Secondly, PITC, an HIV test offered to all clients visiting different departments (i.e., outpatient department (OPD), inpatient department (IPD), prevention of mother to child transmission (PMTCT), and tuberculosis (TB)) within the facility. If agreed, the testing is done within the department; if no qualified staff is available or for any other reason, a client can be referred to another department for testing. Regardless of the actual testing place, client information is captured in the respective department register where the testing was initiated. The National HIV testing guideline utilizes a serial testing approach, using Point of Care Tests (POCT); the first test uses the SD-Bioline test and the second test uses UniGold-HIV rapid test if the first test is reactive.

Participants

All clients recorded in the HIV testing registers aged one year or above in the three facilities from June 2017 to July 2019 were included in the study. This period was chosen as the start date of the Test and Treat Project up to the introduction of a new HTS by the Government in 2020. This study included only adults aged 18 years or above.

Data sources, detail of measurements, and definitions

Data came from individual-level HIV testing registers from the participating facilities. HIV testing registers from all departments of the facility were retrieved, and data were extracted and entered into the National HTS data entry program by trained data clerks.

Demographic variables included were age at testing (in years), sex, and marital status of the clients. Other variables included pregnancy status for women, date of testing, the facility department where HIV testing was initiated, type of counselling given (client alone, client and parents, couple or group), type of test (new or repeat), testing type (PITC or CITC), and HIV test result (positive or negative). Testing data for the TB department were only available at SRRH as they were included in the overall OPD data for the other two facilities. Testing data for PMTCT were only available at Bugisi HC and were evaluated as part of PITC.

Table 1 Participants' characteristics, overall and by testing type

Characteristics (n (%)	Overall n = 24,802(100%)	PITC n = 15,814 (63.8%)	CITC n = 8987 (36.2%)	P-Value*
Gender				
Female	13,181(53.2)	8746(55.3)	4435(49.4)	< 0.001
Male	11,620(46.8)	7068(44.7)	4552 (50.6)	
Age in years (mean (SD)	34.8(14.6)	36.5(15.7)	31.8(11.7)	< 0.001
Age				
18–25 years	7666(30.9)	4400(27.8)	3394(36.3)	< 0.001
25–50 years	13,741(55.4)	8727(55.2)	5014(55.8)	
50 years and above	3394 (13.7)	2687(16.9)	707(7.9)	
Pregnancy status (n = 15,794)				
Yes	101(0.8)	61(0.8)	40(1.0)	0.241
No	12,113(99.2)	7988(99.2)	4125(99.0)	
Marital status				
Single	5803(23.4)	3163(20.0)	2640(29.4)	< 0.001
Married/ cohabiting	17,071(68.8)	11,404(72.1)	5667(63.1)	
union	1282(5.2)	750(4.7)	532(5.9)	
Separated/ divorced	645()2.6)	497(3.1)	148(1.6)	
Widow				
Facility Name				
Bugisi HC	16,653(67.1)	10,354(65.5)	6299(70.1)	< 0.001
Ngokolo HC	2328(9.4)	735(4.7)	1593(17.7)	
SRRH	5820(23.5)	4725(29.9)	1095(12.2)	
Residence				
Rural	16,653(67.1)	10,354(65.5)	6299(70.1)	< 0.001
Urban	8148(32.9)	5460(34.5)	2688(29.9)	
Prior Testing History				
first test	5206(20.9)	3538(22.4)	1668(18.6)	< 0.001
Repeat test	19,595(79.1)	12,276(77.6)	7319(81.4)	
Department within the facility				
CITC	8987(36.2)	8987(100)	-	N/A
IPD	1966(7.9)	-	1966(12.4)	
OPD	13,340(53.8)	-	13,340(84.4)	
TB**	371(1.5)	-	371(2.4)	
Other	137(0.6)	-	137(0.9)	
Counselling type				
Client alone	21,397(86.2)	14,049(88.8)	7348(81.8)	< 0.001
Client and parents	309(1.2)	230(1.4)	79(0.9)	
Couple	2849(11.5)	1419(8.9)	1430(15.9)	
Group	246(0.9)	116(0.7)	130(1.4)	

*** Comparing proportions between PITC and CITC **Only SRRH had information from the TB department separately (others within OPD). Legend: PITC- Provider Initiated Testing and Counseling and CITC-Client initiated testing and counselling, SRRH-Shinyanga Regional and Referal Hospital**

For this study, the residence of clients (urban or rural) was assigned as per the testing facility department: SRRH and Ngokolo HC as urban clients, while Bugisi HC as rural clients. This was done due to lack of information on clients' address in the testing register. Repeat tests were defined as tests performed for clients who self-reported at least one previous HIV test before the current one regardless of their previous HIV test result. First-timers were the clients who had never tested before as self-reported. The self-reported question was used to determine repeat testing as persons could not be linked to any previous testing register entries because no personal identifiers are recorded in the registers.

Data analysis

Data were analyzed using Stata 15 software. Frequencies and percentages described categorical variables and means (SD) or medians (IQR) for continuous variables. Chi-square tests were used to compare the testing yield between different characteristics of clients receiving services stratified by testing strategy. Univariable and multivariable logistic regression models were employed to analyze the risk factors associated with HIV positivity (confounders were defined *a priori*). To allow for clustering within facilities, we used robust standard errors. To assess if there may have been misclassification of CITC-originated testing as PITC testing at SRRH; a sensitivity analysis without the SRRH was performed. A p-value of 0.05 was considered to be significant for all analyses.

Results

Descriptive analysis of testing, overall and by testing strategy (PITC and CITC)

Overall, 24,802 tests were performed during the study period, 63.8% using PITC and 36.2% using CITC. Table 1 describes the characteristics of study participants by testing type. Overall, more females (53.2%) than males tested for HIV, and males tested more often through CITC than PITC (50.6% versus 44.7%, $p<0.001$). There was a difference in counselling type between CITC and PITC: the proportion of clients who received couple counselling was twice as high among CITC (15.9%) than PITC (8.9%). The proportion of first testers was higher among PITC clients (22.4%) than CITC (18.6%), $p<0.001$. Of all the PITC clients, the vast majority of tests were initiated in the OPD (84.4%), followed by IPD (12.4%) and the TB department (2.3%).

Figure 1 presents the HIV testing numbers by facility, comparing PITC and CITC. Most of the tests conducted at SRRH were done via PITC (81.2%), and CITC only accounted for (18.8%) of all HIV tests. A similar trend was observed in the Bugisi HC where the distribution of HIV testing was 37.8% by CITC and 62.2% by PITC. A reverse trend was observed at Ngokolo HC, whereby the

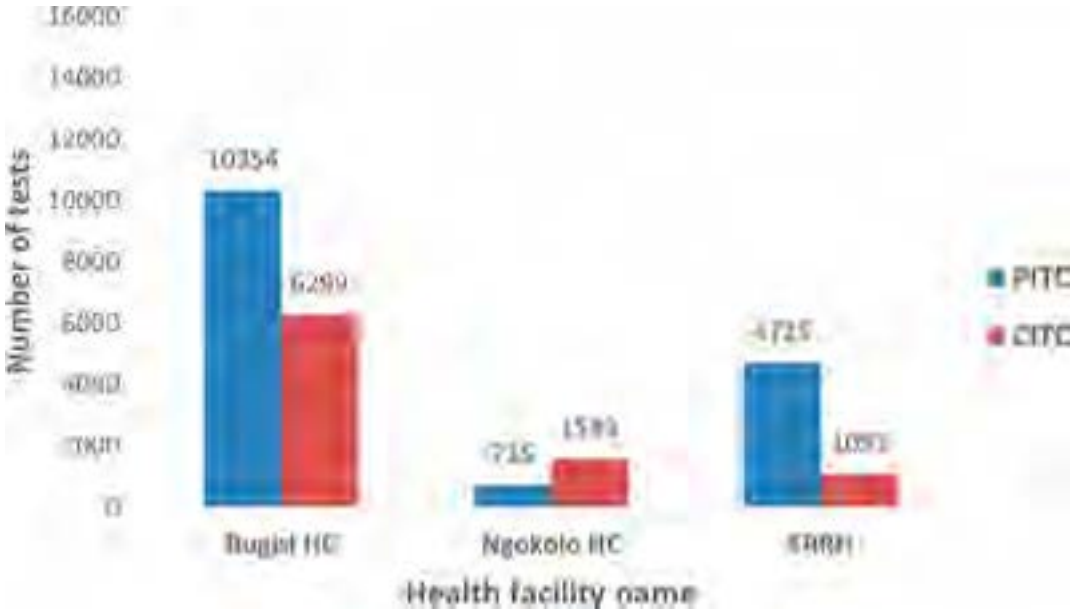

Fig. 1 Testing numbers of CITC and PITC by facility
Legend: PITC-Provider Initiated Testing and Counseling and CITC-Client initiated testing and counselling, SRRH-Shinyanga Regional and Referal Hospital

majority of the tests were done through CITC (68.4%), and PITC only accounted for a third of all tests (31.6%). When further splitting testing numbers by the department in the clinic across all facilities, the majority of PITC tests originated from OPD (84.4%) followed by IPD (12.4%).

Socio-demographic profile of PITC clients attending different testing departments in the facility

Comparing the socio-demographic profile of PITC clients who attended different departments in the facility. Males were more likely than females to receive HIV testing from the TB department (53% males) than from the IPD (34% males) or OPD (46% males). A slightly higher proportion of older adults (aged 50 years or more) tested at the TB department (24.5%), compared to 19.9%, 16.5%, and 7.9% of those tested at IPD, OPD, and CITC, respectively. The majority of clients who tested at IPD (71.7%) and OPD (73.0%) were married or cohabitating. Compared to other departments, the proportion of first-time testers was higher among those tested at IPD (35.6%) than at OPD (20.2%), TB (29.4%), or CITC (18.6%).

HIV positivity yield by testing strategy (PITC vs. CITC), overall and stratified by facility

Table 2 presents HIV positivity yield by testing strategy. Of the 24,801 HIV tests performed, 1414 (5.7%) were found to be HIV positive. The positivity was higher among clients who tested through CITC (6.6%) than PITC (5.2%, $p<0.001$). First-time testers had significantly higher HIV positivity than repeat testers (9.9% versus 4.6%). This difference was more pronounced among clients who tested through CITC (11.5% versus 5.5%, respectively) than PITC (9.1% versus 4.1%). Yield by PITC department was highest in the TB department (11.9%), followed by IPD (7.8%), OPD (4.6%), and lastly, other PITC departments (2.1%). When testing yields were further disaggregated by time, the HIV positivity decreases over time (overall, 6.6% in 2017, 5.5% in 2018 to 5.3% in 2019).

Result of sensitivity analysis

The results from sensitivity analysis to assess if the misclassification of CITC clients who would have been classified as PITC at SRRH have shown no significant difference in the area under the curve for the models with and without SRRH at $p=0.63$.

Factors associated with HIV positivity

Figure 2 presents the Odds Ratios (OR) of the factors associated with HIV positivity. These included age, marital status, department of testing initiation within the facility, and first-time testing. Being separated or divorced and being widowed was associated with a significantly increased likelihood of testing positive compared to being single (4.7-fold and 3.4-fold increase,

Table 2 HIV positivity yield (N and % of all tested) by testing strategy (PITC vs. CITC), overall

Characteristics (N (%)	Overall 1414(5.7)	PITC 820(5.2)	CITC 594(6.6)
Gender			
Female	787(5.9)	449(5.1)	338(7.6)
Male	627(5.4)	371(5.2)	256(5.6)
Age			
18–25 years	231(3.0)	112(2.5)	119(3.6)
25–50 years	950(6.9)	550(6.3)	400(8.0)
50 years and above	233(6.9)	158(5.2)	75(10.6)
Marital status			
Single	231(3.9)	112(3.5)	331(5.8)
Married/cohabiting union	843(4.9)	512(4.5)	106(19.9)
Separated/Divorced	247(19.2)	141(18.8)	119(4.5)
Widowed	93(14.2)	55(11.1)	38(25.7)
Facility Name			
Bugisi HC	851(5.1)	457(4.4)	394(6.2)
Ngokolo HC	165(7.1)	43(5.9)	122(7.7)
SRRH	398(6.8)	320(6.8)	78(7.1)
Residence			
Urban	563(6.9)	363(6.6)	200(7.4)
Rural	851(5.1)	457(4.4)	394(6.2)
Counselling type			
Client alone	1166(5.5)	690(4.9)	476(6.5)
Client and parents	39(12.6)	19(8.3)	20(25.3)
Couple	197(6.9)	106(7.5)	91(6.4)
Group	12(4.9)	5(4.3)	7(5.4)
Department within the facility			
CITC	594(6.6)	-	594(6.6)
IPD	153(7.8)	153(7.8)	-
OPD	620(4.6)	620(4.6)	-
TB	44(11.8)	44(11.8)	-
Other	3(2.1)	3(2.1)	-
Prior testing history			
Repeat test	901(4.6)	499(4.1)	402(5.5)
First test	513(9.9)	321(9.1)	192(11.5)

Legend: PITC- Provider Initiated Testing and Counseling and CITC-Client initiated testing and counselling, SRRH-Shinyanga Regional and Referal Hospital

respectively). The risk of a positive HIV test result was twice as among first-time testers compared to repeat testers.

The department where HIV testing was initiated within the facility was also associated with HIV positivity: when grouping all departments under PITC, the odds of HIV positivity were lower (OR=0.63, 95% CI (0.43–0.90)) in PITC than in CITC. When comparing CITC with different departments of PITC separately, the clients whose testing was initiated at the TB clinic had a significantly higher risk of being positive (OR 1.53, 95%CI: 1.29–1.82). Clients in OPD were less likely to test positive, and clients in IPD had the same likelihood as CITC. There was no association with residence, the time period since the start of the study, or gender.

Discussion

Overall HIV positivity among those tested through PITC and CITC in a large Test and Treat program in the Shinyanga region of Tanzania was 5.7%. HIV positivity was higher for CITC tests compared to PITC (6.6% vs. 5.2%) and was associated with older age, being separated/divorced, and testing for the first time.

Significant variation in the number and proportion of HIV tests by strategy and by health facility was observed. PITC accounted for 82%, 62%, and 32% of all tests done in SRRH, Bugisi HC, and Ngokolo HC, respectively. The higher proportion of PITC at SRRH is likely due to the unavailability of CITC services on some days of the week, which could be due to less project assistance compared to the other two facilities. Verbal communication with the facility in charge of Ngokolo HC revealed a limited number of trained staff and poor knowledge of PITC among clients as a possible reason for low PITC uptake in the facility. This demands further research to understand the actual reasons. Studies done in Tanzania assessing barriers to implementing PITC have listed a lack of staff training on PITC, limited testing equipment, a large number of patients, and a shortage of healthcare workers [14, 15].

The HIV prevalence we found among adults (5.7% in those aged 18 years or older) is comparable to the one reported from a population survey among adults 15 years or older (5.9%) done in this region [3]. Evidence from a systematic review of studies done in Sub-Saharan Africa [7] showed an overall higher prevalence found in facility-based studies than in the general population. Our finding of comparable prevalence estimates in the current study could suggest undertesting in the population visiting the facility. An alternative explanation could be that the majority of HIV-positives in the population have already been identified, and high-risk "pockets" remain who might not come forward for testing using routine approaches.

Studies have found consistent results in terms of the effectiveness of PITC in increasing testing rates [8, 9, 16]. However, its effectiveness in HIV case detection is less clear [9, 17, 18]. Unlike studies on PITC from a general health facility [17, 18] or OPD only [9], this study included various departments within health facilities, which were found to be attended by clients with distinct demographic profiles, which could differentially influence PITC HIV case finding rates.

Our study also compared HIV positivity in different departments of PITC in the facility, which revealed striking differences. Compared to CITC, the TB department of the PITC had the highest case detection, whereas it was lower in OPD, and there was no difference with the IPD. A recent study in Rwanda also showed no difference in HIV case detection between OPD and general facility attendees [9]. Our findings suggest a different HIV risk

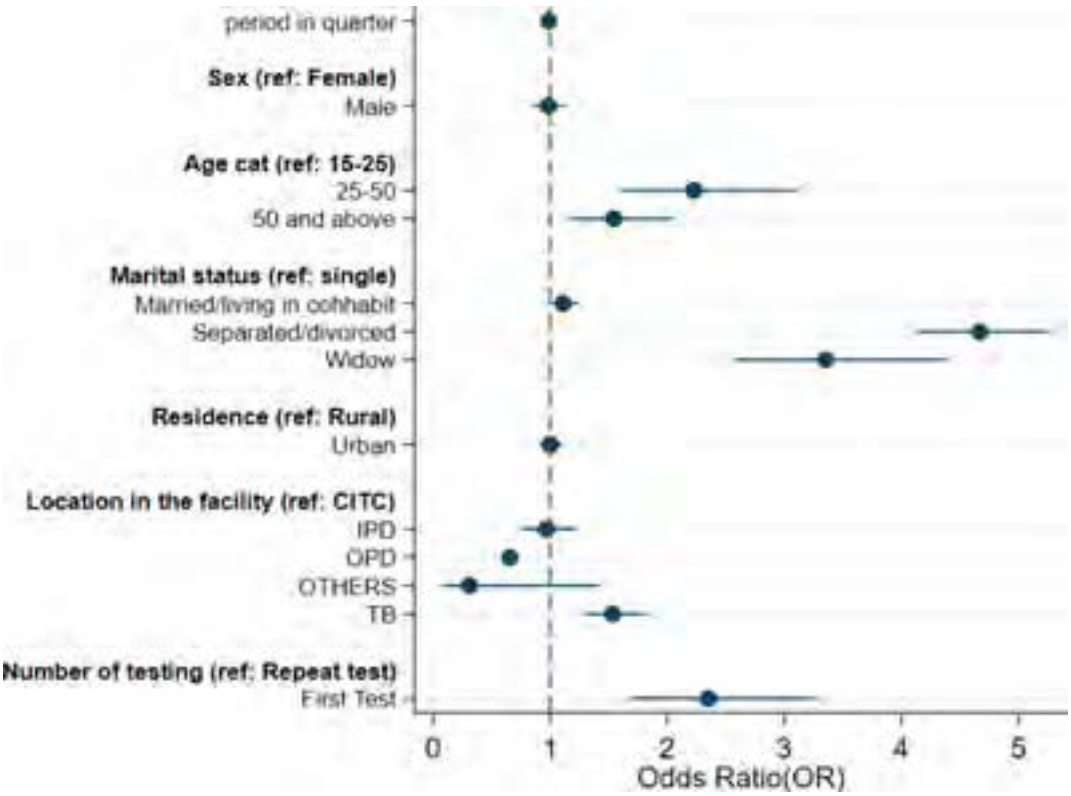

Fig. 2 Adjusted Odds Ratio (OR) for being tested HIV positive
Legend: PITC-Provider Initiated Testing and Counseling and CITC-Client initiated testing and counselling, IPD-Inpatient, OPD-Outpatient

profile for people seeking services at different physical departments within a health facility. An alternative explanation could be different healthcare staff HIV alertness or guidelines per department. The high risk of HIV positivity among presumptive TB patients is well known [19–21]. The evidence provided in this study shows a need for a more focused approach that targets high-risk departments within facilities (TB clinics, in-patient departments).

Our finding of higher HIV positivity in CITC than PITC is contrary to other studies done in similar settings [8, 18, 22]. There are several explanations for this, the most likely being that PITC uptake was not as high as it could have been due to a lack of staff availability, training, or knowledge, as described above. Alternatively, lower PITC HIV prevalence could also be explained by the high number of repeat testers (79%); repeat testing has been associated with low(er) HIV prevalence [23]. Last, there could have been misclassification of CITC as PITC due to CITC staff shortages and/or underreporting of testing which could potentially affect the true PITC prevalence. Also, contrary to the population-based survey [3], this study did not find a significant difference in HIV prevalence between urban and rural populations. The use of facility location as a proxy for urban-rural classification could be the reason, since some of the clients from rural areas might have received HIV testing services from urban facilities and vice versa.

The main limitation of this study is that we could not estimate coverage and uptake of PITC in the facilities, as these data were not included in the testing registers and were not available to us at the time of the study. Comparing characteristics between those who accepted testing to those who refused would have been important to understand the magnitude of the PITC scale-up and the generalisability of our results (the extent of selection bias). PITC utilization information in the TB departments was only collected in SRRH while misclassified as OPD at other facilities, which likely overestimated HIV prevalence at OPD of these facilities and underestimated the magnitude of the risk factor of being tested in TB clinics. The results from SRRH need to be interpreted with

caution as there was no project support to improve HTS during the study period. Although community sensitization campaigns may have led to increased visits to CITC, the lack of staff likely reduced the availability of services, and preferential reporting of HIV-positive cases, biasing toward a higher yield. There may have been misclassification of CITC-originated testing as PITC testing; a sensitivity analysis without the SRRH data did not change our findings, however, and SRRH as a government referral hospital would have incurred higher costs for CITC visits compared to the other two study facilities, which could also partly explain the lower CITC numbers. A limitation of the study design or data was that we were not able to analyze individuals, just tests. The authors used facility location as a proxy for clients' residence; this could have led to misclassification and therefore lack of an association found. The data used for this analysis were from government testing registers, some important information such as why people sought CITC services would be of value but were not collected.

Conclusion

Success in identifying HIV-positive patients was highest among CITC and first-time testers, and for PITC differed between departments at the facility, indicating divergent risk profiles of respective clients and/or divergent HIV alertness of staff. This underscores the importance for PITC of increased targeting to identify HIV-positive patients at high-risk departments within facilities (TB clinics, in-patient departments).

List of Abbreviations

CITC	Client Initiated Testing and Counselling
HC	Health Centre
HIV	Human Immunodeficiency Syndrome
HTS	HIV testing Services
IPD	Inpatient Department
IQR	Inter-Quartile Range
NIMR	National Institute for Medical Research
OPD	Outpatient Department
OR	Odds Ratio
PITC	Provider Initiated Testing and Counselling
PMTCT	Prevention of Mother to Children Transimission
POCT	Point of Care Test
SD	Standard Deviation
SRRH	Shinyanga Regional Referal Hospital
TB	Tuberculosis
UNAIDS	United Nations Programme on HIV/AIDS (UNAIDS)

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Authors' contributions

RA conceptualized the study, drafted the manuscript, conducted analysis, and provided interpretation. SH conceptualized the study, drafted the manuscript, revised the manuscript, and provide interpretation; TW, AP, GM, WM, and SM revised the manuscript and provide interpretation; KC, PK and PM assisted in data acquisition and revised the manuscript. All authors approve the submission of the final draft of the manuscript.

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Data Availability

These data were obtained from the Tanzania National Aids Control Program (NACP), after receiving permission from the Permanent Secretary of the Ministry of Health of Tanzania. Access to the data was limited to the conduct of relevant analysis and publication of results. A request to access the full data can be made to the NACP through the Ministry of Health by writing to the permanent secretary via email at ps@afya.go.tz.

Declarations

Ethics approval and consent to participate

The conduct of this study was approved by the National Institute for Medical Research-NIMR(NIMR/HQ/R.8a/Vol.IX/2711). Permission to access the routine testing data from the testing registers was granted by National Aids Control Programs (NACP) through signed data transfer agreements (DTA) as well as separate permission from the participating facilities.

Consent for publication

Not applicable.

Competing interests

The authors declare no conflict of interest.

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Publisher's Note

Human African Trypanosomiasis (sleeping sickness): Current knowledge and future challenges

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Authors
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Angela H. Lopes,
Federal University of Rio de Janeiro, Brazil

REVIEWED BY
Adekunle Sanyaolu,
Federal Ministry of Health (Nigeria), Nigeria
Stefan Magez,
Vrije University Brussels, Belgium

*CORRESPONDENCE
Roberta Papagni
robertapapagni0@gmail.com

†These authors have contributed equally to this work and share first authorship

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Human African Trypanosomiasis (sleeping sickness): Current knowledge and future challenges

Roberta Papagni[1*†], Roberta Novara[1†], Maria Letizia Minardi[2], Luisa Frallonardo[1], Gianfranco Giorgio Panico[1], Elisabetta Pallara[1], Sergio Cotugno[1], Tommaso Ascoli Bartoli[3], Giacomo Guido[1], Elda De Vita[1], Aurelia Ricciardi[1], Valentina Totaro[1], Michele Camporeale[1], Francesco Vladimiro Segala[1], Davide Fiore Bavaro[1], Giulia Patti[1], Gaetano Brindicci[1], Carmen Pellegrino[1], Michele Fabio Mariani[1], Giovanni Putoto[4], Loredana Sarmati[2], Chiara Castellani[5], Annalisa Saracino[1], Francesco Di Gennaro[1,4] and Emanuele Nicastri[3]

[1]Clinic of Infectious Diseases, Department of Biomedical Sciences and Human Oncology, University of Bari, Bari, Italy, [2]Clinical Infectious Diseases, Department of System Medicine, Tor Vergata University, Rome, Italy, [3]National Institute for Infectious Diseases, Lazzaro Spallanzani, IRCCS, Rome, Italy, [4]Operational Research Unit, Doctors with Africa CUAMM, Padua, Italy, [5]Institut Supérieur des Techniques Médicales (ISTM) Marie-Reine-de-la-Paix de Kenge, Kenge, Democratic Republic of Congo

According to both definitions of US Centers for Disease Control and Prevention and World Health Organization, Neglected Tropical Diseases (NTDs) are a group of preventable and treatable parasitic, viral, and bacterial diseases that affect more than one billion people globally. They generally afflict the more indigent patients of the world and historically have not received as much attention as other diseases. NTDs tend to thrive in low-income regions, where water quality, sanitation and access to health care are substandard. They are common in several countries of Africa, Asia, and Latin America. In this literature review, we want to focus on Human African Trypanosomiasis (HAT), also known as "sleeping sickness", one of the most common neglected diseases in Africa. It is caused by infection with the subspecies of the parasitic protozoan *Trypanosoma brucei*, and it is transmitted by the bite of the tsetse fly. It puts 70 million people at risk throughout sub-Saharan Africa and it is usually fatal if untreated or inadequately treated. This review covers several aspects of the disease. We focused our interests on most recent epidemiological data, novel diagnostic methods with their advantages and limitations, new improved treatment and orphan drugs and eradication programs, including vector control, according to a "One Health" approach, to achieve the new goals recently set by WHO.

KEYWORDS

Human African Trypanosomiasis (HAT), sleeping sickness (trypanosomiasis), Neglected Tropical Disease (NTD), acoziborole, fexinidazole, elimination strategies, rhodesiense HAT, gambiense HAT

Introduction

Human African Trypanosomiasis (HAT), also known as sleeping sickness is a parasitic-borne Neglected Tropical Disease (NTD). It is caused by an extracellular protozoon belonging to the genus *Trypanosoma*, species, *brucei*. It is spread to the susceptible host due to the bite of the blood-sucking tsetse fly of the genus Glossina (1, 2). *Trypanosoma brucei gambiense* and *rhodesiense* are the two subspecies determining the disease in humans. These subspecies have the same morphological structure and life cycle, but they cause unique pathologic entities with distinctive epidemiological and clinical management patterns (3).

Within the vector's geographical distribution, HAT was a leading cause of death in 36 Sub-Saharan African countries. Nevertheless, as an outcome of systematic and coordinated efforts over the past 25 years, the number of reported cases has decreased to historically low levels (1, 4, 5).

NTDs are a group of diseases caused by infections with parasites, viruses and or bacteria. They disproportionately affect poor people and mostly occur in tropical and subtropical areas. They harm individuals, communities, and economies worldwide. Every year, many people die and hundreds are severely disabled, disfigured or unable to work due to the delay in access to treatment and care. Nevertheless, according to the World Health Organization's 2021-2030 roadmap on NTDs and Sustainable Development Goals' targets for NTDs (6, 7), HAT remains one of the most important and challenging NTDs to eradicate due to the numerous gaps in understanding the clinic, the diagnosis, the potential new therapeutic strategies, and complications. Due to the COVID-19 pandemic, numerous essentials tasks of NTDs programs have been postponed, especially the ones directly relating to access to the healthcare system, detection and diagnosis of active cases, rapid drug administration and control and elimination timeline, particularly in high transmission areas. Another risk related to COVID-19 pandemic is the underreporting of the active case and the lack of information about the data collection regarding the eradication program's activities carried out in these last two years. The impact of COVID-19 was studied using mathematical models (NTD Modelling Consortium) (8–10). For NTDs, like HAT, for which intensified testing and case finding is the primary strategy, the resurgence rates are more difficult to estimate. For gambiense HAT (gHAT), incidence is likely to continue to decline if the disruption of eradication and control program last only for one year but may increase in the second year of disruption especially if diagnosis and treatment of cases active detecting or presenting at health facilities continue to be interrupted. Regarding vector control, during the COVID-19 pandemic, continuation of existing measures may help. In this background, new strategies are needed to implement the efficacy of WHO's HAT eradication programs and reach the goals established for 2030 (9, 11).

Methods

We searched PubMed, Scopus, Google Scholar, EMBASE, Cochrane Library, and WHO websites (http://www.who.int) for literature addressing Human African Trypanosomiasis, published from 1995 to June 2022. We searched in the current literature, using the following search strategy: African trypanosomiasis [tiab] OR Trypanosomiases, African [mh] OR African Trypanosomiasis [tiab] OR African Sleeping Sickness [tiab] OR african sleeping sickness [tiab] OR Nagana [tiab]). All studies dealing with epidemiology, physiopathology, clinical characteristics, screening and diagnosis, therapy, management and eradication programs were included.

Structure and biological cycle of *Trypanosoma brucei*

Trypanosoma brucei is a hemoflagellate protozoa. *T. b. gambiense* and *T. b. rhodesiense* are morphologically and microscopically identical (3, 12). One species can be distinguished from the other using molecular techniques (13–15).

T. brucei (both *T. b. gambiense* and *T. b. rhodesiense*) is transmitted by tsetse flies (*Glossina* spp) and has a complex life cycle (Figure 1), with different biological stages in both the insect vector and the mammalian host.

During a blood meal, the tsetse fly swallows the bloodstream forms of the parasite. In the vector's midgut, the parasites can be eliminated or can keep going on their lifecycle (16, 17). In the first case, the infection in the tsetse is unsustainable. Otherwise, if the trypomastigotes differentiate into the pro-cyclic forms, they can start reproduction by binary fission. Pro-cyclic forms enter the proventriculus, where they undergo morphological and structural adaptations, becoming metacyclic trypomastigotes and then epymastigotes. Only the metacyclic form is infectious to vertebrates. It is distinguished by the presence of the variant surface glycoprotein (VSG), which is one of the protection mechanisms used by the parasite to survive in the host. The VSGs are highly immunogenic, but they also protect the parasite from the antibody response because of its rapidly turnover. Antigenic variability causes a three-digit increase in VSGs that could guide the development of new diagnostic tests. Furthermore, genes encoding VSGs are highly susceptible to mutation (18, 19). An internal mechanism that regulates shifting to new variants is the

FIGURE 1
Life cycle of *Trypanosoma brucei gambiense*.

release of a "stumpy induction factor", which triggers the production of non-replicating stumpy forms, adapted to reestablish the life cycle when ingested by the tsetse fly (20).

In the salivary gland, the parasite can reproduce sexually, allowing for genetic exchange and transmission of virulence factors or drug resistance (21–23). Sexual reproduction is not mandatory but can occur and it is especially common in *T.b. rhodesiense* (24). Most widely, in the salivary glands, the metacyclic forms proliferate and become infectious, assuming the trypomastigote form in the host's site of the inoculation. In this shape, the trypanosomes are carried by the bloodstream to other sites. Bloodstream forms can be detected in various body fluids such as lymph and cerebrospinal fluid and are able to cross the placenta (17, 25). The parasitemia is crucial. Individuals with HAT are distinguished into three categories according to parasites detected in the blood and serological tests: Apparently healthy subjects with negative serological and parasitological tests; individuals with both positive tests, and ones with positive serology but negative parasitology. According to WHO guidelines, the treatment is administered to individuals with positive serological and parasitological tests. Untreated subjects are considered a parasite reservoir liable for the persistence of transmission and the occurrence of outbreaks. It has been related to important variations of the parasites' count in the blood strictly caused by the immune response in the host and the genetic variability of the parasite (26–28).

Epidemiology, transmission and risk factors

Human African Trypanosomiasis is endemic in numerous African regions. Both rhodesiense HAT (rHAT) and gambiense HAT (gHAT) can cause epidemics (29). HAT distribution is limited to circumscribed areas called "foci", geographical zones where transmission is possible and where the environment is suitable for the survival of the vector, the parasite, the reservoir, and the host (3). Geographical prevalence of HAT is directly proportional to the distribution of the vector which inhabits plants alongside water sources.

The number of new HAT cases has consistently decreased since vector control measures and systematic screening of the whole population in high-risk areas, along with treatment for the cases found, were performed (Figure 2).

Gambiense HAT cases represent 95–97% of the total proportion of HAT, whereas rHAT has accounted for the remaining 3–5% of cases (30, 31). Three hundred gHAT foci are mentioned and, among these, there are some difficult-to-reach areas where transmission intensity is not well known because of environmental conditions and a lack of an effective surveillance system (32).

In 2021 the number of reported cases of gHAT was 747 and more than half of them (425) was reported in Democratic Republic of Congo (33). Gambiense HAT is an anthroponosis: Humans are the main reservoir, while animals are accidental hosts. Several studies have been conducted to understand the hypothetical role

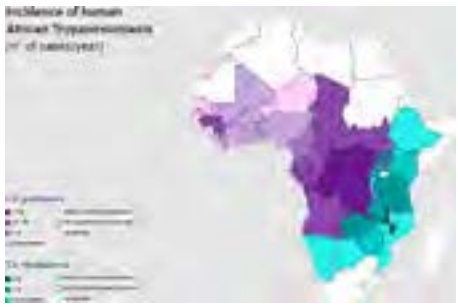

FIGURE 2
Incidence of Human African Trypanosomiasis: *T. b. gambiense* and *T. b. rhodesiense* (number of new reported cases of HAT for year) and geographical distribution in 2020.

of domestic animals as occasional reservoirs of gHAT in the transmission of the disease to humans, but more data are requested (34–38). In the gHAT, human activities are the main determinant risk factors to determine human-fly contact (39–42). In general, gHAT is predominant in young adults and males, involved in productive activities. In some areas, a higher infection rate among adolescent has been documented related to fishing and recreational water activities. Furthermore, equal incidence has been reported between males and females whose primary activity is agriculture or household work near water (Table 1) (43, 44).

Rhodesiense HAT is found in sixty foci spread across thirteen African countries (Figure 2) (30, 45). It is a zoonosis; its transmission cycle mainly involves non-human reservoirs: Wild animals or livestock (46–49). The routes of transmission are strictly related to the geographical distribution of the reservoir. The wild animals are mainly kept in protected areas or national parks, in these areas human cases occur infrequently (3, 50). Exposure is higher for tourists and workers during activities involving wildlife such as trekking and safaris. The livestock is distributed nearby the villages or in the countryside and the human cases occurs regularly (51, 52). The people who carry out activities involving the cattle are at higher risk (Table 1). In some areas, they cohabitate, as is observed in western Tanzania (53). In recent years, only few cases of rHAT have been documented: 55 is the number of reported cases in 2021 and 49 of them were registered in Malawi, however data from several counties are missing (45). The migration of the livestock as a result of human activities and climate changes may be the cause of the expansion of rHAT into new areas, increasing the probability of geographical overlap between both forms. Uganda is the only country in Sub-Saharan Africa where both types of trypanosomiasis are detected (54–56).

The reported cases of HAT in non-endemic countries are strictly related to human population movement, including traveling, business connection and migration. Most non-endemic HAT cases were detected in Europe, USA, and South Africa (57).

Other atypical transmission routes have been described, but they are very rarely:

TABLE 1 HAT epidemiology summary.

Trypanosoma brucei gambiense	Trypanosoma brucei rhodesiense
95-97% of the cases reported	3-5% of the cases reported
Chronic disease, (Gambiense HAT) lasting months to years	Acute disease (Rhodesiense HAT) lasting a few weeks
Western and Central Africa	Eastern and Southern Africa
Anthroponosis, humans are the main reservoir	**Zoonosis,** animals (livestock and wildlife) are the main reservoirs Human are occasionally infected
Transmission: human/mammalian host- tsetse fly- human	**Transmission:** Animal - tse-tse fly - animal Animal - tsetse fly - human Human -tsetse fly- human Seasonal variation in transmission linked to the density of the *Glossina* (higher after the rainy season)
Higher incidence in young adults, involved in productive activities (hunting, fetching firewood and water, fishing, washing clothes or food, cultivating)	**Higher incidence in young adults at working age, tourist visiting areas where wildlife is preserved, workers who carry out activities involving the cattle**

- vertical transmission (diagnosis of HAT in the days following the birth, also in non-endemic countries from infected mothers) (58–60);
- Accidental mechanical transmission in laboratories (61);
- Blood transfusion and organ transplantation (62, 63);
- Possible sexual contact (only one case has been reported) (64).

Clinical manifestations

Infection occurs in two stages: The first stage is the hemolymphatic stage, characterized by the restriction of trypanosomes to the blood and the lymph systems. The second stage is characterized by the active CNS invasion (Table 2) (65).

T. b. gambiense infection has a chronic progressive course that can last over 3 years, mimicking hematological conditions. In contrast, *T. b. rhodesiense* disease is more severe and acute and can lead to death in some months; patients usually present acute febrile septic-pyrexia-like illness (Table 2) (66).

Findings from a long-term follow-up in the Ivory Coast carried out on 50 patients with diagnosis revealed that after 15 years patients who refused treatment for gHAT became asymptomatic, with no parasites detectable in the blood and some patients became seronegative. These findings support the existence of the mechanism of trypanosome-tolerance in humans, already known in animals (67). There has been no strong evidence for self-cures or trypanosome-tolerance in rHAT, which is a more acute and severe disease.

Early-stage symptoms

The typical symptoms' onset is from 1 to 3 weeks after tsetse fly bite, and early-stage phase is non-specific, characterized by headache, malaise, arthralgia, weight loss, fatigue, and intermittent fever. Then, patients may develop various features including lymphadenopathy, splenomegaly and hepatomegaly. In addition, the cardiovascular system can be involved (myocarditis, pericarditis, and cardiac failure). Multiples organ can be target of disease with iritis, keratitis, and conjunctivitis, endocrine impairment (such as dysmenorrhea, sterility, impotence and gynaecomastia), nephropathy; all these clinical presentations are not typically severe, and usually do not lead to death before the initiation of the second phase of the disease. First-stage symptoms may be preceded by the development of a trypanosomal chancre at the site of inoculation within day 2-14 from infected fly bite. It commonly occurs with *T. b. rhodesiense*, rarely with *T. b. gambiense*, although chancres are reported in imported cases of *T. b. gambiense*. Travelers from non-endemic countries have shown atypical manifestations, with mainly gastro-intestinal symptoms and limited lymphatic involvement; this is supposed to be caused by host-genetic factors, but further studies are needed (68).

Posterior cervical lymphadenopathy, known as Winterbottom's sign, is a typical feature of *g*HAT.

Late-stage symptoms

T. b. gambiense infection progresses to the second stage after an average of 300–500 days, whereas *T. b. rhodesiense* infection progresses to the second stage after an estimated 21–60 days.

According to the analysis of Blum et al, almost 74% of patients develops typical symptoms of sleeping disturbance, such as reversal of the normal sleep/wake cycle, with nocturnal insomnia and daytime somnolence, uncontrollable episodes of sleep, and an alteration of the structure of sleep itself (4, 69).

During the late stage of the disease, a wide constellation of symptoms and signs can occur, with almost all regions of the peripheral and central nervous system potentially involved. Motor disturbances include motor weakness, tremor, uncoordinated movements and speech anomalies. Myelitis, myelopathy, muscle fasciculation, and peripheral motor neuropathy might also occur.

Psychiatric involvement is frequent with 25% of patients displaying behavioral disturbances (69).

Other features include sensory disturbances such as deep hyperesthesia, pruritus, anesthesia and paresthesia, seizures, and visual problems such as optic neuritis, double vision, optic atrophy, and papilledema (4). In travelers and expatriates with imported HAT from non-endemic countries progression to late-stage disease is rapid (70), while in African immigrants, HAT can be delayed and characterized by a low-grade fever and few neurological and psychiatric symptoms and signs.

Imported HAT in travelers

The HAT clinical presentation in travelers from non-endemic countries is often atypical as they present with mainly gastro-intestinal symptoms such as diarrhea and jaundice, for unknown reasons, which probably are related to host-genetic factors (68).

Due to the variability and non-specificity of the clinical manifestations, the potentially long latent period, even years, for gHAT and the lack of experience of the healthcare staff in non-endemic countries, the initial diagnosis could be missed and this may lead to further clinical progression of the disease: There are anecdotal reports of patients in whom after many years the disease has made its onset with psychiatric symptoms, so they were admitted to psychiatric wards and treated with psychiatric drugs, before reaching the diagnosis (71). In travelers, most patients affected by *T. b. rhodesiense* or *gambiense* report an unspecific acute clinical syndrome and only an accurate travel history with the identification of chancre, in the site of the tsetse fly bite raise the clinical hypothesis of a HAT diagnosis. The diagnostic hypothesis is guided by anamnestic data and suggestive clinical presentation, especially in patients from east Africa (72).

Diagnosis

The diagnosis is based on the direct examination and visualization of the parasite in peripheral blood, lymph node aspirate, cerebrospinal fluid (CSF) and in the chancre (fresh or fixed and Giemsa-stained preparation), where they can be detected a few days earlier than in the blood (73).

For *T. b. rodesiense*, the diagnosis through microscopic observation of blood or other biological fluids is easier due to the high parasitemia that is reached during the infection. In the case of infection with *T. brucei gambiense* the parasitemia is generally lower and the symptoms often more subtle, therefore serological tests have been introduced to support the diagnosis. The first introduced was CATT (Card Agglutination Test for Trypanosomiasis): This is a fast and simple agglutination assay for detection of *T. b. gambiense*-specific antibodies in the blood, plasma, or serum directed against purified variable surface antigens of the parasite. However, despite the simplicity of execution, this test has important limitations: in fact, in contexts of low prevalence of the disease, if on the one hand the negative predictive value (NPV) of the test remains high (few false negatives), on the other hand it has a low positive predictive value (PPV), estimated between 5 and 50% due to the high false positive rate. Subsequently different RDTs (Rapid Diagnostic Tests) were introduced: In particular, the lateral flow immunochromatographic assays (LFIAs) are based on the search for antibodies directed against trypanosome antigens and they have high sensibility and specificity, but they have the same limitations of the CATT (low PPV) and are unable to distinguish between previous infection and current infection. This implies that, if the CATT o RDTs are used as screening test for gHAT, a positive result still requires microscopy confirmation of the diagnosis, to avoid overtreatment with potentially toxic drugs (74).

Moreover, very low parasitemia requires concentration techniques to detect infection through microscopic examination. The most sensitive technique is represented by mini anion exchange centrifugation technique (mAECT) which consists in separating trypanosomes present in the blood sample by anion exchange chromatography and then concentrating them by low-speed centrifugation. This allows to examine a large volume of blood and therefore to detect concentrations of parasites lower than 50 trypanosomes/ml (75).

The CSF white blood cell count is the most widely used technique for stage determination; also, protein concentration in the CSF is diagnostic because proteins are elevated in HAT patients and range from 100 to 2,000 mg/liter. High level of IgM in CSF is

TABLE 2 Clinical manifestations of Human African Trypanosoma: Signs and symptoms.

	SYMTOMPS	CLINICAL SIGNS
Early stage	Headache Malaise Weakness Fatigue Pruritus Arthralgia	Hepatosplenomegaly Weight loss Fever Lymphadenopathy Winterbottom's sign (posterior triangle cervical lymphadenopathy)
Late stage	Nocturnal insomnia Daytime somnolence Episodes of sleep Motor weakness Peripheral motor Neuropathy Double vision	Tremor Uncoordinated movements Speech anomalies Papilledema

diagnostic for second-stage disease. Other tests are based on polymerase chain reaction (PCR) technology, and serological tests that can demonstrate the antibodies after 3-4 weeks of infection (73).

The staging of the disease by examining the CSF is essential, and an elevated white blood cell count (>WBC 5 cells/µL) or the presence of trypanosomes in the CSF indicate a second stage disease. The quantitative buffy coat (QBC) has the advantages of concentrating the parasites by centrifugation and is a very sensitive technique (76).

Following the recent introduction of fexinidazole in the therapeutic armamentarium (see below), HAT is classified into 3 subclasses according to the number of WBCs on the CSF (Table 3) (5).

Blood parameters that are suspicious for HAT infection are increased sedimentation rate and low hematocrit, but these are non-specific signs of inflammation. Thrombocytopenia is generally mild or absent, liver and renal function tests are usually within normal limits or slightly elevated. Low serum C3 levels and split C3 products can be found, reflecting complement activation (77).

Treatment and management

All HAT patients should undergo anti-trypanosomal treatment. However, the choice of treatment depends on the infecting subspecies (*T. b. gambiense* versus *T. b. rhodesiense*) and the stage of the disease (Table 4).

Drugs overview

- Pentamidine

It is a di-cationic aromatic diamidine and its mechanism of action is due to the binding to the double helix DNA of the trypanosome at the level of the AT-rich sequences, preventing replication and transcription in the kinetoplast and/or in the nucleus. It accumulates in the trypanosome cell and does not leave it even when the drug is removed from the extracellular space (78). Other mechanisms involved in the trypanocide activity of pentamidine appear to be the selective inhibition of the plasma-membrane Ca2+-ATPase of *T. brucei* (79) and the collapse of the mitochondrial membrane potential (80), but it is not clear if the latter is a consequence of the pentamidine-induced kinetoplast dysfunction or constitutes an independent effect of the drug (81). Due to its chemical structure, pentamidine does not cross cell membranes, but requires transporters. The mutation of the genes encoding these membrane transporters explains the eventual resistance to the drug by *T. brucei*. The first discovered was P2 (Purine transporter 2), encoded by the TbAT1 gene, and it is responsible for the uptake of both melarsoprol and pentamidine and its mutation determines a high resistance to melarsoprol and low to pentamidine (82).

Therefore, other possible transporters involved in resistance mechanisms have been studied, identifying a high-affinity transporter for pentamidine and melaminophenyl arsenic drugs, whose mutation is the main responsible for resistance to both these drugs (83). Despite the existence of these resistance mechanisms, the cure rate in case of treatment of the first stage of gHAT with pentamidine is between 93 and 98% and it has not decreased over decades (5). Furthermore, pentamidine does not cross the blood-brain barrier and therefore its use is indicated only in the hemolymphatic phase. However, some studies have demonstrated the efficacy of pentamidine also in the early-second stage (84). Currently it is used for the treatment of the first gHAT stage, if fexinidazole is contraindicated (5). Pentamidine is not indicated as a first-line treatment for the first rHAT stage as several therapeutic failures have been recorded in the past. However, it constitutes the second line of treatment in case of unavailability of suramine (3).

- Fexinidazole

It is a new drug approved by EMA in 2018 for the gHAT treatment. It is a nitroimidazole derivative from which the parasite's nitroreductase generates reactive amines and other metabolites, which have a toxic effect on trypanosomes. The great advantage of this drug over the others is the oral administration, which could avoid hospitalization, and the risks associated with parenteral or intramuscular treatments. Its effectiveness has been demonstrated both in the first and in the second stage of the disease: Specifically, fexinidazole showed an efficacy of over 99% in the first stage and in the early second stage of gHAT, and 91% in the late second stage, lower than the 97% efficacy rate obtained during Nifurtimox/Eflornithine Combination Therapy (NECT). This efficacy rate, however, is fully acceptable considering the great advantage of access to treatment for a greater number of people using the oral formulation and avoiding the need for lumbar puncture to differentiate clinical disease stages (if there is no clinical suspicion of severe second-stage), mostly in areas where access to diagnostic tools and hospital care is limited (85, 86). Fexinidazole could be administered also to non-hospitalized patients. It has few side effects: The most frequent are vomit, nausea and asthenia,

TABLE 3 Categorization of Human African Trypanosoma based on CSF findings (according to WHO guidelines 2019).

STAGE		CSF FINDINGS
FIRST-STAGE	Haemo-lymphatic stage (first-stage)	≤ 5 WBC/µL AND no trypanosomes in CSF
SECOND-STAGE	Meningo-encephalitic stage (early second-stage)	> 5 WBC/µL with or without trypanosomes in CSF
	Severe meningo-encephalitic stage (severe second-stage)	≥ 100 WBC/µL with or without trypanosomes in CSF

prolongation of QT interval and psychiatric disorders (insomnia, hallucinations, ecc) (87). Fexinidazole is currently only indicated for the treatment of gHAT. The safety and efficacy of the drug for the treatment of the first and second stages of rHAT is still being studied with a project launched in 2018 and supported by the Drugs for Neglected Diseases initiative (DNDi) (88, 89).

- NECT (Nifurtimox/Eflornithine Combination Therapy)

Eflornithine is an analogue of the amino acid ornithine and a suicide inhibitor of ornithine decarboxylase (ODC). This is a fundamental enzyme to produce polyamines, essential for cell division. The ODC of *T. b. gambiense* is very stable and

TABLE 4 Schematic overview on drugs used for the treatment of Human African Trypanosomiasis.

DRUG	MODE OF ACTION	INDICATION	DOSAGE	ADVERSE EFFECTS	RESISTANCE
PENTAMIDINE	- preventing replication and transcription in the kinetoplast and/or in the nucleus - inhibition of the plasma-membrane Ca2+-ATPase - collapse of the mitochondrial membrane potential	first stage of gHAT, if fexinidazole is contraindicated	4 mg/kg i.m. once a day for 7 days	- hypotension (if administered iv), - nausea and vomit - hyperazotemia - Diabetes mellitus	- caused by mutations of genes encoding membrane transporters (P2, TbAQP2); - melarsoprol cross-resistance. - low rate of therapeutic failure.
FEXINIDAZOLE	production of reactive amines and other metabolites with toxic effect on trypanosome.	First and early second stage of gHAT (only if patient is > 6 years and body weight > 20 kg)	body weight >35 kg: loading dose 1800 mg orally for 4 days, than 1200 for 6 days body weight 20-34 kg: loading dose 1200 mg orally for 4 days, than 600 for 6 days	- vomit and nausea - asthenia - prolongation of QT interval	Probably type 1 nitroreductase mutations, possibly cross-resistance with Nifurtimox
EFLORNITHINE (monotherapy)	Suicide inhibitor of ornithine decarboxylase (ODC), inhibition of polyamine biosynthesis	Alone only in second-stage gHAT when NECT is not feasible because nifurtimox is unavailable or contraindicated and when fexinidazole cannot be given.	100 mg/kg e.v. every 6 h for 14 days	- Itching - Fever - Headache - Abdominal pain, nausea, vomiting, diarrhea -Myelosuppression.	Loss of a membrane transporter for amino acids (TbAAT6)
NECT (Nifurtimox/ Eflornithine combination therapy)	Nifurtimox: unknown mechanism, perhaps through the generation of free radicals. Eflornithine: see above	- First choice in severe second stage gHAT - Early second stage gHAT if fexinidazole is contraindicated	Nifurtimox: 5 mg/kg every 8 hours for 10 days. Eflornithine 200 mg/kg iv every 12 hours for 7 days.	- frequent (>50%) but mild gastrointestinal symptoms - headache	Nifurtimox: probably type 1 nitroreductase mutations, possibly cross-resistance with fexinidazole Eflornithine: see above
SURAMIN	Inhibition of various enzymes: dihydrofolate reductase, thymidine kinases, glycolytic enzymes, and many others.	First stage rHAT	Test dose of suramin at 4–5mg/kg on day 1, followed by injections of 20 mg/kg every 7 days for 5 weeks	nephrotoxicity, usually reversible	Expression of the variant surface glycoprotein (VSGsur)
MELARSOPROL	formation of toxic adducts with trypanothione and to alterations of the parasite's mitotic processes through action on multiple kinases	- first choice in second stage rHAT - treatment of recurrent relapse after first-line and rescue treatments of gHAT	2.2 mg/kg iv once daily for 10 days + prednisolone 1 mg/kg for 12 days with dose tapering in the last 3 days	-encephalopathic syndrome -heart failure	-Caused by mutations of genes encoding membrane transporters (P2, TbAQP2); - Pentamidine cross-resistance; - High rate of therapeutic failure - The only clinically relevant resistance
ACOZIBOROLE (on clinical trial)		Both stages of gHAT	Single oral dose		

irreversible inhibition by eflornithine ensures that the trypanosome cell is deprived of these polyamines for a long time, since it does not have a transport system for them. The ODC of *T. b. rhodesiense* has a much shorter half-life than that of *T. b. gambiense* and this difference seems to explain the ineffectiveness of eflornithine in the treatment of rHAT (78). It is a trypanostatic drug, therefore it is necessary that the immune system is intact in order to achieve the cure. In immunocompromised subjects, Eflornithine alone can cause therapeutic failure (5). The main mechanism of acquisition of trypanosome resistance to eflorinithine seems to be linked to the loss of a membrane transporter for amino acids, caused by the mutation of the TbAAT6 gene that encodes it, rather than to mutations in the gene that encodes for decarboxylase (79, 90).

Nifurtimox is a nitro-heterocyclic trypanocide whose exact mode of action is unknown: It seems that it can generate free radicals such as superoxide (78), through a NADH-dependent type 1 nitroreductase (NTR), whose reduced expression could explain the onset of resistance to nifurtimox (91) and a cross-resistance with fexinidazole (92). Nifurtimox has low trypanocidal activity therefore its use as monotherapy is not indicated, but its use has been approved in combination therapy with eflornithine, NECT (93). This combination regimen replaced the previous 2 weeks eflornithine monotherapy, considering that NECT is non-inferior (94, 95), simpler, shorter, burdened with fewer side effects and less expensive than eflornithine monotherapy (96–100). NECT became the first-choice treatment for severe second stage gHAT with > 100 WBC/μL in CSF and in early second-stage gHAT (> 6-99 WBC/μL in CSF) when fexinidazole is contraindicated (i.e. children aged < 6 years, body weight < 20 kg). Eflornithine alone is only used in second stage gHAT when NECT is not feasible because the companion drug nifurtimox is unavailable or contraindicated and when fexinidazole cannot be given. Hospitalization of the patient is required as these drugs are administered intravenously (5). Moreover, the combination therapy with two drugs with different pharmacological activity seems to protect against the onset of resistance to individual drugs. Nifurtimox causes oxidative stress while eflornithine, by blocking the biosynthesis of polyamines, causes a reduction in the biosynthesis of trypanothione, which constitutes the main oxidative stress protection system. This combined effect may explain the increased parasiticidal effect when used in combination therapy, even if they do not seem to have a synergistic effect (93). NECT is generally well tolerated and the most frequent side effects are gastrointestinal symptoms that occur in more than 50% of cases but are generally mild and do not require discontinuation of therapy (5).

- Suramin

Is the first drug used for the treatment of sleeping sickness. Suramin carries out its antiparasitic activity by inhibiting various enzymatic targets: dihydrofolate reductase (101), thymidine kinases (102), glycolytic enzymes (103) among the others (104). Suramin is a large molecule that has six negative charges at physiological pH, therefore it does not cross cell membranes and needs transporters to enter the cell. This mechanism seems to be represented by at least two different receptor-mediated endocytosis pathways (104). Due to its chemical characteristics, suramine does not cross the blood brain barrier; therefore, it is indicated only for the first rHAT stage. Although it is active in the first gHAT stage, it is preferred to use fexinidazole or pentamidine due to the greater manageability of these drugs and because suramine is also active on onchocerciasis, whose prevalence is higher in endemic regions for *T. b. gambiense*, and its administration to people co-infected with these two parasites can lead to the development of severe immunological reactions. The main adverse reaction is represented by nephrotoxicity, which however is generally moderate and reversible (3)..

Recent studies have shown that trypanosome strains expressing VSGsur possess heightened resistance to suramine; in fact, VSGsur is capable of binding tightly to suramine unlike the other types, causing phenotypic resistance (105, 106). However, after more than 100 years of using suramine, trypanosome resistance to this drug is still not a problem and, in almost all cases, the treatment of the first rHAT stage is highly effective. Therapeutic failures can occur if the parasite has already crossed the blood brain barrier, where the drug cannot reach it (105).

- Melarsoprol

It is an arsenic-derived drug introduced in 1949 whose mechanism of action seems to be linked to the formation of potentially toxic adducts with trypanothione and to alterations of the parasite's mitotic processes through its action on multiple kinases (81). Melarsoprol needs a specific uptake to enter the cell and exert its action. This uptake occurs *via* P2 adenosine transporter (encode by AT1 gene) and aquaglyceporin 2 (AQP2), that are parasite-specific, being therefore responsible for selective toxicity of the drug (94, 107). The mutations of the genes that code for these transporters are partly responsible for the onset of drug resistance, which emerged already in the 1970s and widely spread at the end of the years '90. In fact, around the 2000s, high rates of therapeutic failure of melarsoprol therapies were recorded (around 20%), especially in DRC (108), Uganda (109, 110), Angola (111) and southern Sudan (112). Pentamidine uses the same transporters as melarsoprol to enter the cell so there can be cross-resistance between these two drugs (83). However, for now, resistance to melarsoprol remains the only clinically relevant one (107).

Other resistance mechanisms have been studied, such as mutations of the genes encoding the kinases involved in the control of the cell cycle of the parasite (81). The main side effect related to this drug is a severe encephalopathy syndrome, that is likely an immune phenomenon, whose incidence ranges from 2 to 10% of all patients treated with melarsoprol and is fatal in about 50% of those affected. It usually occurs 7–14 days after the first injection of the drug. Three clinical forms of melarsoprol-associated encephalopathy have been proposed: Coma type, convulsion type and psychotic reactions. The first two have a worse prognosis than the last (113, 114). In the event of the onset of this syndrome, discontinuation of administration and the use of corticosteroids are indicated (5). Heart failure is also common in patients treated with melarsoprol, but it is unclear whether this is mainly attributable to drug toxicity or the known pathogenicity of HAT on the cardiovascular system (5). Given the high incidence of serious

adverse effects, the availability of other drugs and widespread drug resistance, melarsoprol is now only indicated in rHAT second stage and in the treatment of recurrent relapse after first-line and rescue treatments (including NECT, NECT-long, fexinidazole or eflornithine monotherapy) in gHAT (3, 5). Concomitant administration of oral prednisolone is indicated to prevent encephalopathy. The administration of the drug requires the hospitalization of the patient (5, 115). To solve the problems related to therapy with melarsoprol, the association of melarsoprol with cyclodextrin molecules (melarsoprol-cyclodextrin complex) has been proposed: This association does not seem to affect the trypanocidal effect of the compound, but it seems to improve its ability to cure the second phase of rHAT and reduce the neuroinflammatory reaction; moreover it could be administered orally, avoiding hospitalization and reactions associated with intravenous infusion of the drug (116). This new formulation requires further studies to allow its approval, but in 2012 the WHO added it to the list of orphan drugs (117).

- Acoziborole

Acoziborole is a new oral compound that in preclinical data has shown activity against *T. b. gambiense* and to reach adequate concentrations for the treatment of all stages of gHAT after a single oral dose of 960 mg in the fasted state.

A recent trial reported a success rate at 18 months of 100% in 41 patients with early/intermediate stage and 95.2% in 167 patients with late stage, with a safety profile. Its approval and introduction would be an important tool in achieving the elimination of *T. b. gambiense* sleeping sickness, especially in those areas where access to medical care is limited, because it could eliminate the need for lumbar puncture and hospitalization of the patient and would not require adherence to the assumption of the therapy that currently instead fexinidazole requires (118–120).

Treatment of *T. b. gambiense* HAT

To decide what treatment the patient diagnosed with gHAT will undergo, the presence of signs and symptoms indicative of a severe second-stage disease (e.g. sleep and movement disorders, see above) is evaluated. If these are absent, it is not considered necessary to perform the lumbar puncture and, if the patient is over 6 years old and weighs more than 20 kg, he can be treated with fexinidazole. This therapy will be taken at home if there is probable certainty of the patient's adherence to the therapy and food intake, otherwise it will be administered in the hospital. If there are criteria for exclusion from therapy with fexinidazole or in case of unavailability of this drug, the patient will be a candidate for NECT or pentamidine therapy, therefore lumbar puncture will be indicated. If there is a clinical suspicion that the disease is in a severe second stage, lumbar puncture is required. If the lumbar puncture cannot be performed, it is indicated to prescribe NECT. If, on the other hand, lumbar puncture is performed and there are less than 100 WBC/μL in CSF and the patient is older than 6 and weighs more than 20 kg, oral therapy with fexinidazole is indicated. If there are less than 100 WBC/μL in CSF and the patient is younger than 6 and weighs less than 20 kg, oral therapy is not possible: So if there are 5 WBC/μL in CSF or less and no trypanosomes are present, the patient will be treated with pentamidine. In case of WBC above 5/μL he will be treated with NECT (5) (Table 5).

Treatment of *T. b. rhodesiense* HAT

Treatment options for rHAT are more limited: the drug of choice for the first stage is suramine. If this is unavailable or contraindicated, the alternative is represented by pentamidine. The only drug available for the second stage (WBC > 5/μL of CSF) is melarsoprol, which as mentioned above has high toxicity and significant resistance rates (3) (Table 6).

Elimination strategies

gHAT

As mentioned above, humans are the main reservoir of *T. b. gambiense*, therefore elimination strategies must aim first at the diagnosis and treatment of infected subjects to reduce reservoir and transmission to healthy susceptible patients. Moreover, the symptoms in infected people can be absent or vague for a long

TABLE 5 Algorithm on the management of persons with Gambience HAT in accordance to WHO recommendation.

Characteristics of the patient	Clinical manifestations	Indication to LP	CSF findings	First choice treatment
< 6 years < 20 kg (fexinidazole contraindicated)		Yes	</= 5 WBC/μL	Pentamidine
			6-99 WBC/μL	NECT
			LP not executable	
> 6 years >20 kg	NO sign/symptoms of severe gHAT	Not indicated	-	Fexinidazole
	Presence of sign/symptoms of severe gHAT	Yes	< 100 WBC/μL	Fexinidazole
			>/= 100 WBC/μL	NECT
			LP not executable	

CSF (cerebrospinal fluid), NECT (Nifurtimox/Eflornithine combination therapy), WBC (white blood cells).

time, so often there is an important diagnostic delay. For these reasons, the most effective strategy is the active case detection through mobile teams. The second strategy is vector control, trying to eliminate the tsetse mosquito or prevent its bite. The strategies already used have made it possible to achieve a better target than that set by the WHO for 2020: In fact, the eradication program hoped to reach less than 2000 cases declared per year by 2020, but already in 2019, fewer than 1000 cases were declared. The new goal set by WHO is zero cases of gHAT declared per year by 2030 (interruption of transmission), as indicated in the NTD road map 2021-2030 (6).

- Active case detection

It consists in the mass screening of the population at risk carried out by mobile teams through the use of CATT or RDTs (see above in "Diagnosis" section). The first one requires specialized staff, the maintenance of the cold chain and an agitator (and thus electricity) to be performed and this makes it difficult to use it in screening in rural areas (74, 121).

RDTs are easy to use and interpret, and they have features that allow their use even in rural endemic areas (74). Anyway, both tests are characterized by low PPV (74). In settings where there is a low incidence of the disease, tests with high specificity and high positive predictive value are necessary to identify the reservoirs and treat them (test-and-treat strategy), avoiding false-positives that could generate alarm, the implementation of unnecessary actions and the over-treatment of the population. Therefore, due to their characteristics, both CATT and RDTs are not suitable for screening in the population in which there is a very low incidence of disease or for post-elimination monitoring and other tests are being developed for these settings (122). An algorithm for active screening strategies for the elimination of gHAT in foci where transmission is high or moderate (annual incidence > 1 case per 10,000 people over the last 5 years) has been proposed by WHO (3) (Figure 3).

- Passive case detection

It consists in the diagnosis of trypanosomiasis of patients who seek for care in health centers. The effectiveness of this action in elimination strategies is very limited by several factors: first, in low endemic areas the staff could be unconfident with HAT. Therefore, diagnostic algorithms were developed to suspect the disease based on the three main symptoms: Sleep disturbances, weight loss and neurological symptoms. Health center facilities often do not have rapid tests and blood samples must be sent to referral centers. Third, the patients can be asymptomatic or paucisymptomatic for a long time and can access to a health center several months after symptoms' onset, representing a potential long-lasting human reservoir (123).

rHAT

Prevention and control measures of rHAT are complex because it is a zoonosis and the main reservoir is represented by animals (livestock and wildlife), which ensure the maintenance of a population of infected tsetse flies that occasionally transmit the disease to humans. At this moment, complete transmission disruption and elimination are not possible. For this reason, in NTD road map 2021-2030 rHAT is targeted for elimination as a public health problem (<1 case/10 000 people/year, in each health district calculated on the average of the previous five years) (6).

TABLE 6 Treatment options for rHAT.

Stage	First choice	Alternative regimen
First-stage	Suramin	Pentamidine
Second-stage	Melarsoprol + prednisolone	

FIGURE 3
Algorithm proposed by the WHO for active screening strategies for the elimination of gHAT in foci where transmission is high or moderate.

Control of the parasite in the animal reservoirs and/or reduction of tsetse vector populations play a key part with medical interventions in reducing human cases (3).

- Active case detection

The clinical diagnosis of rHAT is complex because of unspecific symptoms and signs. There are no serological tests to facilitate the diagnosis, although the high level of parasitemia during the infection could improve the detection of an active case. In consideration of the epidemiology and the acute presentation of the disease, active detection of infected individuals is inefficient and cost ineffective.

- Passive case detection

The systemic nature of symptoms in the first stage, the lack of early recognition of the disease by clinicians and the low experience in optical microscopy diagnosis cause important delays in detection and treatment. Such delay increases the chance of the second stage disease, whose fatality rate is 2.5 times higher than that of patients at first-stage disease (124, 125).

The aim of passive case detection is therefore to identify and treat rHAT cases as quickly as possible and to do this it is necessary to develop reliable rapid diagnostic tests and enhance the capacity for treatment of the health care facilities (53).

- Control of animal reservoirs.

Control of transmission from the animal reservoir is required to control rHAT (3). While the treatment of livestock with anti-trypanosome drugs and specific insecticides is relatively cheap and easily feasible and has proven to be effective in reducing reservoir and vectors, on the other hand, treatment of the wildlife is not a viable option as it would be extremely expensive and difficult to implement. For this reason, contact between humans and wildlife should be limited or, if it is not possible, appropriate protective measures should be used to avoid tsetse fly bites (53, 126).

Vector control: Methods and efficacy to reduce the diffusion of Human African Trypanosomiasis

Vector control is used to diminish the tse-tse fly population to a level at which the transmission infection is significantly reduced and is the primary method to control animal trypanosomiasis (3).

Over the years, different methods have been used, depending on economic resources, epidemiology and specific environmental factors. The principal methods are: clearing of vegetation; ground spraying of insecticide at the tse-tse breeding sites (127); persistent insecticides (no longer used due to environmental concerns); live animal or artificial baits like insecticide-treated cattle (128) or traps (129–131) and insecticide impregnated screens (132, 133),

The elaboration of cost-effective vector control strategies needs to consider various factors including the geography of the place, the human and vector population density, the presence of animal reservoirs, the operational costs, the prevalence of the disease, the environmental impact, etc.

With regards to gHAT, although active case detection and treatment and passive surveillance are considered the main strategies for elimination of the disease and have made it possible to greatly reduce the incidence of the disease, several studies have demonstrated the importance and efficacy of vector control in reducing the tsetse fly population to achieve the interruption of the transmission and the elimination of the diseases (134).

Previously vector control strategies for gHAT were considered too expensive for low resource countries (135), however the introduction of Tiny Targets, insecticide-impregnated panels that attract and kill tse tse flies, has proven to be advantageous and economically sustainable in these settings (132, 136–138).

As mentioned, the goal of vector control strategies is not to completely eliminate tse tse flies, but to reduce their density by at least 70%, as it has been seen that this allows to reach the interruption of the transmission of the disease. For example, in a study carried out in Uganda the use of Tiny Target near watercourses has been shown to reduce tsetse population density by more than 90% and achieve the goal of stopping transmission in these areas. However, Tiny Targets require maintenance and a median life of 61 days of these instruments was recorded, with discrete variability based on their location (139).

Moreover the vector control strategies and the use of Tiny Targets cannot be standardized and replicated in the same way for each situation, but it must be elaborated according to the specific characteristics of each setting (140).

Therefore a recent study examined five different health districts of the Democratic Republic of Congo (the country with the highest burden of gHAT) and for each one developed the most appropriate and cost-effective elimination strategy pattern, combining active screening, passive screening and vector control, based on the particular features of the setting and also considering the role of the recently introduced oral drug, fexinidazole (141).

The role of animals as a reservoir of infection for *T. b. gambiense* and their impact on achieving elimination of the disease is still debated: however, the implementation of vector control strategies can also have an effect in reducing any transmission between animals and humans (142, 143).

A study based on mathematical models found that animal transmission appears to be statistically significant in 24 of 158 geographic areas considered in the study. From the same model that takes animal transmission into account, it emerged that by reducing the population of vectors (responsible for the transmission of the disease from both animals and humans) in addition to the medical activities, in 147/158 zones it would be possible to achieve the goal of elimination of transmission by 2030, compared to 61/158 foreseen by the model without vector control (144).

With regards to rHAT, vector control plays a fundamental role in reducing the animal reservoir and therefore the risk of transmission to humans. Among the methods proposed, one of the most cost-effective seems to be the use of insecticide-treated cattle (ITC), in particular the restricted application of insecticides in the areas of the body of the animals most exposed to vector bites (foot and belly) every two weeks (145). In a study based on

mathematical models this vector control strategy was found to be more advantageous than the use of trypanocides in a setting in Uganda where the presence of wild reservoirs is limited (146).

A Progressive Control Pathway has been proposed to achieve elimination of African Trypanosomiasis in animals and, in the context of vector control, suggests a first suppression phase, aimed at reducing the population density of tsetse, followed by an elimination phase. Some techniques are considered more effective in the suppression phase, as ITC (insecticide-treated cattle, see above), ITT (insecticide-treated target) and SAT (aerial spraying), while SIT (Sterile Insect Technique) seems to be more useful for the phase of elimination, considering that it is more effective when the number of vectors is lower (147).

However, according to a One Health approach, not only the economic sustainability of these techniques must be evaluated, but also the impact on the environment, biodiversity and human and animal health. In this regard, the sterile insect technique seems to be one of the most environment friendly (148).

Maybe even more than gHAT, vector control strategies for rHAT are extremely complex and require specific evaluations with teams of experts from various sectors (ecology, veterinary, medicine, epidemiology, etc.) and the awareness and involvement of stakeholders, including farmers, to develop the most appropriate strategies for each setting and the sustainability of these strategies should be assessed periodically.

Moreover, in order to optimize vector control activities for Human and Animal African Trypanosomiasis and not waste important resources in low-income settings, the impact of climate change on the distribution of the tsetse fly population must be considered. In fact, some mathematical models predict that the rising temperatures will cause the disappearance of tsetse flies from some current habitats and their movement to higher and cooler zones, currently inhospitable for them. This could lead to outbreaks of disease in areas that are not currently affected and it could make the strategies already put in place useless (149–151).

Discussion and conclusions

The early achievement of the objectives set by the WHO roadmap makes it possible to reach the goals by 2030. It would be useful to enhance training programs for healthcare workers and implement the development of highly reliable and easy-to-use rapid diagnostic tests taking into account practical needs (e.g. tests that do not require the cold chain and electricity). This would reduce the diagnostic delay which often characterizes both forms of HAT and which implies an increase in mortality and the persistence of human reservoirs.

Furthermore, the availability of new oral drugs for gHAT capable of crossing the blood-brain barrier, such as fexinidazole, would make it possible to overcome the diagnostic and therapeutic difficulties associated with peripheral settings. It would be useful to assess the efficacy of fexinidazole in the treatment of rHAT to expand the therapeutic armamentarium with low toxic, affordable and more manageable drugs, even reducing the direct and indirect costs associated with prolonged hospitalization.

Moreover the availability of an oral drug as acozoribole, which requires once administration and that could be active also in late stage, could make elimination strategies even more effective and simple, especially in peripheral settings (test-and-treat). The integration of efficient surveillance and health systems can play a key role in the elimination strategy of African trypanosomiasis. Furthermore, the effectiveness of these strategies could be increased through the implementation of a One Health approach, coordinating and strengthening the interaction between the various sectors involved (ecology, epidemiology, health system, veterinary services, sociology), as is being experienced in some countries (152, 153) and considering the impact of Climate Change on disease distribution in the coming years.

Author contributions

Conceptualization: RP, RN, and MLM; methodology FDG, DB, and AS; writing - original draft preparation LF, GGP, EP, SC, GG, and EDV; writing -review and editing: AR, VT, MC, GuP, CP, MFM, and FVS; supervision: TAB, GB, GiP, LS, CC, and EN. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Stool Xpert MTB/RIF as a possible diagnostic alternative to sputum in Africa: a systematic review and meta-analysis

PAPER

Authors
Segala F.V., Papagni R., Cotugno S., De Vita E., Susini M.C., Filippi V., Tulone O., Facci E., Lattanzio R., Marotta C., Manenti F., Bavaro D.F., De Iaco G., Putoto G., Veronese N., Barbagallo M., Saracino A., De Gennaro F.

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EDITED BY
Niaina Rakotosamimanana,
Institut Pasteur de Madagascar, Madagascar

REVIEWED BY
Jonathan Hoffmann,
Fondation Mérieux, France
Maryline Bonnet,
Institut de Recherche pour le Développement, France

*CORRESPONDENCE
Francesco Vladimiro Segala
✉ fvsegala@gmail.com

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Stool Xpert MTB/RIF as a possible diagnostic alternative to sputum in Africa: a systematic review and meta-analysis

Francesco Vladimiro Segala[1,2*], Roberta Papagni[1], Sergio Cotugno[1], Elda De Vita[1], Maria Chiara Susini[3], Valeria Filippi[3], Ottavia Tulone[4], Enzo Facci[3], Rossana Lattanzio[1], Claudia Marotta[2], Fabio Manenti[3], Davide Fiore Bavaro[1], Giuseppina De Iaco[1], Giovanni Putoto[2], Nicola Veronese[4], Mario Barbagallo[4], Annalisa Saracino[1] and Francesco Di Gennaro[1,2]

[1]Department of Precision and Regenerative Medicine and Ionian Area, Clinic of Infectious Diseases, University of Bari, Bari, Italy, [2]Operational Research Unit, Doctors With Africa CUAMM, Padua, Italy, [3]Doctors With Africa CUAMM, Wolisso, Ethiopia, [4]Geriatric Unit, Department of Internal Medicine and Geriatrics, University of Palermo, Palermo, Italy

Introduction: Worldwide, COVID-19 pandemic lead to a large fall in the number of newly reported TB cases. In sub-Saharan Africa, microbiological diagnosis of TB is generally based on smear microscopy and Xpert MTB/RIF on sputum samples, but good quality sputum samples are often difficult to obtain, leading clinicians to rely on more invasive procedures for diagnosis. Aim of this study was to investigate pooled sensitivity and specificity of Xpert MTB/RIF on stool samples compared to respiratory microbiological reference standards in African countries.

Methods: Four investigators independently searched PubMed, SCOPUS, and Web of Science until 12th October 2022, then screened titles and abstracts of all potentially eligible articles. The authors applied the eligibility criteria, considered the full texts. All the studies reported the data regarding true positive (TP), true negative (TN), false positive (FP) and false negative (FN). Risk of bias and applicability concerns were assessed with the Quadas-2 tool.

Results: overall, among 130 papers initially screened, we evaluated 47 works, finally including 13 papers for a total of 2,352 participants, mainly children. The mean percentage of females was 49.6%, whilst the mean percentage of patients reporting HIV was 27.7%. Pooled sensitivity for Xpert MTB/RIF assay for detecting pulmonary tuberculosis was 68.2% (95%CI: 61.1–74.7%) even if characterized by a high heterogeneity (I^2 =53.7%). Specificity was almost 100% (99%, 95%CI: 97–100%; I^2 = 45.7%). When divided for reference standard, in the six studies using sputum and nasogastric aspirate the accuracy was optimal (AUC = 0.99, SE = 0.02), whilst in the studies using only sputum for tuberculosis detection the AUC was 0.85 (with a SE = 0.16). The most common source of bias was exclusion of enrolled patients in the analysis.

Conclusions: Our study confirms that, in Africa, stool Xpert MTB/RIF may be a useful rule-in test for children above and below 5 years of age under evaluation for pulmonary tuberculosis. Sensitivity increased substantially when using both sputum and nasogastric aspirate as reference samples.

KEYWORDS

pulmonary tuberculosis, stool Xpert MTB/RIF, meta-analysis, systematic review, diagnostic microbiology

1. Introduction

Before the advent of COVID-19, tuberculosis was the leading cause of death from a single infectious agent, *Mycobacterium tuberculosis* (MTB). Despite being a preventable and treatable disease, it infects roughly 25% of the world population and caused at least 1.6 million deaths only in 2021, reversing a long-lasting reduction trend that started in 2000 (1). Along with an increase in TB-related deaths, the immediate consequence of the pandemic was a large fall in the number of newly reported TB cases and an estimated increase of incident cases of rifampicin-resistant TB, all indicators that represent a relevant drawback in the pursue of the 2025 End TB Milestones (2).

Since mortality of untreated TB approaches 50% and cure rates are high (3), overall disease burden is strictly dependent on diagnostic capacity. In sub-Saharan Africa, microbiological diagnosis of TB is generally based on Xpert MTB/RIF (Cepheid, USA), an automated, PCR-based assay able to detect mycobacterial DNA on respiratory samples, A newer, more sensitive version of the test has been approved by WHO in 2021, Xpert MTB/RIF Ultra, with a sensitivity approaching the one reported for culture assays (4).

In sub-Saharan Africa and other high-burden, resource-limited settings, good quality sputum samples are often difficult to obtain, leading clinicians to rely on more invasive procedures for diagnosis—such as nasogastric aspirate (5) and sputum induction, that are painful, not routinely available and require additional resources and costs such as the ones related to hospitalization and the use of suction machine and nebulizers. Besides the challenges in sample collection, MTB detection on respiratory samples in high-burden TB settings is further obstacle by extra-pulmonary tuberculosis (EPTB) (6), smear-negative pulmonary tuberculosis (PTB) and pauci-bacillary TB (7), and sputum sample collection may put healthcare workers at risk of infection due to exposure to MTB infected aerosols (8). Rapid, accurate, sputum-free diagnostics for tuberculosis are of critical need (9).

In recent years, attention has been attracted by Xpert MTB/RIF on stool samples, since mycobacteria-containing sputum may be swallowed and then be available for molecular testing. The use of Xpert MTB/RIF and Xpert MTB/RIF Ultra on stool samples has been introduced in the 2020 WHO guidelines as initial diagnostic test for children with signs and symptoms of pulmonary TB (10). However, this recommendation is based on low certainty of evidence. Also, in 2022, as part of the Global Laboratory Initiative (11) the WHO endorsed two simple, centrifuge-free methods for stool processing: the optimized sucrose flotation (OSF) method developed by the TB-Speed consortium (12), and the simple one-step (SOS) method developed by the KNCV Tuberculosis Foundation (13).

Aim of this study was to investigate pooled sensitivity and specificity of Xpert MTB/RIF on stool samples compared to respiratory microbiological reference standards in African countries.

2. Materials and methods

This systematic review adhered to the MOOSE guidelines (14) and PRISMA statement (15), following a predetermined but unpublished protocol.

2.1. Inclusion and exclusion criteria

Inclusion criteria are as follows: (i) Research highlighting the comparative assessment of the Xpert MTB/RIF or Xpert MTB/RIF Ultra assay to a reference standard, which could be either the microbiological detection of MTB (MRS, with culture, molecular or smear microscopy from either respiratory or nasogastric aspirate samples) or composite reference standard (CRS) including clinical symptoms, biochemical tests reports, radiographic results, histopathological findings, and microbiology (as defined by the authors of the individual studies), (ii) Research providing sufficient information to calculate the diagnostic performance of Xpert MTB/RIF and Xper MTB/RIF Ultra and (iii) studies conducted in African countries.

Exclusion criteria are as follows: (i) Duplicate literature studies, (ii) Research with non-human samples and animal models, (iii) Conference abstracts, lectures, commentaries, letters and case reports, (iv) Research without data (e.g., only sensitivity or specificity data), (v) performed in countries other than Africa, and (vi) publications in languages other than English.

2.2. Data sources and literature search strategy

Four investigators (SC, EdV, VF, MCS) independently searched PubMed, SCOPUS, and Web of Science until 12th October 2022. The search terms used in PubMed included combinations of the following keywords: (feces OR stool) AND (tuberculosis OR Mycobacterium tuberculosis OR TB OR MTB OR EPTB OR PTB) AND (Xpert Gene OR Xpert OR Xpert MTB/RI OR GeneXpert OR GeneXpert MTB/Rif). We considered the reference lists of all included articles and of previous related reviews.

2.3. Study selection

Following the searches as outlined above, after removal of duplicates, four independent reviewers (SC, EdV, VF, MCS) screened titles and abstracts of all potentially eligible articles. The authors applied the eligibility criteria, considered the full texts, and a final list of included articles was reached through consensus with a third senior author (NV).

2.4. Data extraction

Four authors were involved in data extraction in a standardized Microsoft Excel database. For each article, we extracted information

about authors, year of publication, number of patients, setting, country, study design, age, percentage of females and of patients with HIV, the use of stool GeneXpert or Xpert Ultra, number of true positive, true negative, false positive and false negative results.

2.5. Outcomes

The primary outcomes were sensitivity, specificity, positive and negative likelihood ratios, and the area under the curve (AUC) of stool Xpert MTB/RIF and stool Xpert MTB/RIF Ultra.

2.6. Assessment of study quality

Based on the revised quality assessment of diagnosis, accuracy studies-2 (QUADAS-2) criteria, the included articles were evaluated as at high risk (–) or low risk (+) by four key domains: Patient selection, index test, reference standard, and flow and timing (16).

2.7. Data synthesis and statistical analysis

We used Meta-Disc software 5.1.4 to conduct this meta-analysis. All the studies reported the data regarding true positive (TP), true negative (TN), false positive (FP) and false negative (FN). Therefore, we were able to calculate the pooled sensitivity (TP/TP + FN), specificity (SPE) (TN/TN + FP), negative likelihood ratio (LR–), positive likelihood ratios (LR+) with their 95% confidence intervals. At the same time, we constructed the summary receiver operator characteristic (SROC) curve and calculated the area under the SROC curve based on the sensitivity and specificity of each study. Heterogeneity was estimated using the I^2, with a value over 50% or a $p < 0.05$ as indicative of high heterogeneity. The pooled

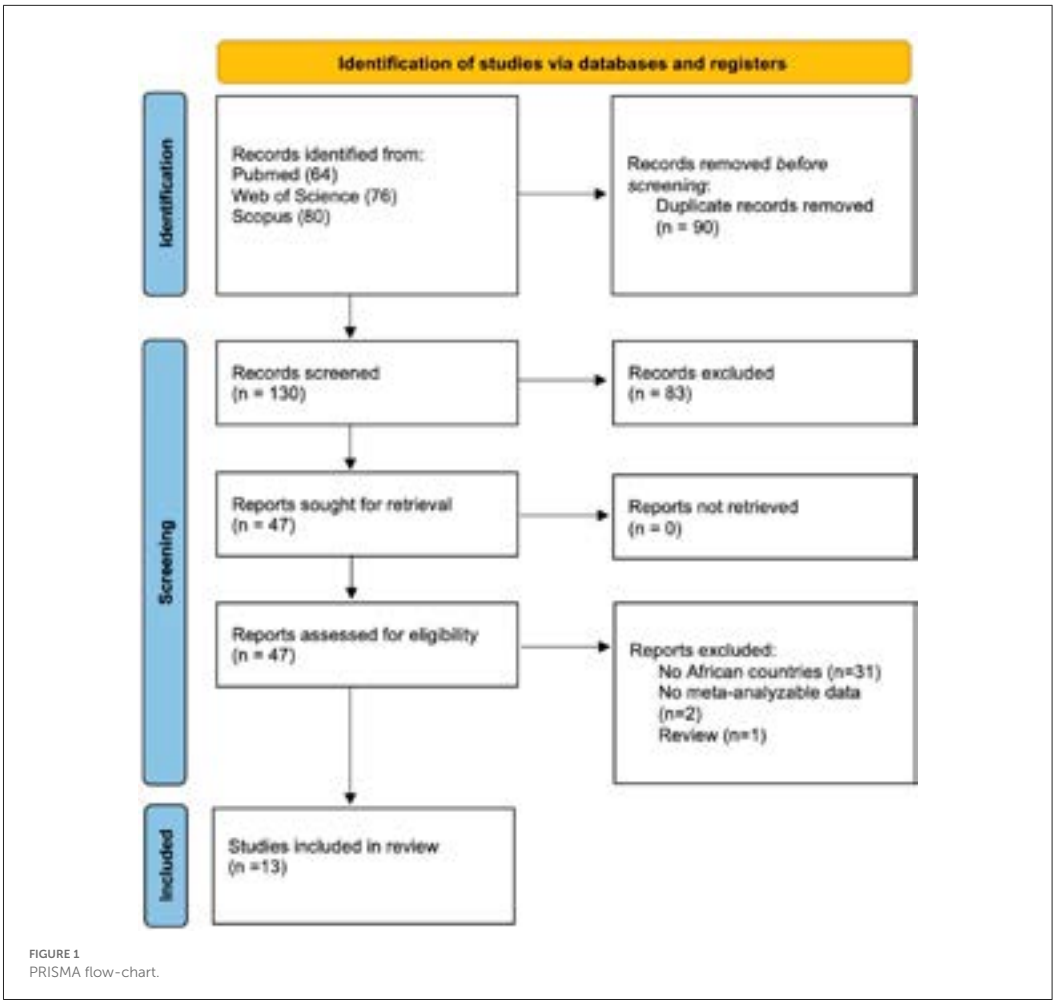

FIGURE 1
PRISMA flow-chart.

TABLE 1 Descriptive characteristics of the studies included.

Author, year	Country	Setting	Total sample size	Age at baseline; median (Q1–Q3)	% of females	%HIV	Stool processing method	Reference standard	
								Sample	Assay
Ainan et al. (17)	Tanzania	Health Center	225	2.17 (1.16–5.19)	47.1	6.5	Homemade centrifuge free method	Sputum and nasogastric aspirate	Culture and NAAT
Banada et al. (18)	South Africa	Hospital	38	NR	55	42	Snap vortexing with stool processing buffer	Induced sputum and nasogastric aspirate	NAAT
Chipinduro et al. (19)	Zimbawe	Hospital	218	11 (9–13)	55	5.96	Stool processed using the MP Fast DNA kit for soil with a 6-minute homogenization via bead-beating disruption	Sputum	Culture, Xpert MTB/RIF and smear microscopy
DiNardo et al. (20)	Eswatini	Health Center	38	6.8 (NR)	65	32	Stool processed using the MP Fast DNA kit for soil with a 6-min homogenization via bead-beating disruption	Sputum	Culture
Dubale et al. (21)	Ethiopia	Hospital	152	3 (0.58–14)	51.3	NR	Single step, centrifuge-free protocol adapted from KNCV TB foundation (13)	Sputum and nasogastric aspirate	Culture, Xpert MTB/RIF and smear microscopy
Lacourse et al. (22)	Kenya	Hospital	164	2 (13–58)	43.4	100	Sedimentation based method with centrifugation	Sputum and nasogastric aspirate	Culture and Xpert MTB/RIF
Moussa et al. (23)	Egypt	Hospital	115	NR	40.33	0	Sedimentation based method with centrifugation	Sputum	Culture
Nicol et al. (24)	South Africa	Health Center	115	2.58 (19–57)	NR	14.8	Supernatant-based method with centrifugation	Induced sputum and nasogastric aspirate	Culture
Orikiriza et al. (25)	Uganda	Hospital	392	NR	45.5	31.2	Sedimentation based method with centrifugation	Sputum	Culture
Orikiriza et al. (26)	Uganda	Hospital	219	1.36 (9.7–29.7)	48.9	32	Sedimentation based method with centrifugation	Any sample (excluding stool)	Culture and Xpert MTB/RIF
De Haas et al. (13)	Ethiopia	Hospital	123	NR	NR	NR	Single step, centrifuge-free protocol adapted from KNCV TB foundation (13)	Sputum and nasogastric aspirate	Culture and Xpert MTB/RIF Ultra
Song et al. (27)	Kenya	Mixed	294	2 (1–3.6)	50.3	23	Not described	Sputum	Culture and Xpert MTB/RIF
Walters et al. (28)	South Africa	Hospital	259	1.29 (0.88–2.4)	43.6	12.5	Sedimentation based method with centrifugation	Sputum	Culture and Xpert MTB/RIF

NR, not reported.

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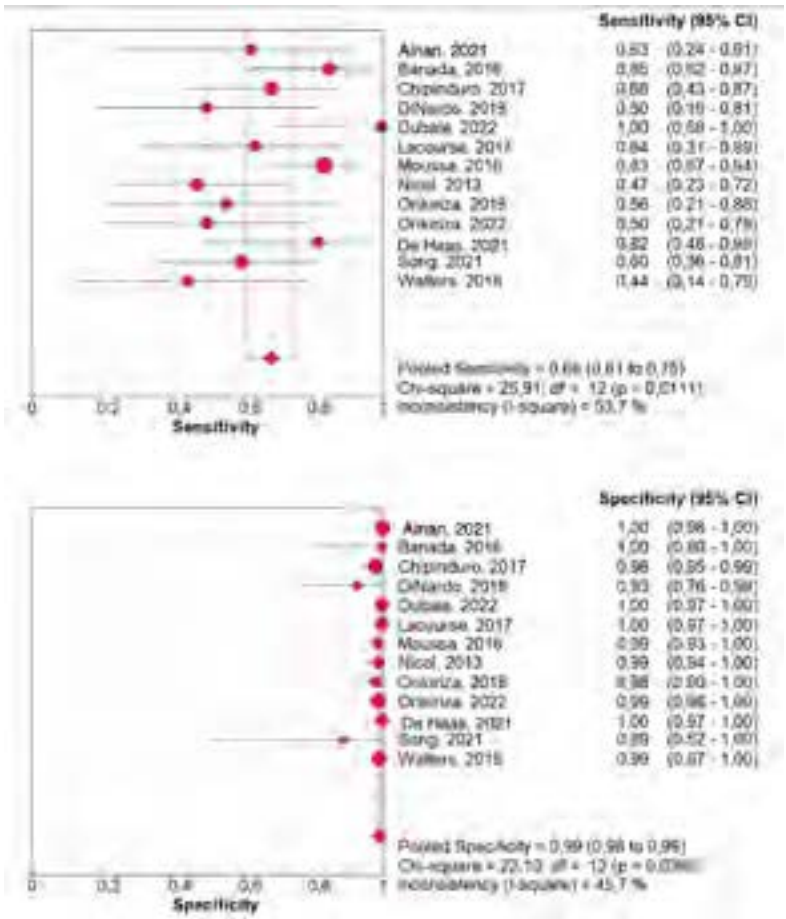

FIGURE 2
Forest plots of sensitivity and specificity of the Xpert MTB/RIF Ultra assay for tuberculosis detection. Power of the single studies is indicated by dot size, while horizontal lines indicate emerging from the box indicate the magnitude of the confidence interval. Dot size is proportional to the studies' sample size. and that the lozenge and box represents the pooled numbers with 95% CI error margins.

estimates were also reported by reference tool (divided in sputum vs. the association between sputum and nasogastric aspirate).

3. Results

The flow-chart of this systematic review is shown in Figure 1. Overall, among 130 papers initially screened, we evaluated 47 works, finally including 13 papers.

Table 1 reported the data of the 13 works eligible for a total of 2,352 participants, mainly children. The setting most represented was the hospital ($n = 9$), followed by health center ($n = 3$) and mixed settings ($n = 1$). The mean percentage of females was 49.6%, whilst the mean percentage of patients reporting HIV was 27.7%. When considering the reference standard, the use of sputum, particularly when associated with nasogastric aspirate was the most used methodology.

Considering all the 13 studies together, the pooled sensitivity for stool Xpert MTB/RIF assay for detecting tuberculosis was moderate (68.2%, 95%CI: 61.1–74.7%) even if characterized by a high heterogeneity ($I^2 = 53.7\%$) (Figure 2). In fact, the sensitivity of the studies included ranged from 44% to 100%. On the contrary the specificity of stool Xpert assay was almost 100% (99%, 95%CI: 97–100%; $I^2 = 45.7\%$) (Table 2, Figure 2). Almost all the studies reported a specificity higher than 95% in diagnosing tuberculosis, as shown in Figure 2. Therefore, the LR+ was optimal (38.581; 95%CI: 20.994–70.900) as well as the LR- (0.383; 95%CI: 0.295-0.497) (Table 2). These data led to an AUC = 0.8983 with a standard error (SE) of 0.0763, even if, as shown in Figure 3, only four studies had an AUC over 0.80.

TABLE 2 Performance of Xpert MTB/RIF Ultra on stool sample from patients with pulmonary tuberculosis compared to reference standard type.

	Number of studies	Pooled sensitivity (95% CI)	Pooled specificity (95% CI)	Positive Likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)
All sample	13	0.682 (0.611–0.747)	0.991 (0.985–0.995)	38.581 (20.994–70.900)	0.383 (0.295–0.497)
Sputum and nasogastric aspirate	6	0.727 (0.614–0.823)	0.999 (0.992–1.000)	105.78 (36.708–304.802)	0.317 (0.189–0.533)
Only sputum	6	0.670 (0.570–0.759)	0.981 (0.967–0.991)	22.884 (10.407–50.321)	0.397 (0.274–0.574)

CI, Confidence Intevals.

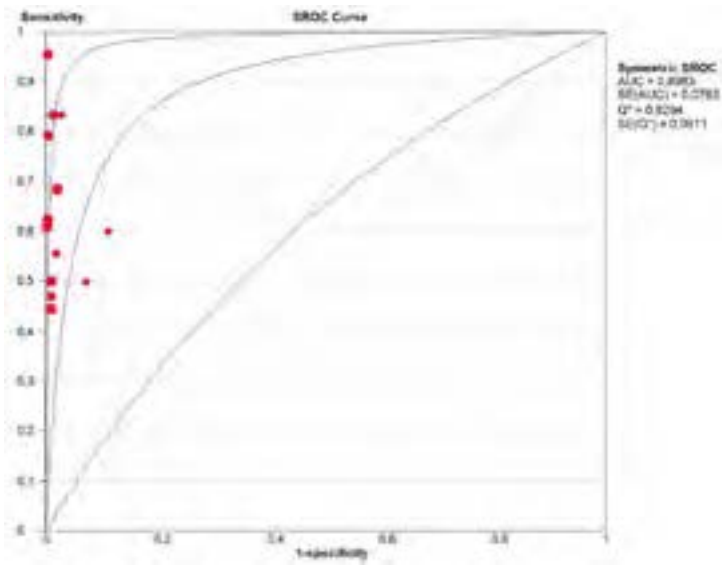

FIGURE 3
Summary receiver operating characteristic (SROC) curve of the diagnostic accuracy of Xpert MTB/RIF Ultra assay for tuberculosis detection. In this figure, the blue lines represent the AUC (central line) with its 95% CI (external lines) calculated with a meta-analytic approach, while red dots represent the sensitivity and specificity data for each study.

Stratifying the analysis for the reference standard, the six studies using both sputum and nasogastric aspirate showed higher sensitivity, a similar specificity, and a higher LR+ than studies using only sputum for tuberculosis detection, as shown in Table 1. In the six studies using sputum and nasogastric aspirate the accuracy was optimal (AUC = 0.99, SE = 0.02), whilst in the studies using only sputum for tuberculosis detection the AUC was 0.85 (with a SE = 0.16). In our systematic review, despite the initial protocol included both composite and microbiological reference standards, we found only one study evaluating diagnostic accuracy of stool Xpert with both CRS and MRS (26). In this case, interestingly, sensitivity dropped from 50% against MRS to 11.4% against CRS. However, for this study, we included in the meta-analysis only diagnostic accuracy data obtained against MRS.

The quality of the included studies, as assessed by the QUADAS-2, is reported on Figure 4; the most common source of bias was exclusion of enrolled patients in the analysis (Figure 4). On the other side, the most common concern in terms of applicability was due to the fact that our systematic review aimed to explore the diagnostic accuracy of stool Xpert in the general population, while most of the included studies recruited only pediatric patients. A detailed description of risk of bias and applicability concerns is provided in Supplementary Table 1.

4. Discussion

In this systematic review and meta-analysis, we investigated diagnostic accuracy of stool Xpert MTB/RIF in African settings. In our study, pooled sensitivity and specificity were, respectively, 68% (95%CI 61–75%) and 99% (95%CI 98–99%) for the diagnosis of people with presumptive pulmonary TB. Our results are consistent

FIGURE 4
QUADAS-2 risk of bias and applicability concerns graph.

with the ones reported by other meta-analysis conducted on children living in both African and non-African settings (29–31). Moreover, also consistently with other studies, diagnostic accuracy reported here on stool samples is comparable to the performances of the same test on respiratory samples (32). Of note, this is the first meta-analysis including only patients living in African countries.

In low-resource settings, patients evaluated for TB often experience diagnostic delays due to several factors, such as economic constrains, lack of awareness on the importance of timely diagnosis and poor availability of diagnostic tools in primary healthcare facilities (9). This scenario was further challenged by the COVID-19 pandemic, that reversed the progresses made during the last decades and lead, worldwide, to a large drop in the reported number of newly diagnosed TB (1). This is relevant, since every loss in TB diagnostic capacity inevitably leads to an increase in the number of untreated TB and TB deaths. Despite their requirements in costs and infrastructure—which limits the availability to the settings with adequate transportation systems and funding—molecular tests such as Xpert MTB/RIF and Xpert MTB/RIF Ultra on stool sample may provide added value in TB diagnostic workflow in high burden settings. Also, another limit of rapid molecular tests is that they are sputum dependent, since population at high risk of developing TB [such as people living with HIV (33) and children (34)] is often unable to expectorate. Among children, sputum unavailability is generally replaced by nasogastric aspirate, which is invasive and poorly tolerated. In our systematic review, 7 studies out of 13 reported a median age below 5 years, accounting for 66.7% ($n = 1,571$) of the pooled population, that is the age category in which stool Xpert is expected to have the greatest clinical utility. The importance of implementing rapid, accurate, non-invasive, sputum-free assays for detection of MTB has been recognized by the WHO as high priority target for the development of new tuberculosis diagnostics in 2014 (35).

Consistently with other meta-analysis (29–31), we recorded a substantial between-study heterogeneity, especially in sensitivity, which ranged from 44% to 100%. This was likely a consequence of the differences in reported HIV-prevalence and in terms of used reference test. Furthermore, heterogeneity might also have been affected by the stool processing protocols used, since the majority of included articles reported non-standardized sample processing methods. In this study we found that, despite WHO endorsement of SOS and OSF methods, implementation of stool Xpert processing strategies in sub-Saharan Africa is still lacking standardization. This is relevant, since many in-house, not-standardized methods require laboratory expertise dedicated equipment which, in some settings, may discourage implementation of PCR-based diagnostics on stool samples. For future, perspective research, we emphasize the importance to adopt and report a standardized protocol for sample preparation.

A strength of this study is that diagnostic accuracy was evaluated using, in all articles, a microbiological (and non-clinical) reference standard, represented by both culture and Xpert (8/13), culture (12/13), or Xpert alone (1/13). In fact, when the reference standard used to evaluate diagnostic accuracy of stool Xpert was both sputum and nasogastric aspirate, pooled sensitivity increased to 72% and AUC was as high as 0.99.

This study has some limitations. First, data did not allow us to perform meta-regression analyses to investigate the reasons of recorded heterogeneity. Second, we could not evaluate the accuracy of stool Xpert on adults or other age groups, since we found no studies addressing this population in African countries. Third, we found only one study investigating diagnostic performances of stool Xpert Ultra (13), which contributed for 5% of the total population and reported a sensitivity of 81%. For the purposes of this study, Xpert Ultra has been included in the analysis but we recognize that it may have contributed to increase heterogeneity. Hence, future research should focus on investigating diagnostic accuracy and cost-effectiveness of Xpert Ultra on stool samples in sub-Saharan settings. Also, in the upcoming years, research should address the sensitivity advantage of this test on adults and when used in combination with other currently used assays.

5. Conclusions

Our study confirms that, in Africa, stool Xpert MTB/RIF may be a useful rule-in test for patients under evaluation for pulmonary tuberculosis. Sensitivity increased substantially when using both

sputum and nasogastric aspirate as reference samples. Further studies are needed to explore stool Xpert MTB/RIF Ultra and both Xpert MTB/RIF and Xpert Ultra diagnostic performance in the adult population.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

FD, CM, and NV contributed to conception and design of the study. RP, SC, ED, MS, VF, OT, EF, RL, FM, DB, and GD collected the data. FV organized the database and wrote the first draft of the manuscript. NV performed the statistical analysis. GP, NV, FD, and MB wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1117709/full#supplementary-material

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Successful Management, in a Low-Resource Setting, of Disseminated Tuberculosis in a 3-Year Old Boy: A Case Report

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Authors
Chilundo J., Muhelo A., Ahivaldino Z., Zucula H., Macuácua S., Mussagi A.C., Pizzol D., Smith L., Maggioni G.

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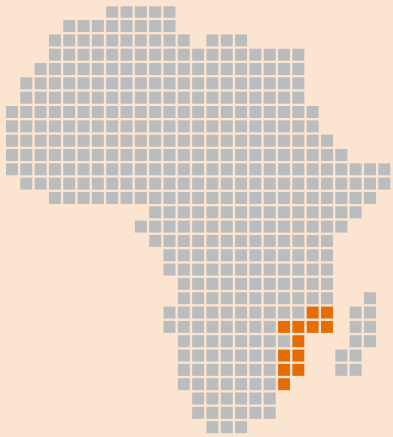

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Case Report

Successful Management, in a Low-Resource Setting, of Disseminated Tuberculosis in a 3-Year Old Boy: A Case Report

Josina Chilundo [1,2], Arlindo Muhelo [3], Zita Ahivaldino [3], Helton Zucula [3], Sheila Macuácua [3], Ana Cristina Mussagi [3], Damiano Pizzol [4,*], Lee Smith [5] and Giuseppe Maggioni [6]

1 Department of Pneumology, Central Hospital of Maputo, Maputo 1113, Mozambique; jchalufo@yahoo.com.br
2 Faculty of Medicine, Eduardo Mondlane University Maputo, Maputo 1113, Mozambique
3 Department of Paediatry, Central Hospital of Maputo, Maputo 1113, Mozambique; arlindomuhelo@gmail.com (A.M.); ahyvaldo@hotmail.com (Z.A.); heltonzucula@gmail.com (H.Z.); sheyla.macuacua@gmail.com (S.M.); hannahcristinna89@gmail.com (A.C.M.)
4 Operative Research Unit, Doctors with Africa Cuamm, Beira 1100, Mozambique
5 Centre for Health, Performance and Wellbeing, Anglia Ruskin University, Cambridge CB1 1PT, UK; lee.smith@aru.ac.uk
6 Department of Medicine, University of Padua, 35128 Padova, Italy; maggioni.giuseppe@hotmail.it
* Correspondence: damianopizzol8@gmail.com or d.pizzol@cuamm.org; Tel.: +39-3668731237

Abstract: Disseminated or military tuberculosis (TB) is defined as the presence of at least two non-contiguous sites of *Mycobacterium tuberculosis*, occurring as a result of progressive primary infection, reactivation and spread of a latent focus or due to iatrogenic origin. Disseminated TB represents a life-threatening condition, especially in at-risk children and when diagnosis and treatment are delayed. We report on a case of a 3-year old boy who presented with long-lasting unrecognised disseminated TB that was successfully managed in a low-resource setting.

Keywords: tuberculosis; disseminated TB; low-income setting

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1. Introduction

Tuberculosis (TB) is among the top ten causes of death worldwide. TB represents a marker of inequality as the overwhelming burden of TB is found among low- and middle-income countries, where it is estimated that over 90% of global TB cases and deaths occur [1,2]. Disseminated or miliary tuberculosis is defined as the presence of at least two non-contiguous sites resulting from lymphohematogenous dissemination of *Mycobacterium tuberculosis*, occurring as a result of progressive primary infection, reactivation and spread of a latent focus or due to iatrogenic origin [3]. Disseminated TB represents a life-threatening condition, especially in at-risk children and when diagnosis and treatment are delayed [4–6]. Clinical presentation of disseminated TB is nonspecific, it is commonly associated with fever of unknown origin and, depending on involved sites, with other generic symptoms attributable to other common diseases [7]. In addition, in low-income settings, the paucity of tools available for confirmatory laboratory diagnosis, such as the low sensitivity of acid-fast bacilli (AFB) smear, time-consuming cultures, and the inability to easily detect miliary changes in a chest X-ray, makes diagnosis a very challenging task [7]. The time from symptoms presentation to diagnosis is highly variable, ranging from few days to several months depending on health professionals' training, diagnostic tools, and clinical presentation that usually includes subacute or chronic constitutional symptoms such as fever, weight loss, and night sweats. Commonly, most children are treated based on a combination of clinical and radiologic signs suggestive of TB without bacteriological confirmation [8]. To date, mortality due to disseminated TB is still high, ranging from 25% to 30% mainly due to the delay in diagnosing and the onset of meningismus, liver cirrhosis, leukopenia, leukocytosis, advancing age, presence of underlying disease, altered mental status, and night sweats [9]. In the present paper, a case

Pathogens **2023**, *12*, 1163

of a 3-year-old boy who presented with long-lasting unrecognised disseminated TB that was successfully managed in a low-resource setting, is reported.

2. Case Report

A 3-year-old boy was transferred, on June 2023, from a rural health centre to a regional hospital in Mozambique due to suspected acute flaccid paralysis and paraparesis. Eight months before, October 2022, he developed intermittent fever, which improved with paracetamol administration. In December 2022 the clinical status evolved with the appearance of a swelling in the right wrist, treated with an incision and drainage and prescription of paracetamol and antibiotics in a rural health centre. After a week, further swelling appeared in the region of the spine along with an oedema in the right ankle, accompanied by intense and progressive pain, and paracetamol was prescribed in the same health centre. In April 2023, the condition worsened with increased swelling in the spine region, worsening pain, difficulty in sitting and walking. He also mentioned occasional dry cough, night sweats, asthenia, and weight loss, denying chest pain and dyspnea. Due to the worsening conditions, the health centre decided to transfer the boy to a regional hospital, but due to lack of means, the mother was recommended to wait at home with the boy for the availability of transport. After two more months and the further worsening of the condition he was transferred to the regional hospital on suspicion of acute flaccid paralysis and paraparesis. He presented with a deformity of the lumbar spine (Figure 1A), solution of skin continuity on the anterior surface of the distal 1/3 of the right forearm, measuring approximately 2.5 × 1.5 cm (Figure 1B), and a cold, soft oedema in the region of the right ankle (Figure 1C). He also presented a pathological gait (Alderman), with a tendency to support the left arm over the waist. The initial diagnosis was Pott's Disease, and he started the specific following treatment on daily regimen: isoniazid (H), rifampicin (R), ethambutol (E), and pyrazinamide (Z) for 2 months followed by HRE for 10 months. The curettage was performed on the wound that was subsequently cleaned and medicated daily. Five days after starting treatment, he developed an episode of generalised tonic-clonic seizures lasting two minutes without sphincter relaxation, associated with fever. The results of the biochemical test performed at admission, after 2 and 5 days, are reported in Table 1.

Table 1. Biochemical results performed at admission, after 2 and 5 days.

Parameter	Admission	After 2 Days	After 5 Days
WBC	**13.3 × 10^3/uL**	**15.04 × 10^3/uL**	**14.17 × 10^3/uL**
LYM	5.8 (43.7%)	5.5 (37%)	6.36 (44.9%)
NEUT	6.5 (48.7%)	7.9 (52.5%)	5.88 (41.4%)
RBC	4.77 × 10^6/uL	4.62 × 10^6/uL	4.72 × 10^6/uL
HGB	**7.5 g/dl**	**7.4 g/dl**	**7.7 g/dl**
MCV	**57.9 fL**	**54.1 fL**	**54.2 fL**
MCH	15.7 pg	16.0 pg	16.3 pg
MCHC	**27.2 g/dL**	**29.6 g/dL**	**30.1 g/dL**
PLT	**1000 × 10^3/uL**	**944 × 10^3/uL**	**1030 × 10^3/uL**
Na	133 mEq/L	NR	132.9 mEq/L
K	4.37 mEq/L	NR	5.44 mEq/L
Cl	98 mEq/L	NR	98 mEq/L
Creatinine	20.3 umol/L	NR	22.33 umol/L
ALT	16.54 U/L	NR	26 U/L
AST	31.33 U/L	NR	43 U/L
Urea	3.01 mg/dL	NR	2.47 mg/dL
Glucose	4.86 mmol/L	NR	3.5 mmol/L
ESR	51 mm/h	NR	NR
ALB	NR	NR	3.8 g/dL
Iron	NR	NR	84 mcg/dL
BPL	NR	NR	6.7 g/dL
Cholesterol	NR	NR	148 mg/dL
TBIL	NR	NR	1.1 mg/dL

Legend to Table 1. Bold are indicates the abnormal values. List of abbreviations: ALB—albumin; ALT—alanine aminotransferase; AST—aspartate aminotransferase; BPL—blood protein level; Cl—chlorine; ESR—erythrocyte sedimentation rate; HGB—haemoglobin; K—potassium; LYM—lymphocytes; MCV—mean corpuscular volume; MCH—mean corpuscular haemoglobin; MCHC—mean cell haemoglobin concentration; Na—sodium; NEUT—neutrophils; PLT—platelets; RBC—red blood cells; TBIL—total bilirubin; WBC—white blood cells.

Figure 1. Disseminated tuberculosis at presentation in 3-year-old boy: deformity of the lumbar spine (**A**), solution of skin continuity on the distal right forearm (**B**), and cold, soft oedema in the right ankle (**C**).

In addition to those tests at admission, HIV and GeneXpert MTB/RIF test results were negative. A plain X-ray of the spine showed a loss of anterior and posterior alignment of L2 and L3, change in height of the L2 vertebral body and altered bone density of the L2 and L3 vertebral bodies (Figure 2). The chest X-ray showed heterogeneous infiltration in both lung fields (Figure 3A) while the X-ray of the right forearm showed an osteolytic lesion in the distal 1/3 of the radius (Figure 3B), and the X-ray of the right leg showed signs of calcaneal osteolysis (Figure 3C). Based on clinical history, examination, and X-ray results, the diagnosis of disseminated TB, including Pott's Disease pulmonary and cutaneous TB, was made. The conditions improved slowly but consistently, with gait improvement healing of the forearm injury and reduction of ankle oedema. The boy was discharged after 23 days with a one-year prescribed treatment and follow-up in 12 months if no complications occur.

Pathogens **2023**, *12*, 1163

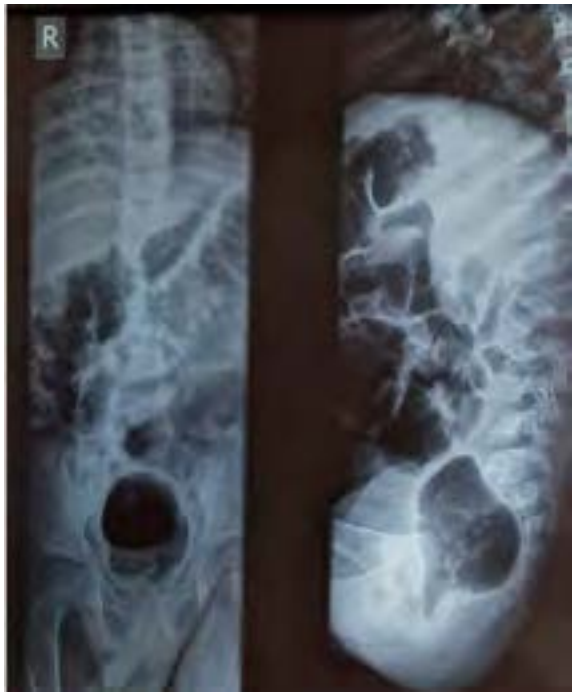

Figure 2. Plain X-ray of the spine.

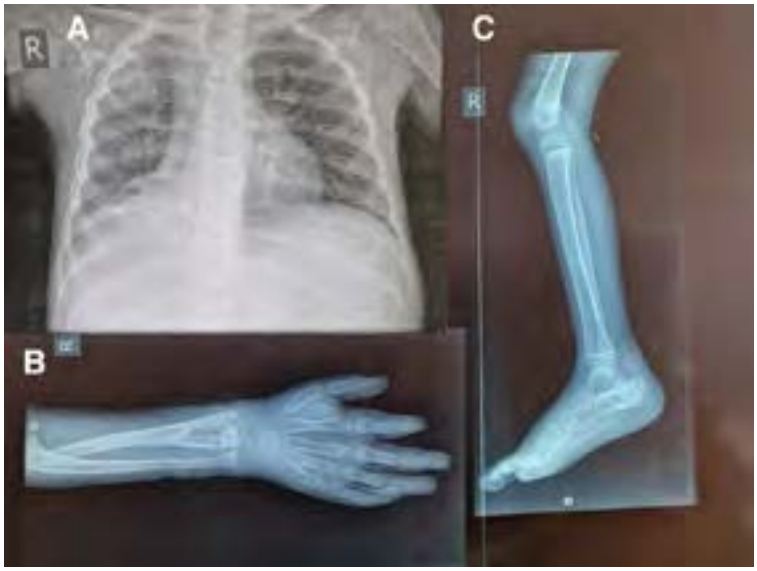

Figure 3. The chest x-ray (**A**), X-ray of the right forearm (**B**) and the X-ray of the right leg (**C**).

3. Discussion

Mozambique has one of the highest TB burdens in the world, with an estimated TB incidence rate of 551/100,000 population in 2015. Moreover, TB treatment covers only 38% of the population, and an increasing rate of TB–HIV co-infection is usually documented (36% of TB patients were HIV-positive) [10,11]. Despite these dramatic data, TB and especially disseminated TB remain underrecognized and undiagnosed due to a lack of well-trained health workers and adequate tools for assessment and appropriate follow-up. In particular, in the present case, eight months elapsed from the first visit to the correct diagnosis. The reasons for such a delay are multiple. First, the child had no specific TB symptoms and health workers were not able to identify the disease, then the rural health centre was not properly equipped for deeper investigation. Finally, two additional months were necessary to wait to transfer the child. As precise and timely diagnosis is crucial for a favourable prognosis. It is thus essential to, on the one hand, to strengthen existing structures and, on the other, to find alternative solutions. In this regard, recent evidence suggests the possible role of Stool Xpert MTB/RIF on stool samples, especially in sub-Saharan settings, although its diagnostic accuracy and cost-effectiveness are still under investigation [12]. Despite possible future solutions, it is essential to support and collaborate in defeating TB, not only for low-income countries but also in terms of global and globalised health. Importantly, the recent COVID-19 pandemic highlighted the weakness of world health systems, and high-income countries are increasingly exposed to TB due to immigrants from regions with a high rate of TB and a high prevalence of multidrug-resistant or extensively drug-resistant TB [13]. Another important aspect is the mutual link between TB and some non-communicable diseases that represent an increasing burden worldwide. This association creates a vicious cycle, with TB increasing non-communicable disease complications and vice versa. It also makes diagnosis and management more difficult and worsens disease courses and outcomes [14]. This case contains the main characteristics of the health systems in low-income countries, including a lack of trained health workers, a lack of means in community health centres, and a lack of effective health policies in combating endemic diseases such as TB.

4. Conclusions

This evidence, although rising just from a case report, allows one to make some considerations. First of all, it is essential and urgent to strengthen the development and implementation of tailored health policies for all countries affected by TB, including screening protocols for migrants, in an integrated, culturally sensitive, social-determinant- driven manner. It is also crucial to enable health workers and health facilities to achieve correct and timely diagnoses. Finally, as a pharmacological approach is necessary in the treatment of TB and costs of treatments per patient are significantly high, particular attention should be paid to social determinants of TB that influence its contraction, as well as outcome, in low-resource settings.

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Exploring the use of cluster analysis to assess antibiotic stewardship in critically-ill neonates in a low resource setting

PAPER

Authors
Benoni R., Balestri E., Endrias T., Tolera J., Borellini M., Calia M., Biasci F., Pisani L.

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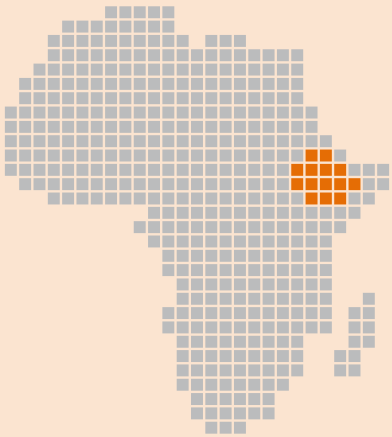

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Exploring the use of cluster analysis to assess antibiotic stewardship in critically-ill neonates in a low resource setting

Roberto Benoni[1,2,3*], Eleonora Balestri[4,5], Tariqua Endrias[6], Jiksa Tolera[6], Martina Borellini[1,3], Margherita Calia[5], Filippo Biasci[5] and Luigi Pisani[3,7]

Abstract

Background Sepsis is the third leading cause of neonatal death in low and middle-income countries, accounting for one third of all deaths in Ethiopia. A concerning issue is the increasing number of multidrug-resistant microorganisms facilitated by suboptimal antibiotic stewardship. The study aims to identify clusters of newborns switching antibiotic lines for sepsis in a neonatal intensive care unit (NICU) in Ethiopia, and to explore their potential association with sepsis outcomes.

Methods A retrospective cohort study was conducted including all newborns discharged with a diagnosis of probable neonatal sepsis from the St. Luke Catholic Hospital NICU between April and July 2021. The antibiotic management protocol included two lines according to WHO guidelines and a third line based on internal hospital guidelines. In the cluster analysis, the Gower distance was estimated based on the antibiotics employed in the different lines and the duration of each line. Mortality and respiratory distress (RD) were the response variables.

Results In the study period, 456 newborns were admitted to the NICU and 196 (42.8%) had probable neonatal sepsis. Four antibiotic management clusters were identified. Cluster 1 (n = 145, 74.4%) had no antibiotic switches, using only the first line. Cluster 2 (n = 26, 13.3%) had one switch from the first to the second line. Cluster 4 (n = 9, 4.6%) had two switches: from first to second and then to third line. In cluster 3 (n = 15, 7.7%), newborns were switched from ceftriaxone/cloxacillin as second line to off-protocol antibiotics. There were no differences in sex, age, weight on admission or crude mortality between clusters. Cluster 3 included a higher frequency of infants who did not breathe at birth (53.3%, p = 0.011) and that necessitated bag ventilation (46.7%, p = 0.039) compared to the other clusters.

Conclusions The first antibiotic line failed in one out of four newborns with probable sepsis while third-generation cephalosporins were insufficient in one in ten patients. Cluster analysis can provide valuable insights into antibiotic treatment patterns and their potential implications. This approach may support antibiotic stewardship and aid in contrasting antimicrobial resistance in limited resource settings.

Keywords Neonatal sepsis, Antibiotic stewardship, Cluster analysis, Multidrug resistance

*Correspondence:
Roberto Benoni
roberto.benoni90@gmail.com

Full list of author information is available at the end of the article

Background

Neonatal mortality is a concerning issue in low- and middle-income countries (LMIC) where most of the estimated 2.6 million yearly global deaths occur. Neonatal sepsis is the third leading cause of neonatal mortality being responsible for 13% of all neonatal deaths, and of 42% of deaths in the first week of life [1]. In Ethiopia, prematurity (37%), sepsis (28%), and asphyxia (24%) are reported to be the most common causes of death in newborns [2].

Neonatal sepsis is defined by the systemic manifestation of infection, due to the presence in the bloodstream of a bacterial pathogen. Neonatal sepsis is classified as 'confirmed' if bacteremia is proved by a positive blood culture, 'probable' if signs and symptoms are supported by suggestive laboratory results, and 'suspected' if only clinical suspicion is present [1]. Differentiating between early-onset sepsis (EOS) and late-onset neonatal sepsis (LOS) is important for tailored management of etiological pathogens [1–3]. Respiratory distress (RD) is one of the most common severe clinical presentations of neonatal sepsis and it is associated with poor outcomes [4, 5].

Multidrug resistance for pathogens involved in sepsis is worsening, both globally and in LMICs, with greater attention advocated for antibiotic stewardship [6]. Antimicrobial resistance, or reduced susceptibility, to the combination of penicillin and gentamicin and to third-generation cephalosporins was reported, in more than 40% of cases of neonatal bacteremia acquired in a community setting [7]. Overall resistance to third-generation cephalosporins in Gram-negative bacteria, estimated to be around 50% in Africa, is increasing [8]. Recent initiatives advocate the need to investigate new management algorithms to reduce unnecessary antibiotic use for neonatal sepsis, especially in the neonatal intensive care unit (NICU) setting [9].

Cluster analysis is a machine learning technique that aims to group observations that are similar within the same cluster. This analysis includes a cluster construction phase and a subsequent validation phase. There may be an internal validation (calculating an index to assess how well the clusters fit the data) and an external validation (using an external dataset or survival curves) [10]. The development of decision support systems based on historical data using machine learning algorithms is an opportunity in healthcare to obtain predictive information and improve decision making and clinical practice [11]. This can be particularly useful in resource-limited settings. Cluster analysis was already applied in infectious disease, analyzing biomarkers and predictors of neonatal sepsis, but to the best of our knowledge, no study has applied it to antibiotic stewardship in LMICs NICU setting [12, 13]. Therefore, we aimed to identify clusters of patients switching between different antibiotic lines and to explore their potential associations with survival probability or severe clinical presentation in terms of RD. We also sought to report the prevalence of early versus late probable neonatal sepsis in this setting. The primary hypothesis is that specific clusters of antibiotic switching can be identified, and that they are associated with more severe clinical presentation and poorer outcome.

Methods

Study Design

We used a retrospective cohort study design to explore the use of cluster analysis in depicting antibiotic management of neonatal sepsis and its association with newborns' outcomes in a limited resources NICU.

Ethical approval

The research was performed following the ethical standards of the 1964 Declaration of Helsinki and was approved by the Ethical Committee of St. Luke Catholic Hospital (SLCH) on the 14th of September (protocol number 1293/2021).

Study setting

SLCH is a referral hospital located in Wolisso Town, about one hundred km from the capital Addis Ababa. It is situated in the South-West Shoa Zone (SWSZ) of the Oromia region (Ethiopia), with an estimated population of 1,311,406 inhabitants, of which 15% are under five years of age [14]. SLCH catchment area includes the *woreda* of Ameya, Wenchi, Waliso rural, Woliso town, Becho, and Goro representing the reference hospital for 743.797 individuals. The number of deliveries assisted at SLCH was 4455 in 2019 and 4015 in 2020. The SLCH NICU has 16 beds with an annual average bed-occupation rate of 112% in 2020 [15]. Vital parameters and blood oxygen saturation are routinely monitored, and respiratory support comprises intranasal oxygen, bubble CPAP and electric CPAP.

Population

All newborns admitted in NICU between 1st April 2021, and 31st July 2021 and discharged with the diagnosis of probable neonatal sepsis were included. Exclusion criteria were missing information about antibiotic management or regarding the type of neonatal sepsis.

Operational definitions

Probable neonatal sepsis was defined as the presence of two or more of the following clinical signs and symptoms: hypo-hyperthermia (BT < 35.5 °C or > 37.5 °C), heart rate > 180 or < 100 bpm, respiratory rate > 60 breaths/min with grunting or desaturations, lethargy or altered mental status, glucose intolerance (plasma glucose > 10mmol/l), feed intolerance; plus at least one

of the following laboratory results at birth: leukocytosis (WBC count > 34,000*109/l), leukopenia (WBC count < 5,000*109/l), thrombocytopenia (platelets count < 100,000*109/l) [1].

Neonatal sepsis was defined as early-onset (EOS) if the sepsis symptoms started within 72 h of birth and late-onset (LOS) if they began later than72 hours from birth [2, 3].

Respiratory distress was defined as the presence of two or more of the following signs: abnormal respiratory rate (>60 or <30 breaths/minute, respiratory pauses, or apnea), grunting, nasal flaring, intercostal recessions, xiphoid recessions, with or without cyanosis [16]. RD was assessed at the time of admission to the neonatal intensive care unit and daily throughout the entire length of stay.

Data collection

For each subject, the following data were collected: sex, age and weight at admission, date of hospital admission and of hospital discharge, number of antenatal care (ANC) visits, mode of delivery, delivery place, presence of maternal chorioamnionitis, occurrence of premature rupture of membranes (PROM), maternal pre-eclampsia/eclampsia, Apgar score at 1st, 5th, 10th minute, respiratory status at birth, use of oxygen and/or positive pressure ventilation with AMBU bag at birth. We also collected data on type of neonatal sepsis, type of every antibiotic used during hospitalization, start and end date of every antibiotic type, presence of RD, number, type and length of every respiratory support device used during hospitalization and the outcome at NICU discharge. Due to the study setting (a low-resource neonatal intensive care unit), microbiological tests (pathogen typing and AMR profiling) were not available and were therefore not included in the analysis.

Antibiotic regimens

The antibiotic management protocol at the SLCH NICU had three different antibiotic lines. The first two lines were based on WHO and Ethiopian guidelines [17]: the first line was ampicillin plus gentamicin and the second line included ampicillin (higher dosage) – or cloxacilline if any sign or suspicion of staphylococci infection, plus cefotaxime or ceftazidime as the first choice - or ceftriaxone if the previous two were not available. The third line used ciprofloxacin plus cloxacilline (or vancomycin). Ciprofloxacin was empirically chosen as a third line as in Addis Abeba Central Hospital, where blood cultures and antibiotic resistance profile are available, several cases of resistance to gentamicin and cephalosporins but high sensitivity to meropenem and ciprofloxacin were found [18]. First line duration of antibiotic treatment was recommended for 5–7 days. If no improvement was observed in the first 48 to 72 h, the second line regimen was started. The third line was under specialist prescription based on the clinical status of the newborns.

Study endpoints

The primary endpoints were the number of newborns assigned to each cluster of antibiotic line switch and the development of respiratory distress or death in NICU. The secondary endpoints were the proportion of patients diagnosed with early and late-onset neonatal sepsis subtypes.

Statistical analysis

For descriptive purposes, frequency rates and percentages were used for categorical variables and medians with interquartile range (IQR) for continuous variables. Proportions for categorical variables were compared by the $\chi 2$ and Fisher's exact test. Continuous variables were compared via Mann-Whitney-U non-parametric test.

The optimal number of antibiotic management clusters to be imputed in the algorithm was evaluated through silhouette coefficient fitted on Gower distance computed as the average of partial dissimilarities across individuals included in the study. Variables included to be used in the Gower distance estimation were the type of antibiotics used as the first, second, or third line, respectively, and the length of therapy (LOT, in days) of each antibiotic line. The Gower distance was selected because data had both continuous and categorical variables, and it allows for mixed variables to be used simultaneously. The individuals were assigned to the different clusters through the partitioning around medoids (PAM) technique with the k-medoids algorithm fitted on the previous computed optimal number of clusters and Gower distance [19].

The PAM algorithm is based on the search for medoids ('k' representative objects) among the observations of the database. It has two phases. Build phase: (1) select k objects that will become the medoids; (2) calculate the dissimilarity matrix; (3) assign each object to the nearest medoid. Swap phase: (4) for each cluster, assess whether one of the objects decreases the average dissimilarity coefficient; if so, this is selected as the new medoid for this cluster; (5) if at least one medoid has swapped, go to step 3, otherwise end the algorithm. The goal of the algorithm is to minimize the average dissimilarity of objects with respect to the closest selected object.

The differences between the clusters in terms of descriptive socio-demographic and clinical characteristics were assessed via Fisher's exact test and the non-parametric Mann-Whitney-U test for categorical and continuous variables, respectively.

The median survival time was examined by Kaplan–Meier estimates. To assess the effect of the antibiotic management clusters and the clinical variables on

mortality a Cox Proportional-Hazards model was used with type of neonatal sepsis, age, weight, antibiotic management cluster, and presence of RD as potential determinants. Results were presented as hazard ratio (HR) with 0.95 confidential interval (CI). Since time at RD onset was not available, to explore its association with type of neonatal sepsis, age, weight, and antibiotic management clusters a logistic regression model was applied. Results were presented as odds ratio (OR) with 0.95CI. Additionally, the main clinical features were tested between clusters through Fisher's exact test and Mann-Whitney-U non-parametric test. Dunn's test with Bonferroni adjustment was used for nonparametric pairwise multiple comparisons. Post-hoc multiple comparison between clusters in the logistic regressions was carried out through Tukeys' test.

Finally, the same set of analyses ($\chi 2$, Fisher's exact test and non-parametric Mann-Whitney-U test, logistic regression) was conducted to assess differences in the distribution of the main clinical characteristics between patients with EOS and LOS.A p-value < 0.05 was considered significant. All analyses were performed using the R software (version 4.1.1) using package "cluster", "ggplot2" and "Rtsne" to perform the cluster analysis and data visualization [20].

Results

Patients' characteristics

In the study period 456 newborns were admitted to the NICU of SLCH and 196 (42.8%) were discharged with a diagnosis of probable neonatal sepsis. One newborn was excluded due to missing data (Fig. 1). EOS was the predominant phenotype with 146/195 newborns (74.9%). Median age and weight at admission were 1.0 day (IQR 1.0-5.5) and 2,900 g (IQR 2,315-3,300), respectively. The majority of neonates were hospital inborn (119–61.0%). The prevalent mode of delivery was spontaneous

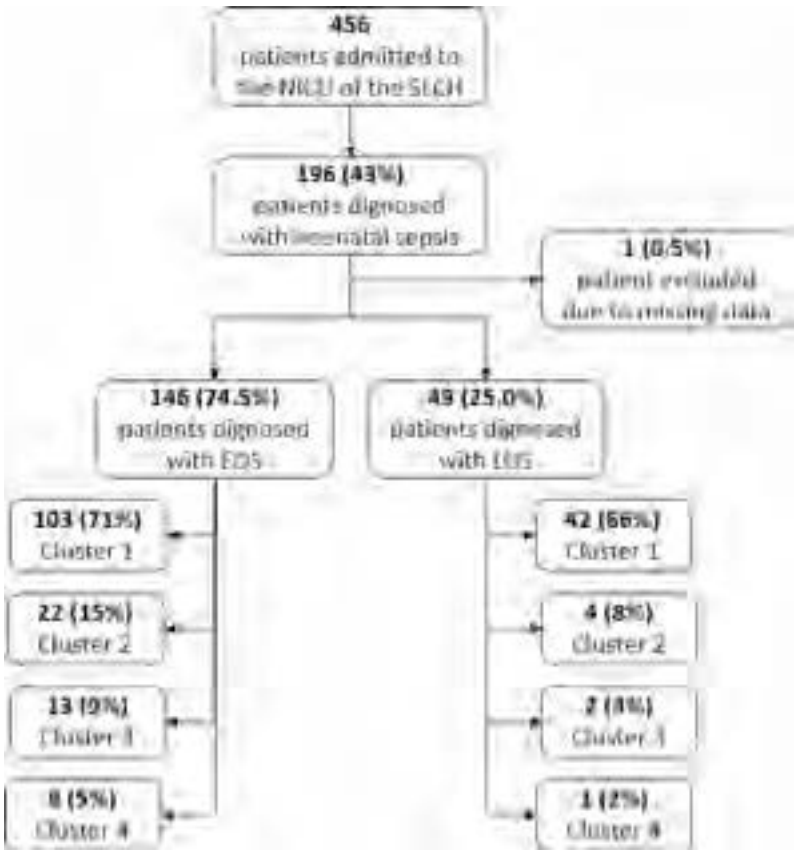

Fig. 1 Flowchart of the newborns sample included in the study. EOS = Early-Onset Neonatal Sepsis; LOS = Late-Onset Neonatal Sepsis; NICU = Neonatal Intensive Care Unit; SLCH = St. Luke Chatolic Hospital (Ethiopia

vaginal delivery followed by C- section and assisted breech (Table 1).

Antibiotic management clusters

All patients with neonatal sepsis received at least the first antibiotic line. The second and third line of antibiotic therapy were used in 50 (25.6%) and 15 (7.7%) neonatal sepsis cases, respectively. Four antibiotic management clusters were identified (**Table S2**, Fig. 2).

The silhouette coefficient for a number of cluster k=4 was 0.788, indicating a very good clustering (Fig. S1). Data visualization of the four clusters is provided in Fig. 3. The first cluster included 145 (74.4%) patients with no switching thus requiring only the first antibiotic line.

Table 1 Demographic, epidemiological, and clinical characteristics of newborns with probable neonatal sepsis, distinguished by the type of neonatal sepsis

	Overall (n = 195)	EOS (n = 146)	LOS (n = 49)	p-Value*
Sex				0.319
Female	83 (42.6%)	59 (40.4%)	24 (49.0%)	
Male	112 (57.4%)	87 (59.6%)	25 (51.0%)	
Age (day)				< 0.001
Median (IQR)	1.0 (1.0-5.5)	1.0 (1.0–2.0)	15.0 (10.0–21.0)	
Weight at admission (g)				< 0.001
Median (IQR)	2900 (2315–3300)	2710 (2100–3200)	3100 (2725–3690)	
Place of delivery				0.008
Inborn	119 (61.0%)	102 (69.9%)	17 (34.7%)	
Health center	49 (25.1%)	32 (21.9%)	17 (34.7%)	
Home	27 (13.8%)	12 (8.2%)	15 (30.6%)	
Mode of delivery				0.002
Spontaneous vaginal delivery	136 (69.7%)	92 (63.0%)	44 (89.8%)	
C- section	38 (19.5%)	33 (22.6%)	5 (10.2%)	
Vacuum	15 (7.7%)	15 (10.3%)	0 (0.0%)	
Assisted breech	6 (3.1%)	6 (4.1%)	0 (0.0%)	
Premature rupture of membranes (N/A = 2)				0.004
	41 (21.0%)	38 (26.0%)	3 (6.1%)	
Chorioamnionitis (N/A = 2)				0.015
	19 (9.7%)	19 (13.0%)	0 (0.0%)	
Eclampsia (N/A = 2)				0.999
	3 (1.5%)	3 (2.1%)	0 (0.0%)	
Apgar 1st minute				0.109
Median (IQR)	6.0 (3.0–8.0)	6.0 (3.0–7.0)	8.0 (3.5-9.0)	
Apgar 5th minute				0.081
Median (IQR)	7.0 (6.0–9.0)	7.0 (6.0–9.0)	9.0 (4.5–10.0)	
Breath at birth (N/A = 2)				< 0.001
	155 (79.5%)	108 (74.0%)	47 (95.9%)	
Positive pressure ventilation at birth (N/A = 2)				< 0.001
	39 (20.0%)	39 (26.7%)	0 (0.0%)	
Oxygen given at birth (N/A = 2)				< 0.001
	47 (24.1%)	47 (32.2%)	0 (0.0%)	
Respiratory distress syndrome				0.412
	90 (46.2%)	70 (47.9%)	20 (40.8%)	
Length of stay				0.119
Median (IQR)	7.0 (6.0–11.0)	8.0 (6.0–11.0)	7.0 (5.0–9.0)	
Outcome at discharge				0.014
Alive	161 (82.6%)	114 (78.1%)	47 (95.9%)	
Dead	26 (13.3%)	24 (16.4%)	2 (4.1%)	
Referred	8 (4.1%)	8 (5.5%)	0 (0.0%)	

* Fisherman-s exact and χ2 test, Mann-Whitney-U non-parametric test.

** Early (EOS) and late (LOS) neonatal sepsis.

N/A = data were missing in the medical records.

Fig. 2 Graphical representation of the 4 identified neonatal sepsis antibiotic management clusters. The bars represent the duration in days of treatment of each antibiotic or combination of antibiotics. "n" is the number of subjects for each antibiotic line in the different clusters. "d" is the median duration in days of each type of antibiotic combination. AMP = Ampicillin, GEN = Gentamicin, CTX = Ceftriaxone, VAN = Vancomycin, CLOXA = Cloxacillin, AZM = Azithromycin, CPFX = Ciprofloxacin, TZP = Piperacillin /Tazobactam, PCN = Penicillin

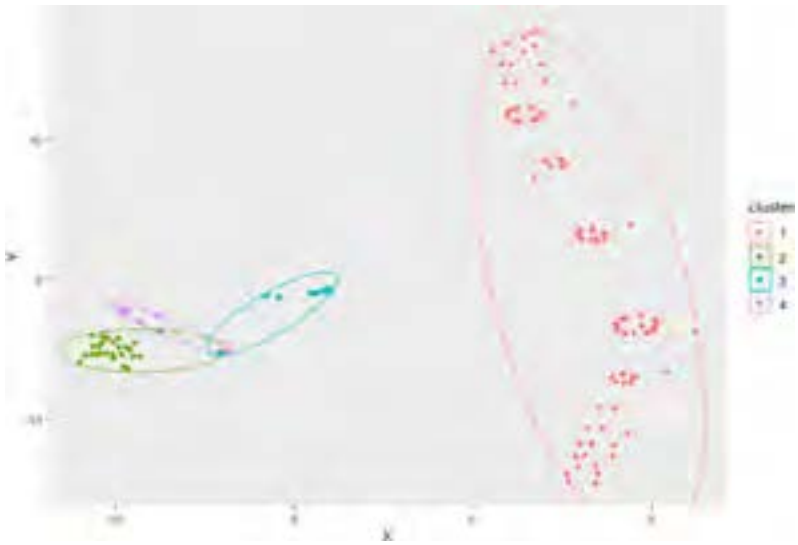

Fig. 3 Scatter plot visualization of the four clusters of antibiotic management. The scatter plot used the t-distributed stochastic neighborhood embedding over the Gower distance estimated on type of antibiotics used as the first, second, or third line, respectively, and the length in days of each antibiotic line

In the second cluster there were 26 (13.3%) newborns switching from first line to ceftriaxone as second antibiotic line. The third cluster was made by 15 newborns who switch from the first line to a second line of ceftriaxone plus cloxacillin in 12 cases (6.2%), and plus a further second line antibiotic (azithromycin) in 3 cases (1.5%). A further switch to off-protocol antibiotics was required by 5 (2.7%) patients in cluster 3. The fourth cluster was made by 9 (4.6%) patients with two switches: from first to second line (ceftriaxone only) and from second to the third antibiotic line (ciprofloxacin plus cloxacillin) in 7 (3.6%) cases.

Demographic and clinical characteristics stratified by cluster are shown in Table S1. There were no differences in sex ($p=0.693$), admission weight ($p=0.432$), type of sepsis ($p=0.274$), and Apgar at 1st ($p=0.430$) and 5th ($p=0.264$) minute between the antibiotic management clusters. Type of respiratory support and ventilation length were also not different between the clusters ($p=0.221$). The frequency of newborns who did not breathe at birth (n=8, 53.3%, $p=0.011$) and required manual positive pressure ventilation (n=7, 46.7%, $p=0.039$, Table S1) was higher in cluster 3. Length of stay was shorter in cluster 1 when compared to the other clusters ($p<0.001$, Table S1).

Table 2 Results of the logistic regression models fitted on the presence of respiratory distress (RD) as dependent variable and age, weight at admission, sepsis type, antibiotic management cluster as potential determinants. Cluster 3 was chosen as reference because it accounts for the cluster outside the protocol antibiotic lines

	Odds Ratio	0.95 CI	p-Value
RD (yes/no)			
Admission age (days)	1.027	0.930–1.135	0.592
Admission weight (hg)	0.936	0.893–0.980	0.006
Neonatal sepsis type (LOS)	0.855	0.184–3.811	0.838
Antibiotic cluster (3)			
1	0.088	0.013–0.357	0.003
2	0.133	0.018–0.637	0.022
4	0.389	0.037–3.981	0.405

Early (EOS) and late (LOS) onset neonatal sepsis

Respiratory distress (RD)

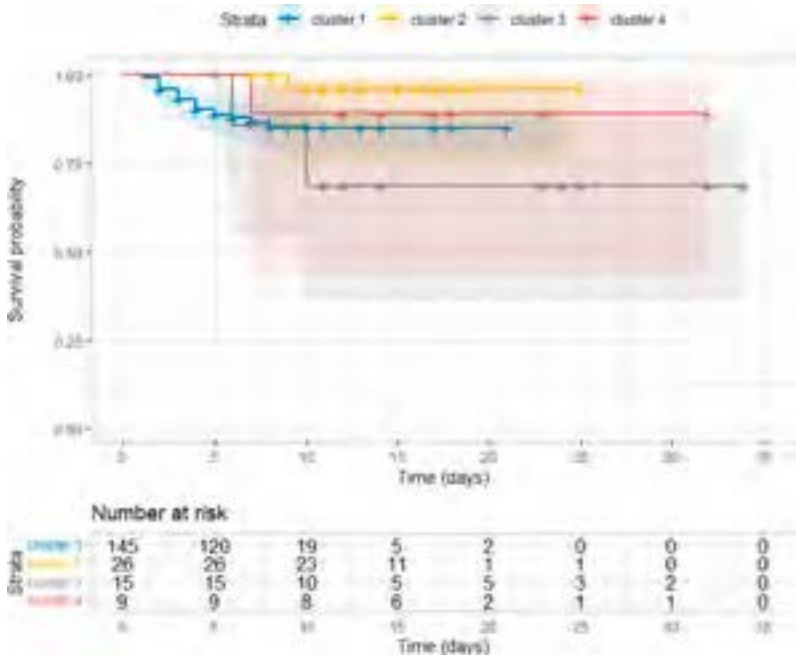

Fig. 4 Kaplan–Meier curves for survival probability in newborn with neonatal sepsis distinguished by antibiotic management clusters

The probability of developing RD for newborns with neonatal sepsis was 91% and 87% higher for antibiotic management cluster 3 compared to clusters 1 and 2, respectively. The odds of developing RD decreased by 6.4% for the increment of 100 g in body weight at admission (p=0.006) and was higher in the cluster 3 group when compared with clusters 1 and 2 (Table 2).

Since less than 50% of the cohort died (death rate=13.3%), the Kaplan-Meier estimate median survival time was not computed (Fig. 4). Death HR was not significantly different based on assignment to antibiotic management clusters (Table 3). Death probability was 6.3 times higher for patients who developed RD (p=0.004) compared to newborns who did not and decreased by 8% for the increment of 100 g in body weight at admission (p=0.006).

Clinical features of EOS and LOS

The main clinical features are listed in Table 1. EOS was associated with both PROM and chorioamnionitis (p=0.004; p=0.015); no differences were found in the frequency of mothers with pre- or eclampsia between the two types of neonatal sepsis (p=0.998). RD was observed in 90 (46.2%) newborns with neonatal sepsis, 70

Table 3 Survival hazard ratio (HR) estimated in the multivariable Cox Proportional-Hazards model with age, weight at admission, sepsis type, antibiotic management cluster, and the presence of RD as potential determinants. Cluster 3 was chosen as reference because it accounts for the cluster outside the protocol antibiotic lines

	HR	0.95 CI	p-Value
Outcome (dead/alive)			
Admission age (days)	1.13	0.85–1.50	0.414
Admission weight (hg)	0.92	0.86–1.50	0.006
Neonatal sepsis type (LOS)	0.04	0.00-7.66	0.235
RD	6.30	1.78–22.22	0.004
Antibiotic cluster (3)			
1	1.16	0.38–3.54	0.788
2	0.18	0.02–1.62	0.126
4	0.40	0.04–3.57	0.410

Early (EOS) and late (LOS) onset neonatal sepsis

Respiratory distress (RD)

(47.9%) in EOS and 20 (40.8%) in LOS. Newborns requiring electric-CPAP were 30 (33.3%), bubble-CPAP were 41 (45.6%) and only intranasal oxygen was required by 19 (21.1%) patients. No differences were found between respiratory support types in the two groups of neonatal sepsis (p=0.122). Risk of RD and death was not different between the two sepsis types groups (p=0.838, p=0.268, Table 3).

Discussion

In this proof-of-concept study we explored the use of cluster analysis as a tool to discern the antibiotic lines used for neonatal sepsis in a resource-limited setting. Clustering allowed to identify a group of patients needing advanced or off-protocol antibiotic lines, and to assess frequency and types of switching between antibiotic lines in complex critically ill newborns. While three of the four clusters reflected the three lines of antibiotic therapy set out in the protocol (cluster 1, 2 and 4), cluster 3 was characterized by the use of ceftriaxone/cloxacillin as a second-line antibiotics and the use of off-protocol antibiotics for the third line. Interestingly, cluster 3 had a higher odd of RD compared to both cluster 1 and 2. The severity of the disease impacts patient management as it trickles urgent use of broader spectrum antibiotics. As ceftriaxone broad spectrum focuses on gram-negative bacteria, clinicians decided to extend the spectrum by adding cloxacillin for gram-positive bacteria. When considering the survival probability, no differences were found based on antibiotic cluster assignment. The small sample size and the low number of patients in clusters 2, 3 and 4 may have led to this result. At the same time, it could also be related to the fact that prompt switch to a different line of antibiotics or the use of broader-spectrum antibiotics may have offset more severe infections or to the fact that some newborns may have died before switching antibiotic lines.

Cluster analysis also identified the frequency of antibiotic lines used, estimating the need to switch between lines due to ineffectiveness related to sepsis severity or antibiotic-resistant pathogens. In one out of four newborns of these cases (Cluster 2, 3 and 4), the first line antibiotic therapy with ampicillin plus gentamicin was not sufficient, in line with an increase in resistance to WHO-suggested first line therapy. The 5 common groups of Gram-negative bacteria (E. Coli, Klebsiella spp, Enterobacter spp, Pseudomonas spp, Acinetobacter), the main cause of neonatal sepsis in LMIC, are resistant to ampicillin and gentamicin in 40–100% of cases, depending to the bacteria involved [21–23].

The second line including a third-generation cephalosporin (i.e. ceftriaxone) required additional antibiotics in 12.3% of cases, leading to the emergence of clusters 3 and 4 in the present study. A review and meta-analysis in sub-Saharan Africa showed Gram-negative resistance to ceftriaxone ranging between 33% and 49% [23] while studies in Ethiopia reported higher resistance to cefotaxime (61.1-95.1%) [22, 24, 25]. Gram-positive bacteria showed resistance rates to third generation cephalosporin ranging from 50 to 95% [21–25], while resistance to fluoroquinolone and piperacillin/tazobactam is still low, ranging from 7 to 37% [25]. Yet, the number of multidrug resistant pathogens is increasing in Ethiopia [24, 25] and the above-mentioned alternative antibiotics are often unavailable and expensive, making the resistance to common antibiotics a very concerning issue [23].

Compared with high-income countries, the incidence of neonatal sepsis has been reported to be 40 times higher in LMICs [26]. In the present study, prevalence of neonatal sepsis in the overall patients admitted to the SLCH NICU (42.8%) was in line with recent Ethiopian data, showing a range from 33.6 to 40.7% [23, 25]. It should be noted that this prevalence was based on the diagnosis of probable neonatal sepsis based solely on clinical and laboratory findings. Confirmed sepsis, requiring a positive

blood culture, was estimated in literature as one third of all probable neonatal sepsis [24, 28].

In our study, EOS had a prevalence three times higher than LOS. A study in Nepal showed a similar prevalence of EOS (71.2%) when considering clinically suspected neonatal sepsis. Higher EOS prevalence (between 84.1% and 90.2%) was reported in two studies conducted in different areas of Ethiopia [25, 27]. LOS were significantly more frequent in infants born at home and in health centers. This may be due to newborns receiving better care in hospitals as compared to home and health center births, where there is no trained or non- specialized staff and less equipment. In the study sample, EOS was associated with chorioamnionitis and PROM, two well-known risk factors for EOS development [18, 28].

Mortality rate was higher for infants with EOS (16.4%) compared to those with LOS (4.1%). A similar case fatality ratio was reported in literature for EOS (18%) and it was higher when compared to both community and hospital acquired LOS [29]. When evaluating the death and RD odds ratio in the study sample, it was higher as weight at admission decreased. Prematurity and low birth weight are well-known factors associated with the higher sepsis mortality and development of respiratory complications [30]. A neonatal mortality rate of 27 deaths per 1000 live births has been reported in sub-Saharan Africa for neonatal sepsis alone [31]. The achievement of the reduction of neonatal mortality in all countries to less than 12 deaths per 1,000 live births by 2030, envisioned by the Sustainable Development Goals, is jeopardized by the still high mortality from neonatal sepsis [32].

The main limitation of the study is the retrospective design and the small sample size of patients with neonatal sepsis and the small number of newborns assigned to clusters 2, 3 and 4. Cluster analysis, as an unsupervised learning technique, works best with large numbers. In addition, the small sample size did not allow the cluster to be used as a time-varying covariate making survival analysis to be interpreted with caution in the first 6 days since infants assigned to cluster 1 might have died before they had a chance to switch antibiotics and thus be assigned to another cluster. Nevertheless, to the best of our knowledge, this is the first study that seeks to apply an indirect technique to study antibiotic stewardship in settings where disease severity, patient complexity and lack of microbiological laboratory capacity leads to piling up of antibiotic prescriptions. Second, the lack of blood culture and pathogen isolation has prevented the diagnosis of confirmed neonatal sepsis and characterization of the antibiotic resistance profile. In addition, because of the lack of more specific blood tests (e.g., blood gas analysis) and blood cultures, some of the infants diagnosed with neonatal sepsis, based on symptoms and white blood cells, may actually have had perinatal asphyxia. Moreover, respiratory distress was collected as binary data; this prevented the application of a competing risk analysis. Finally, the study was conducted in a referral hospital and therefore involved a population of newborns that may have had more severe characteristics than those in peripheral health centers.

Conclusions

The present proof of concept study used cluster analysis to depict the challenges of antibiotic management in a LMIC NICU. First-line antibiotics recommended by the WHO were not sufficient in one quarter of probable sepsis cases. Second-line treatment with third-generation cephalosporins was also insufficient in one in ten patients. The use of a machine learning technique allowed disentangling a patient group that received a different treatment than protocolized and more frequently evolved in RD. The use of different statistical methodologies should be encouraged to collect data where laboratory tests for sepsis typing and bacteria identification are not available so as to expand data pools from low resourced settings.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13756-023-01325-w.

Supplementary Material 1

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Author contributions
In this work RB and LP conceptualized and designed the study, made substantial contributions to original writing. RB was responsible for the data analysis. EB contributed to the interpretation of data and original writing. MB reviewed the study critically. MC and FB contributed to data collection and interpretation. TE and JT contributed to data collection. All authors reviewed the study critically.

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Data Availability
The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethical Committee of St. Luke Catholic Hospital on September 14th, 2021 (protocol number 1293/2021). Informed consent was waved by the Ethical Committee of St. Luke Catholic Hospital.

Consent for publication
Not Applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Woman's and Child's Health, University of Padua, Via Giustiniani, 3, Padua 35128, Italy
[2]Section of Hygiene, Department of Diagnostics and Public Health, University of Verona, Strada Le Grazie, 8, Verona 37134, Italy
[3]Section of operational research, Doctors with Africa CUAMM, Padova, Italy
[4]Neonatal Intensive Care Unit, AUSL-IRCCS of Reggio Emilia, Reggio Emilia, Italy
[5]Doctors with Africa CUAMM Ethiopia, Wolisso, Ethiopia
[6]Neonatal Intensive Care Unit, St Luke Catholic Hospital, Wolisso, Ethiopia
[7]Mahidol Oxford Research Unit, Bangkok, Thailand

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Impact of the COVID-19 pandemic on malaria in pregnancy indicators in Northern Uganda: a joinpoint regression analysis

PAPER

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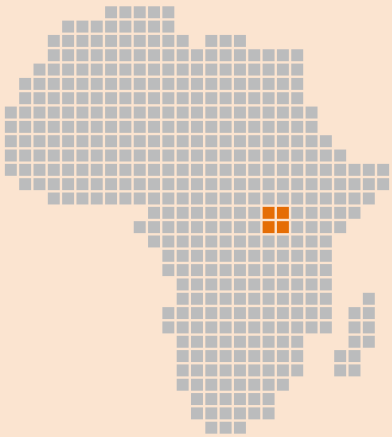

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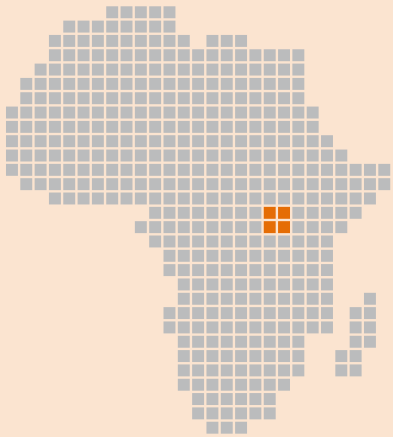

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COVID Perceptions among Pregnant Women Living in a Malaria Hyperendemic Rural Region in Uganda: A Cross-Sectional Study

Francesco Vladimiro Segala,[1] Giulia Patti,[1] Lameck Olal,[2] Elda De Vita,[1]* Nelson Olung,[3] Roberta Papagni,[1] James Amone,[3] Valentina Totaro,[1] Emmanuel Onapa,[3] Roberta Novara,[1] Benedict Ngole,[2] Mariangela L'Episcopia,[4] Samuel Okori,[3] Giovanni Dall'Oglio,[5] Jerry Ictho,[5] Carlo Severini,[4] Giovanni Putoto,[6] Peter Lochoro,[5] Francesco Di Gennaro,[1] and Annalisa Saracino[1]

[1]*Clinic of Infectious Diseases, Department of Precision and Regenerative Medicine and Ionian Area, University of Bari "Aldo Moro," Bari, Italy;* [2]*African Network for Change, Kampala, Uganda;* [3]*St. John's XXIII Hospital Aber, Jaber, Uganda;* [4]*Department of Infectious Diseases, Istituto Superiore di Sanità, Rome, Italy;* [5]*Doctors with Africa, CUAMM, Kampala, Uganda;* [6]*Operational Research Unit, Doctors with Africa CUAMM, Padua, Italy*

Abstract. Both SARS-CoV2 and *Plasmodium falciparum* infection during pregnancy increases the risk for adverse maternal and fetal outcomes, including abortion, severe disease, and death. Indeed, although malaria and COVID-19 show an overlapping clinical presentation, they require a profoundly different approach. The aim of this study was to explore COVID-19 awareness among pregnant women living in a *P. falciparum* hyperendemic region in rural Uganda. This cross-sectional, prospective study was conducted in one Hospital and two Health Centers (HC) in Lango region, Uganda, from July 14, 2022, to March 14, 2023. Data about demographics, COVID-19 history, and COVID-19 and malaria perceptions were collected using RedCap mobile app platform. Study endpoint was a context-specific COVID-19 awareness score, accounting for the most common disease misconceptions. Association between study variables and good COVID-19 awareness was assessed by χ^2 and *t* test, as appropriate, and variables found to be statistically significant were further explored in multivariate logistic regression analysis. A total of 888 pregnant women were recruited. Median age was 24 (interquartile range: 20–29) years, whereas 79% ($n = 704$) attained only primary education and 66.6% ($n = 591$) were used in agriculture. SARS-CoV2 vaccination rate was 92%. In multivariate analysis (Table 3), variables associated with high COVID knowledge were presenting at antenatal care visit in Atipe HC (adjusted odds ratio [aOR]: 8.1, 95% CI: 4.1–16.48) having a previous good knowledge about malaria (aOR: 1.76, 95% CI: 1.21–2.56). Among pregnant women living in rural Uganda, COVID-19 awareness relies on the overall educational level, malaria knowledge and reference HC. Among pregnant women living in *P. falciparum* endemic areas, community-level malaria awareness might guide educational interventions during future pandemics.

INTRODUCTION

In 2020, the WHO reported an increase in the estimated total number of malaria cases occurring globally, reaching 247 million cases from the 230 million reported in 2015. The rise that occurred in 2020 has been largely attributed to the disruption of malaria control strategies caused by COVID-19,[1] because malaria control relies on individual choice to seek care, while people were warned to stay home in case of fever; supplies such as insecticide-treated nets or antimalarial drugs could not be provided; and the healthcare workforce was constrained.[2]

In this context, pregnant women are particularly vulnerable because of their increased risk of developing severe malaria and of experiencing preterm delivery and intrauterine growth retardation due to a buildup of *Plasmodium falciparum*–infected red blood cells in the placenta. In malaria hyperendemic regions, pregnancy is a risk factor for both the acquisition of *P. falciparum* infection and the development of severe malaria. Complications of malaria infection in pregnancy affect both the mother and the child and include maternal anemia, low birth weight, prematurity, infant malaria, childhood anemia, and congenital malaria.[3] Likewise, compared with nonpregnant women of reproductive age, pregnant women infected by SARS-CoV-2 are at increased risk of mortality and of progression toward severe disease requiring respiratory support, admission to an intensive care unit, invasive ventilation, dialysis, or extracorporeal membrane oxygenation,[4] also due to the still poor therapeutic options available, which makes them more vulnerable to the progression of the disease. Furthermore, babies born to mothers with COVID-19 were more likely to be admitted to the neonatal intensive care unit than those delivered to non-COVID mothers.

As a consequence, during the COVID-19 pandemic, pregnant women living in communities with high-malaria burden had to face the multiple challenges posed by two highly incident diseases that had similar clinical presentation,[5] threatened their own life and the life of their fetuses, but required profoundly different approaches in terms of community prevention, healthcare seeking, and disease control.[6,7] Also, for both diseases, community-level awareness demonstrated to be among the main driver of prevention success.[8,9]

In Uganda, the country with the third highest burden of malaria cases worldwide,[1] COVID-19 cases progressively increased with three major waves that peaked in December 2020, June 2021, and January 2022, respectively, leading to a total of nearly 172,000 cases and 3,632 deaths up to August 2023.[10,11] Furthermore, Oyam district, a rural area in Northern Uganda, has a malaria incidence and mortality both above the national average.[12] In Lango region, *P. falciparum* is responsible for 97% on malaria cases, and overall maternal mortality is 336 maternal deaths every 100,000 live births.[13] However, despite the high vulnerability of pregnant women to both *P. falciparum* and SARS-CoV-2 infection, little is known about the interplay between these two conditions in terms of disease awareness, behaviors, and preventive attitudes.

*Address correspondence to Elda De Vita, Clinic of Infectious Diseases, Department of Precision and Regenerative Medicine and Ionian Area, University of Bari "Aldo Moro," 70124 Bari, Italy. E-mail: elda.devita@libero.it or devitaelda@gmail.com

The aim of this study was to explore awareness of COVID-19 among pregnant women living in a *P. falciparum* hyperendemic region in rural Uganda.

MATERIALS AND METHODS

This study is a part of a broader research project "Impact of Antimalarial Resistance and COVID-19 Pandemic on Malaria Care among Pregnant Women in Northern Uganda (ERASE)."[2]

Study design, setting, and population. This is a cross-sectional, prospective observational study. The study was conducted in one Hospital (St John's XXIII Hospital of Aber) and in a third and fourth level Health Centers (HCs)[14] (Atipe HC and Aboke HC), located in the districts of Oyam and Kole, Lango Region, Uganda. All pregnant women presenting to the antenatal care clinic between July 14, 2022, and March 14, 2023 were eligible for recruitment. Study protocol was approved by Lacor Hospital Research and Ethics Committee (prot. no. LACOR-2022-95). All women included in the study provided written informed consent.

Study procedures. Data were collected by administering structured questionnaires. Study questionnaires were prepared together with local health operators and community leaders. Malaria knowledge was evaluated with a 5-point questionnaire based on the Malaria Indicator Survey developed by Ugandan Ministry of Health.[11] From June to August 2020, a dedicated training about COVID transmission and prevention measures was carried out in all study centers informing the population about local epidemiology of COVID-19, SARS-CoV2 route of transmission, risk factors for pregnant women, and prevention methods such as use of facemasks and adherence to the vaccination campaign. Study data were collected and managed using REDCap Mobile App electronic data capture tool[15] hosted at Catholic University of the Sacred Heart, Rome.

Study endpoint. Endpoint of the study was a context-specific, internally validated COVID-19 awareness score developed with local community leaders and healthcare operators. The awareness score accounted for the most common disease misconceptions in Oyam and Kole districts. The score ranged from a minimum of 0 and a maximum of 5 points.

Statistical analysis. A descriptive analysis was performed to define the distribution of baseline variables and characteristics of the sample. The dependent variable was COVID-19 awareness, and a score of at least 4 points was considered as "good knowledge" of COVID-19. Continuous variables were compared between groups using independent *t* tests, and categorical variables were analyzed using a χ^2 test. A logistic regression model was used, with COVID-19 good knowledge as the dependent variable and the available factors at the baseline evaluation as independent variables in the univariate analysis. Factors with a P value < 0.10 from the univariate analysis were included in the multivariate analysis. The strength of the association between baseline factors (exposure) and COVID-19 knowledge (outcome) was measured using adjusted odds ratios (aORs) with 95% CIs. All statistical tests were two-tailed, and a P value < 0.05 was considered statistically significant.

Statistical analyses were performed using R Statistical Software (v4.1.3; R Core Team 2021) in R Studio Version.[15]

RESULTS

As shown in Table 1, a total of 888 women were recruited in the study. Almost all ($n = 883$; 99.4%) lived in rural setting. Seven-hundred and nineteen women (81%) were recruited in Aber Hospital, and 97 (10.9%) in Aboke HC and 72 (8.1%) in Atipe HC. Median age was 24 (interquartile range: 20–29) years. Seventy-nine percent of the population ($n = 704$) attended only primary school, whereas only 4.7% ($n = 42$) reported to have attained tertiary education. Most of the women were farmworkers (66.6%, $n = 591$). Ninety-three percent ($n = 830$) reported being married.

Ninety-two percent ($n = 817$) of the women reported being vaccinated against COVID-19, but the rate of vaccination with more than two doses was 13.4% ($n = 119$). Only four women (0.05%), all belonging to the "poor COVID knowledge group," reported having been diagnosed with SARS-CoV2 infection in the past. Most women (66.8%, $n = 593$) believed that COVID-19 is more dangerous than malaria.

Figure 1 shows the results of the COVID-19 awareness score. Overall, 173 women scored at least 4 and were identified as having good knowledge about COVID-19. At this regard, 93.8% ($n = 833$) of the women believed that COVID-19 might be prevented by eating garlic or mangoes, 50% ($n = 444$) by drinking a locally produced alcoholic beverage, and 55.2% ($n = 490$) thought that COVID-19 is dangerous only for White people.

DISCUSSION

Despite their similar clinical presentation, both SARS-CoV2 and *P. falciparum* infection poses a substantial threat for pregnant women and their fetuses, who are at increased risk to progress toward pregnancy loss, severe disease, and death. The present study aimed to explore the awareness of COVID-19 among pregnant women living in a rural area in northern Uganda with a high burden of *P. falciparum* malaria.

In this study, we found a very poor level of COVID-19 awareness, with four out of five women scoring below the threshold of high awareness. This is consistent with findings from a recent systematic review and meta-analyses investigating COVID-19 knowledge among pregnant women conducted by Jahromi et al.,[16] in which Uganda ranked as the country with the lowest level of awareness about SARS-CoV2 infection. Also, the present study confirms that COVID-19 awareness in Uganda was generally lower than the one found in other sub-Saharan African countries.[17]

In particular, in this study, most women believed in common misconceptions, such as that COVID-19 might be prevented by eating garlic or mangoes or by drinking *waragi*: a locally produced, hard alcohol distilled spirit. Worryingly, this fallacy was identified also in a survey conducted by the United Nations High Commissioner for Refugees[18] in Congo, South Sudan, Uganda, Rwanda, and Burundi in late 2020, thus underscoring the fact that some diffuse—and potentially harmful—misconceptions should be explicitly addressed by public health interventions.[19]

Furthermore, more than half of the pregnant women included in our sample thought that COVID-19 is dangerous only for White people. In fact, the belief that COVID-19 is dangerous only for White, rich people appears to be a widespread belief in sub-Saharan Africa.[20] This is consistent with the finding that, compared with high-income countries, the estimated infection-fatality ratio of SARS-CoV2 infection was significantly lower in Sub-Saharan African countries, even when controlling for age, vaccination status, clinical covariates, and health system performances.[21] Several hypotheses have been proposed

TABLE 1
Descriptive statistics and monovariate analysis

Variable	Overall (N = 888)	Low COVID awareness (n = 715)	High COVID awareness (n = 173)	P value*
Age at enrollment				0.57
Median (IQR)	24.0 (20.0–29.0)	24.0 (20.0–29.0)	25.0 (21.0–29.0)	
Missing, *n* (%)	2 (0.2)	2 (0.3)	0 (0)	
Setting, *n* (%)				
Rural	883 (99.4)	713 (99.7)	170 (98.3)	0.839
Urban	2 (0.2)	1 (0.1)	1 (0.6)	
Missing	3 (0.3)	1 (0.1)	2 (1.2)	
Health center, *n* (%)				
Aber	719 (81.0)	604 (84.5)	115 (66.5)	**< 0.001**
Aboke	97 (10.9)	78 (10.9)	19 (11)	
Atipe	72 (8.1)	33 (4.6)	39 (22.5)	
Educational level, *n* (%)				
Lower primary	462 (52.0)	399 (55.8)	63 (36.4)	**< 0.001**
Upper primary	242 (27.3)	179 (25.0)	63 (36.4)	
Lower secondary	82 (9.2)	67 (9.4)	15 (8.7)	
Upper secondary	40 (4.5)	25 (3.5)	15 (8.7)	
Tertiary	42 (4.7)	31 (4.3)	11 (6.4)	
No education	20 (2.3)	14 (2.0)	6 (3.5)	
Occupation, *n* (%)				
Used	77 (8.7)	57 (8.0)	20 (11.6)	**< 0.001**
Farming	591 (66.6)	493 (69.0)	98 (56.6)	
Housewife	153 (17.2)	107 (15.0)	46 (26.6)	
Tailor	67 (7.5)	58 (8.1)	9 (5.2)	
Religion, *n* (%)				
Anglican/Protestant	236 (26.6)	189 (26.4)	47 (27.2)	0.714
Catholic	549 (61.8)	440 (61.5)	109 (63.0)	
Muslim	6 (0.7)	5 (0.7)	1 (0.6)	
Other	94 (10.6)	80 (11.2)	14 (8.1)	
Missing	3 (0.3)	1 (0.1)	2 (1.2)	
Marital status, *n* (%)				
Divorced	10 (1.1)	8 (1.1)	2 (1.2)	0.879
Married	830 (93.5)	667 (93.3)	163 (94.2)	
Never married	48 (5.4)	40 (5.6)	8 (4.6)	
Ever diagnosed with COVID-19, *n* (%)	4 (0.5)	4 (0.6)	0 (0)	0.723
Missing	1 (0.1)	1 (0.1)	0 (0)	
Received vaccination against COVID-19, *n* (%)	817 (92.0)	663 (92.7)	154 (89.0)	0.128
Missing	1 (0.1)	1 (0.1)	0 (0)	
Vaccine doses, *n* (%)				
More than two doses	119 (13.4)	89 (12.4)	30 (17.3)	0.138
Two doses	353 (39.8)	293 (41.0)	60 (34.7)	
One dose	345 (38.9)	281 (39.3)	64 (37.0)	
Unvaccinated	71 (8.0)	52 (7.3)	19 (11.0)	
Belief that COVID is more dangerous than malaria, *n* (%)	593 (66.8)	491 (68.7)	102 (59.0)	**0.0199**
Missing	4 (0.5)	3 (0.4)	1 (0.6)	
Good knowledge about malaria, *n* (%)	316 (35.6)	236 (33.0)	80 (46.2)	**0.0015**

IQR = interquartile range.
* Chi-squared test or *t* test, as appropriate. Bold *P* values represent statistically significant variables.

to explain the lower than anticipated burden of severe COVID-19 in sub-Saharan Africa, including age structures, the hygiene hypothesis,[22] microbiome diversity,[23] and previous malaria exposure.[24]

Another peculiar finding of this study is that two-thirds of the recruited women believed that COVID is more dangerous than malaria. This is interesting because it goes in contrast with the disease burden experienced by the pour population, both in terms of COVID-19 and malaria, because only four women reported to have ever been diagnosed with COVID-19. Even though SARS-CoV2 infection rate was likely higher,[25] this finding deserves consideration because is a proxy for COVID-induced medical attention seeking. Also, as part of a broader ongoing cohort study,[2] *P. falciparum* infection rate is under investigation in the same population, and preliminary analysis suggest that blood smear positivity rate is as high as 18% (unpublished data). In Uganda, malaria is the second leading cause of all-age death and disability[26] and the first nonobstetric cause of death among hospitalized pregnant women.[27] For these reasons, to implement the delivery of services to pregnant women, a collaboration between local and nongovernmental organizations was of a great importance together with the role of community health workers in the promotion of the use of antenatal clinic services.[28] In the present study, a correct perception of the relative danger posed by COVID-19 compared with malaria correlates with an overall high awareness of COVID-19 at multivariable analysis.

Despite the high diffusion of COVID misconceptions, overall adherence to the vaccination against SARS-CoV2 was very high. These data corroborate the findings that in low- and middle-income countries, vaccine acceptance is generally high, sometimes even higher than that reported in most high-income countries.[29]

At multivariate analysis, other factors that were identified to be associated with good COVID awareness were higher educational level, good knowledge about malaria, and visiting the ANC clinic located in Atipe HC. During the pandemic, the same educational intervention was carried out in all three

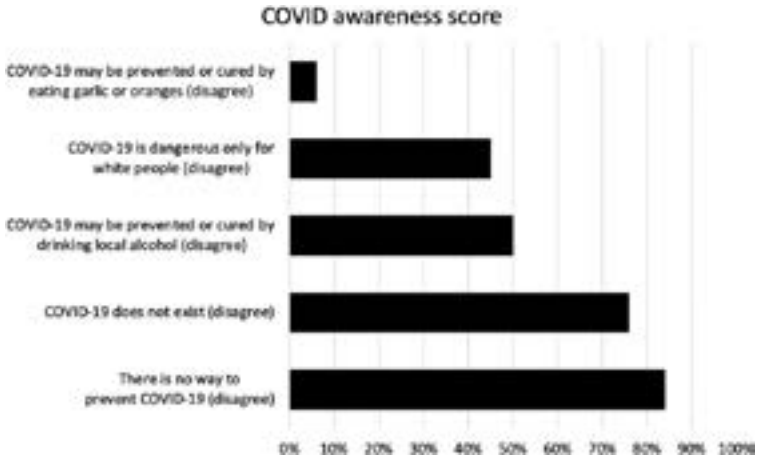

FIGURE 1. In the multivariate analysis (see Table 2), variables associated with high COVID awareness were as follows: presenting at antenatal care visit in Atipe health center (adjusted odds ratio [aOR] 8.1, 95% CI: 4.1–16.48), having attained at least upper secondary school (aOR 3.05, 95% CI: 1.36–6.7), and having good knowledge about malaria (aOR 1.76, 95% CI: 1.21–2.56).

TABLE 2
Multivariate logistic regression analysis

Variable	aOR	95% CI low	95% CI high	*P* value
Age	1.00	0.972	1.038	0.75
Presentig at Aboke HC for ANC visit	3.22	0.622	20.667	0.19
Presenting at Atipe HC for ANC visit	8.179	4.146	16.484	**< 0.001**
Highest level of education that you attained: upper secondary	3.052	1.359	6.708	**0.006**
Occupation: farming	0.828	0.414	1.718	0.603
Occupation: unemployed	0.821	0.369	1.854	0.632
Occupation: tailor	0.519	0.194	1.316	0.176
Belief that COVID is more dangerous than malaria	0.506	0.34	0.753	**< 0.001**
Good knowledge about malaria	1.761	1.211	2.56	**0.003**

ANC = antenatal care; aOR = adjusted odds ratio; HC = health center. Bold *P* values represent statistically significant variables.

study sites, but by different teams; therefore, this finding suggests that healthcare officers may play a crucial role in disseminating accurate information and promoting awareness among pregnant women. Further studies are required to assess the impact of standardized educational strategies in improving disease awareness and promote prevention.

This study has several limitations that should be acknowledged. First, it was conducted in a specific region of rural Uganda, and the sample may not be representative of the entire country or other contexts. However, sample size was high, and our sample should be representative of the population of pregnant women living in rural areas of Northern Uganda. Second, the study relied on self-reported data, which may be subject to social desirability bias. However, to minimize this bias, research assistants working in ANC clinic were trained to create a safe space for pregnant women, encouraging them to be sincere and not to feel judged. Third, the 5-point score used as study endpoint was highly context- and disease-specific, which limits its reproducibility. Fourth, we did not directly assess preventive behaviors.

CONCLUSIONS

In conclusion, this study provides valuable insights into the awareness of COVID-19 among pregnant women in a malaria hyperendemic region of rural Uganda. The findings highlight the presence of misconceptions and knowledge gaps that need to be addressed through targeted health education interventions. It is mandatory to implement plans and strategies for malaria and COVID-19 prevention with proper information and interventions, placing importance on the collaboration between clinicians and maternal health experts. Furthermore, a monitoring program of education with an appropriate update over time is essential. Strengthening health education within healthcare facilities, promoting literacy and education, and integrating disease-specific knowledge can enhance the overall understanding of both malaria and COVID-19. In *P. falciparum* hyperendemic areas, community-level malaria awareness among pregnant women might guide educational interventions during future pandemics.

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Authors' addresses: Francesco Vladimiro Segala, Giulia Patti, Elda De Vita, Roberta Papagni, Valentina Totaro, Roberta Novara, Francesco Di Gennaro, and Annalisa Saracino, Clinic of Infectious Diseases, Department of Precision and Regenerative Medicine and Ionian Area, University of Bari "Aldo Moro," Bari, Italy, E-mails: fvsegala@gmail.com, giuliapatti22@gmail.com, devitaelda@gmail.com, robertapapagni0@gmail.com, valentinatotaro11@gmail.com, robertanovara@gmail.com, cicciodigennaro@yahoo.it, and annalisa.saracino@uniba.it. Lameck Olal and Benedict Ngole, African Network for Change, Kampala, Uganda, E-mails: olalam2012@gmail.com and ngolebenedict3@gmail.com. Nelson Olung, James Amone, Emmanuel Onapa, and Samuel Okori, St. John's XXIII Hospital Aber, Jaber, Uganda, E-mails: olung2006@gmail.com, jamnet5@gmail.com, onapae@yahoo.com, and drokori@gmail.com. Mariangela L'Episcopia and Carlo Severini, Department of Infectious Diseases, Istituto Superiore di Sanità, Rome, Italy, E-mails: mlepiscopia@gmail.com and carlo.severini@iss.it. Giovanni Dall'Oglio, Jerry Ictho, and Peter Lochoro, Doctors with Africa, CUAMM, Kampala, Uganda, E-mails: g.dalloglio@cuamm.org, j.itcho@cuamm.org, and p.lochoro@cuamm.org. Giovanni Putoto, Operational Research Unit, Doctors with Africa CUAMM, Padua, Italy, E-mail: g.putoto@cuamm.org.

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SARS-CoV-2 seroprevalence and associated factors, based on HIV serostatus, in young people in Sofala province, Mozambique

PAPER

Authors
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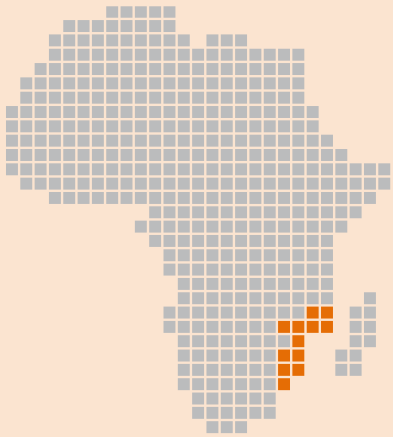

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SARS-CoV-2 seroprevalence and associated factors, based on HIV serostatus, in young people in Sofala province, Mozambique

Roberto Benoni[1,2,3*], Virginia Casigliani[2,4], Annachiara Zin[1], Dara Giannini[2], Niccolò Ronzoni[2,5], Costanza Di Chiara[1], Kajal Chhaganlal[6], Daniele Donà[1], Ada Merolle[2], Helga Guambe Dos Anjos[7], Fernando Chenene[2], Francesca Tognon[8], Giovanni Putoto[8] and Carlo Giaquinto[1]

Abstract

Introduction In Sofala province (Mozambique), young people living with HIV (YPLHIV) are estimated at 7% among people aged 15–24 years. Even though the COVID-19 pandemic threatened HIV health services, data on the impact of COVID-19 on YPLHIV people are lacking. This study aimed at exploring the seroprevalence of SARS-CoV-2 and associated factors among young people based on their HIV status.

Methods A cross-sectional study was conducted, including people aged 18–24 attending a visit at one of the adolescent-friendly health services in Sofala province between October and November 2022. People vaccinated against SARS-COV-2 or YPLHIV with WHO stage III-IV were excluded. A SARS-CoV-2 antibodies qualitative test and a questionnaire investigating socio-demographic and clinical characteristics were proposed. SARS-CoV-2 seroprevalence was calculated with Clopper-Pearson method. The odds ratio (OR) of a positive SARS-CoV-2 antibodies test was estimated through multivariable binomial logistic regression.

Results In total, 540 young people including 65.8% women and 16.7% YPLHIV participated in the survey.. The mean age was 20.2 years (SD 2.0). Almost all the sample (96.1%) reported adopting at least one preventive measure for COVID-19. The weighted seroprevalence of SARS-CoV-2 in the whole sample was 46.8% (95%CI 42.6–51.2) and 35.9% (95%CI 25.3–47.5) in YPLHIV. The adjusted OR of testing positive at the SARS-CoV-2 antibodies test was higher in students compared to workers (aOR:2.02[0.95CI 1.01–4.21]) and in those with symptoms (aOR:1.52[0.95CI 1.01–2.30]). There were no differences based on HIV status(aOR:0.663[95%CI 0.406–1.069]). Overall, COVID-19 symptoms were reported by 68 (28.2%) people with a positive serological SARS-CoV-2 test and by 7 (21.7%) YPLHIV ($p=0.527$). No one required hospitalization.

Conclusions SARS-CoV-2 seroprevalence was 46.8% without differences in risk of infection or clinical presentation based on HIV status. This result may be influenced by the exclusion of YPLHIV with advanced disease. The higher risk among students suggests the schools' role in spreading the virus. It's important to continue monitoring the impact of COVID-19 on YPLHIV to better understand its effect on screening and adherence to treatment.

Keywords SARS-CoV-2, Seroprevalence, COVID-19, HIV, Mozambique, YPLHIV

*Correspondence:
Roberto Benoni
roberto.benoni90@gmail.com
Full list of author information is available at the end of the article

Introduction

The Human Immunodeficiency Virus (HIV) represents a global public health emergency, despite the first clinical case being identified more than 40 years ago.

In 2021, 38.4 million people were living with HIV (PLHIV) worldwide, of whom 9.7 million were not on treatment due to a lack of knowledge of their serological status or difficulties in accessing therapy. In the same year, there were an average of 4,000 new cases per day, 60% in sub-Saharan Africa with 30% concentrated in the 15–24 age group [1, 2].

In 2021, Mozambique registered 94,000 new cases of HIV, making it the second country in sub-Saharan Africa with the highest number of infections. In the same year, it is estimated that there were 1,976,250 PLHIV in the country [2, 3]. In the province of Sofala, in Beira, HIV prevalence is estimated at 7% among adolescents between 15 and 24 years of age [4].

The COVID-19 pandemic hit the African continent, albeit more lightly than other continents, regarding disease severity and mortality. However, the spread of infection is not easily assessed due to the difficulties of surveillance and contact tracing systems and the limited capacity of the necessary laboratory facilities. For this reason, prevalence studies based on the detection of antibodies against SARS-CoV-2 are essential to understand the real spread of the virus in the African continent and, thus, guide public health policies. According to the last available systematic review, the estimated pooled prevalence in Africa, linked to infection or vaccination, reached 65% in September 2021, with a prevalence of 56.1% in southern Africa; however, most studies were only carried out in South Africa [5, 6].

In Mozambique, confirmed cases of SARS-CoV-2 infection were approximately 233,000 on 27/02/2023, with 2,242 deaths [7]. However, the country has had limitations in testing capacity during all the pandemic period: serological studies are therefore essential to better understand which was the real extent of the spread of the virus [8].

The COVID-19 pandemic had a double impact on PLHIV: on the one hand, the risk of contracting SARS-CoV-2 infection and developing a serious illness, on the other hand, the reduction of services with consequent difficulty in access to antiretroviral treatment [9]. During the first year of the pandemic, the HIV testing and antiretroviral therapy (ART) initiation showed a significant decrease, especially among children and adolescents, while the provision of the treatment and the retention in care of PLHIV seemed to be less affected by the pandemic [10]. It may be explained by the multiple interventions adopted, such as the multi-month dispensing of ART [11].

Currently, in low- and middle-income countries (LMIC), and particularly in sub-Saharan Africa, there are not enough studies on the epidemiology of COVID-19 in children and young people living with HIV, nor are there enough data on risk factors and disease outcomes in this population. Therefore, it became a priority to carry out a seroepidemiological study to estimate target group immunity, an essential indicator of the spread of infection in the community, to understand the challenges in accessing and retaining treatment associated with COVID-19.

The aim of the study was to estimate the seroprevalence of antibodies against SARS-CoV-2 at the end of 2022 and to explore its associated factors in young people living with HIV (YPLHIV) who attended the healthcare facilities in the province of Sofala in Mozambique.

Methods

Study design, population and intervention

A cross-sectional study was conducted to estimate the prevalence of SARS-COV-2 antibodies in young people accessing healthcare centers in the province of Sofala. We included all young people aged 18 to 24, who attended the adolescent-friendly service within the healthcare centers in Beira City and Nhamatanda (Mozambique) from October to November 2022, regardless of their HIV status. Inclusion criteria to participate in the study were the following: signing the informed consent, not presenting acute symptoms of SARS-COV-2 at the time of the test, not being vaccinated against SARS-COV-2, not being pregnant, not having been diagnosed in the last 6 months and not presenting an advanced clinical stage of HIV (WHO stage III-IV or CD4 < 200/ < 15%). Each participant underwent a questionnaire performed by a trained healthcare worker and had a rapid serological SARS-CoV-2 test done with a capillary blood test.

Study setting

All eight SAAJs of the Beira district, where Doctors with Africa CUAMM work, and the SAAJ of Nhamatanda Rural Hospital were selected. The city of Beira and the district of Nhamatanda are in the province of Sofala, in the central area of Mozambique. It has an estimated population of 2,528,442, of which 897,467 (35.5%) are aged between 10 and 24 years [12]. For this age group, the government of Mozambique has a special adolescent-friendly service within the health centers that provides education, prevention, and treatment for adolescents and young people, called Serviços amigos dos adolescentes e jovens (SAAJ).

Sample size calculation

A sample size of 540 youth was calculated using the following formula:

$$z^2 * P(1 - P)/\Delta^2$$

where z refers to the confidence level (set at 95%, so z = 1.96), P is the estimated prevalence of individuals testing positive ($P = 0.40$, based on the latest available seroprevalence in Beira and Omicron data from South Africa), and Δ is the desired precision (set at 5%) [9].

Considering a dropout around 10%, the final sample size was projected to be 540 participants, allowing an estimated prevalence of 40% (with a 95% confidence interval of 36–44%) adjusted by the sensitivity (96.7%) and specificity (97%) of the diagnostic test as reported by the manufacturer [13].

Endpoints

The primary endpoint of the study was the prevalence of SARS-CoV-2 antibodies in young people aged 18–24 years who access SAAJ of Beira and Nhamatanda, performed with a rapid diagnostic test. Secondary endpoints were (I) odds ratio of a positive serological test and (II) the number and type of symptoms of SARS-CoV-2 infection and hospitalizations, stratified by HIV status.

Data collection

A qualitative serological analysis to identify SARS-CoV-2 serostatus was performed through the IgM/IgG rapid test by lateral flow immunochromatographic method (Panbio™ COVID-19 IgG/IgM Rapid Test Duo, Abbott Laboratories, Orlando, USA).

A questionnaire (Additional file) was used to collect sociodemographic characteristics (age, sex, religion, profession, level of education, house density, defined as the number of persons living in the house divided by the number of house rooms, and area of residence), adhesion to SARS-CoV-2 preventive measures, COVID-19 epidemiological information (e.g., COVID-19 cases in the family), and clinical characteristics (i.e., HIV status, comorbidities, COVID-19 related symptoms in the previous 8 months).

The questionnaire was administered in the official local language (Portuguese) by the medical officer of the SAAJ. Data were collected from October to November 2022 and were entered into the REDcap platform to set up the database for subsequent analysis [14].

Ethical approval

The research was performed following the ethical standards of the 1964 Declaration of Helsinki and was approved by the Interinstitutional Bioethics Committee for Health (Comité Interinstitucional de Bioética para Saúde - CIBS), Sofala, on the 29th of August 2022 (protocol number 002/CIBIS/2022).

Statistical analysis

A descriptive statistical analysis was performed. Frequencies and proportions were calculated for categorical variables; means and standard deviation were used for continuous data. Sample distribution was tested via $\chi 2$ and Fisher exact test for categorical variables or ANOVA test for continuous variables, as appropriate.

Unweighted and weighted estimates of seroprevalence of SARS-CoV-2 with 95% CI were calculated with Clopper Pearson method as the number of positive test results divided by the total number of tests performed during the survey period. The weighted estimate was obtained with the Rogan-Gladen estimator considering a sensitivity and specificity of 96.7% and 97.0%, respectively, according to data provided by the manufacturer.

The univariate association between individual characteristics and seropositivity was explored using the $\chi 2$ test and multivariable associations by binomial logistic regression, including all variables found to be statistically significant in univariate analyses. Missing data were handled through pairwise deletion.

A p-value < 0.05 was considered significant. All analyses were performed using the R software (version 4.1.1).

Results

Patients' characteristics

Of the 540 young people included, 355 (65.7%) were females. The mean age was 20.2 years (SD 2.0). YPLHIV were 90/540 (16.7%, females = 57/90, 63.3%), with no differences compared with those without HIV based on sex and age. Socio-demographic characteristics are reported in Table 1.

Most patients had a middle school degree ($n = 393/540$, 72.8%). YPLHIV more frequently had a lower level of education than HIV-negative patients ($p = 0.026$, Table 1). YPLHIV were more frequently workers (17.8%) and fewer students (40.0%) than those without HIV ($p = 0.002$, Table 1).

SARS-CoV-2 prevalence

During the study period, 253/540 (46.9%) people tested positive with the rapid serological test for SARS-CoV-2 antibodies. The weighted seroprevalence of SARS-CoV-2 in the whole sample was 46.8% (95%CI 42.6%-51.2%). The seroprevalence by antibodies type was: 1.1% (95%CI 0.0–3.3) for IgM, 1.9% (95%CI 0.2%-4.2%) for IgM + IgG and 37.3% (95%CI 32.9%-41.8%) for IgG. The adjusted seroprevalence was 35.9% (95%CI 25.3%-47.5%) and 49.1% (95%CI 44.1%-54.1%) in the HIV+ and HIV- groups, respectively.

Table 1 Sociodemographic characteristics of the sample by HIV status

	HIV- (*n* = 450)	HIV + (*n* = 90)	*p*-Value*	Overall (*n* = 540)
Sex			0.685	
Females	298 (66.2%)	57 (63.3%)		355 (65.7%)
Males	152 (33.8%)	33 (36.7%)		185 (34.3%)
Age (years)			0.515	
Mean (sd)	20.2 (1.9)	20.4 (2.1)		20.2 (2.0)
School			0.026	
None	8 (1.8%)	0 (0.0%)		8 (1.5%)
Primary	54 (12.0%)	20 (22.2%)		74 (13.7%)
Secondary	329 (73.1%)	64 (71.1%)		393 (72.8%)
University	59 (13.1%)	6 (6.7%)		65 (12.0%)
Job			0.002	
Workers	29 (6.4%)	16 (17.8%)		45 (8.3%)
Unemployed/ temporary job	183 (40.7%)	38 (42.2%)		221 (40.9%)
Student	238 (52.9%)	36 (40.0%)		274 (50.7%)
District			0.843	
Rural	44 (9.8%)	10 (11.1%)		54 (10.0%)
Suburban	300 (66.7%)	61 (67.8%)		361 (66.9%)
Urban	106 (23.6%)	19 (21.1%)		125 (23.1%)
Religion			0.318	
Protestant/Anglican	241 (53.6%)	44 (48.9%)		285 (52.8%)
Catholic	99 (22.0%)	26 (28.9%)		125 (23.1%)
None	76 (16.9%)	14 (15.6%)		90 (16.7%)
Muslim	22 (4.9%)	6 (6.7%)		28 (5.2%)
Zione/Ião	12 (2.7%)	0 (0.0%)		12 (2.2%)
Housemates			0.737	
0–3	149 (33.1%)	26 (28.9%)		175 (32.4%)
4–5	151 (33.6%)	32 (35.6%)		183 (33.9%)
> 6	150 (33.3%)	32 (35.6%)		182 (33.7%)
Rooms			0.607	
1	81 (18.0%)	21 (23.3%)		102 (18.9%)
2	137 (30.4%)	26 (28.9%)		163 (30.2%)
3	155 (34.4%)	31 (34.4%)		186 (34.4%)
> 3	77 (17.1%)	12 (13.3%)		89 (16.5%)
Children			0.205	
None	340 (75.6%)	75 (83.3%)		415 (76.9%)
1	100 (22.2%)	15 (16.7%)		115 (21.3%)
2	10 (2.2%)	0 (0.0%)		10 (1.9%)
Comorbidities			0.553	
No	431 (95.8%)	88 (97.8%)		519 (96.1%)
Yes	19 (4.2%)	2 (2.2%)		21 (3.9%)

* Fisher's exact and χ2 test, Student's t-test

In the univariate analysis, there was no association between a positive test result and sex, age, house density, district or educational level (Table 2). In the multivariable analysis a positive result at the SARS-CoV-2 antibodies test was associated with both job type and COVID-19 symptoms. The OR was higher in students compared to workers (aOR: 2.02 [95%CI: 1.01–4.21]) and in those with symptoms (aOR: 1.52 [95%CI 1.01–2.30]). There were no statistically significant differences based on HIV status (aOR: 0.663 [95%CI: 0.406–1.069], Table 2).

SARS-CoV-2 symptoms

COVID-19 symptoms were reported by 68/241 people (28.2%, NA = 12) with positive results at the SARS-CoV-2

Table 2 Results of the univariable (odds ratio - OR) and multivariable (adjusted odds ratio - aOR) logistic regression models fitted on the results at SARS-CoV-2 serological test as dependent variables and HIV status, presence of COVID-19 symptoms and job as potential determinants

	OR [0.95CI]	aOR	0.95 CI
Positive SARS-CoV-2 test (yes/no)			
HIV status (+)	0.603 [0.375–0.956]	0.663	0.406–1.069
COVID-19 symptoms (yes)	1.544 [1.030–2.323]	1.525	1.014–2.303
Job (worker)			
Student	2.572 [1.322–5.274]	2.018	1.014–4.206
Unemployed	2.051 [1.042–4.246]	1.729	0.861–3.633
Sex (M)	0.910 [0.637–1.300]		
Age (years)	0.964 [0.884–1.051]		
School (none)			
Primary	0.780 [0.172–3.531]		
Secondary	0.854 [0.199–3.657		
University	1.241 [0.272–5.664		
District (rural)			
Sub-urban	1.760 [0.977–3.25]		
Urban	1.406 [0.730–2.764]		
House density	0.948 [0.810–1.107]		

antibodies test, with no differences based on HIV status ($p=0.527$). Symptoms are shown in Table 3.

The most prevalent symptoms were cough ($n=55$, 82.3%) and fever ($n=53$, 67.7%). The mean number of symptoms was 2.5 (SD 1.0). In most patients ($n=52$, 76.6%), the symptoms lasted between three and seven days. Differences based on HIV status were not observed for the number ($p=0.812$) or the duration of symptoms ($p=0.204$). None of the symptomatic patients required hospitalization. Only one patient reported the persistence of symptoms after the resolution of acute SARS-CoV-2 infection (fatigue and chest/throat pain).

There were no differences in reporting COVID-19 symptoms based on HIV status in both the overall sample ($p=0.519$) and in the subgroup of patients who tested positive for SARS-CoV-2 antibodies ($p=0.715$).

COVID-19: risk factors and testing

Almost all the sample ($n=519$, 96.1%) reported adopting at least one preventive measure for COVID-19. Those who did not follow preventive measures came mainly from rural areas ($n=14$, 26%, $p<0.001$). The type of preventive measures adopted are shown in Table 3. People residing in suburban areas reported most often avoiding crowded areas (42%, $p<0.001$) and maintaining physical distancing (50%, $p<0.001$) as preventive measures for COVID-19.

Patients with a previous COVID-19 test were 22 (4.1%); of those, 5 (22.7%) reported being tested positive. Those with a university education or higher underwent a previous COVID-19 test more frequently than the others (primary: $n=2$, 2.7%, secondary: $n=11$, 2.8%, university: $n=9$, 13.8%; $p=0.003$).

People reporting close contact with a COVID-19 case were 59 (10.9%), and 71 (13.1%) did not remember. Of those with close contact, only 5 (8.5%) underwent a

Table 3 Number and frequency of different types of COVID-19 preventive measures used and COVID-19 symptoms distinguished by HIV status

	HIV- ($n=450$)	HIV + ($n=90$)	*p*–Value*	Overall ($n=540$)
COVID-19 preventive measures				
Wearing a mask	430 (95.6%)	86 (95.6%)	0.998	516 (95.6%)
Keeping distance	191 (42.4%)	36 (40.0%)	0.726	227 (42.0%)
Avoiding crowded areas	167 (37.1%)	28 (31.1%)	0.336	195 (36.1%)
Hand wash	374 (83.1%)	77 (85.6%)	0.643	451 (83.5%)
	HIV- ($n=220$)	**HIV + ($n=33$)**		**Overall ($n=253$)**
COVID-19 Symptoms[a] (N/A = 12)				
Total with symptoms	61 (29.2%)	7 (21.9%)	0.527	68 (28.2%)
Fever	47 (22.5%)	6 (18.8%)	0.820	53 (22.0%)
Cough	49 (23.4%)	6 (18.8%)	0.821	55 (22.8%)
Sore throat	38 (18.2%)	3 (9.4%)	0.315	41 (17.0%)
Anosmia	14 (6.7%)	1 (3.1%)	0.701	15 (6.2%)
Breathing difficulty	3 (1.4%)	2 (6.3%)	0.128	5 (2.1%)
Hospitalization	0 (0.0%)	0 (0.0%)	0.998	0 (0.0%)

* Fisher's exact and χ2 test

[a] Among people with a positive result for SARS-CoV-2 antibodies

COVID-19 test without differences compared to those without or not remembering ($p=0.182$).

At least one family member with COVID-19 related-symptoms in the past 8 months was reported by 63 (11.7%) people, and they tested for COVID-19 more frequently ($n=7$, 11.1%) than those without ($n=14$, 3.4%, $p=0.02$). People with a relative with COVID-19 symptoms were more often from urban areas ($n=41$, 32.8%, $p<0001$).

Discussion

This study aimed to explore the prevalence of SARS-CoV-2 antibodies in young people in Beira, Mozambique, which was found to be 46.9% (95%CI 42.6%-51.2%) as of November 2022. The SARS-CoV-2 seroprevalence by HIV status was 35.9% (95%CI 25.3%-47.5%) in YPLHIV and 49.1% (95%CI 44.1%-54.1%) in people without HIV but the difference was not statistically significant.

Although 3 years have passed since the WHO declared the COVID-19 pandemic, data on its impact on Africa are still scarce [15]. The poor accessibility to diagnostic tests has prevented a timely overview of the pandemic's progression in these countries. Contrary to high-income countries, where the availability of human, material and economic resources made diagnostic tests readily available, in sub-Saharan Africa, this was limited, erratic and in some cases non-existent [16]. In our sample, only 4.1% had a previous COVID-19 test, although some (10.9%) had reported close contact. The number of people who underwent a test having had a relative with COVID-19 symptoms was higher, but still very low, around 11%. Not only the lack of material resources may have contributed to this limited access to SARS-CoV-2 testing. Cultural factors and stigma, often driven by misinformation, also could have played a significant role. In particular, the fear of being shunned by one's community and evicted from one's rented home or even from shops and work may have led to testing avoidance and reliance on self-medication [17, 18].

Because of the under-diagnosis challenge, seroprevalence studies are central to tracking the spread of SARS-CoV-2 in the sub-Saharan African population. A systematic review and meta—analysis conducted until May 2022 on seroprevalence studies aligned with the WHO SEROPREV protocol found a global SARS-CoV-2 seroprevalence of 59.2% (95%CI 56.1–62.2). In the WHO African region, seroprevalence increased from 3.5% (95%CI 2.9–4.2) in June 2020 to 86.7% (95%CI 84.6–88.5) in December 2021 due to new and more infectious SARS-CoV-2 variants (i.e., Beta and Omicron) [19]. In our sample, overall seroprevalence was 46.8% (95%CI 42.6–51.2). The latest available data for the city of Beira from 1 to 31 March 2020 reported a seroprevalence of 5.8% [20]. Our findings reflect the Omicron variant's impact on the region's infection rate. However, a higher prevalence was reported in the third quarter of 2021 in the UN area of Southern Africa, equal to 56.1% (95%CI 44.6–66.9) [5]. The studies in the abovementioned systematic review showed a high heterogeneity of the results. This wide variability can be attributed, on the one hand, to the different study designs, such as the time when it was carried out (i.e., the spread of different variants), the location (urban or rural area), the type of test used, the population involved, and on the other hand to different public health policies adopted, such as non-pharmacological interventions and adherence to prevention measures and vaccination. Moreover, the different seroprevalence reported in our sample may be due to the exclusion of vaccinated people, who were instead considered in the studies mentioned above.

The odd of testing positive was higher among students. Schools are a well-known place of possible contagion. SARS-CoV-2 school-based transmission has been reported in contexts where the level of community infection is high, as is the case in Mozambique after the Beta variant hit the country [21].

Infection probability was also associated with symptoms. The most reported symptoms among SARS-CoV-2 seropositive individuals in our cohort were cough (22.8%), fever (22%), and sore throat (17%), consistent with Omicron predilection for upper respiratory tract infection [22]. The low prevalence of anosmia in our sample also reflects the decreased incidence of this previously more specific sign of SARS-CoV-2 infection during the Omicron era [23]. Symptoms' duration ranged from 3 to 7 days in most patients; data from a large, observational trial involving self-reporting symptoms among SARS-CoV-2 positive people (16–99 years) reported a median duration of Omicron symptoms of 5 days (IQR 3–9) [23]. Overall, no long-COVID-19 symptoms were experienced by our cohort, except for a single patient who reported fatigue and chest/throat pain but whose duration was not indicated.

Our cohort showed a high prevalence of asymptomatic SARS-CoV-2 infection (71.8%), similar to the high asymptomatic rate reported in other LMICs. A systematic review and meta-analysis showed an asymptomatic prevalence of 71% (IQR 48.4%–80.8%) among SARS-CoV-2 seropositive individuals during the pre-Omicron era in Africa (up to December 2021). However, a possible overestimation of SARS-CoV-2 seroprevalence could have been due to serologic test cross-reaction with other infections [5]. Garrett et al. reported a percentage of 60% of asymptomatic PCR-confirmed Omicron infection in a South African cohort of individuals (mainly YPLHIV) enrolled in a clinical trial [24]. Similarly, our analysis

was conducted after the widespread emergence of the Omicron variant from November 2021 in Botswana and South Africa and reflects the milder disease course associated with the Omicron variant compared to the other variants of concern (VOC) [25–28]. In our sample of non-vaccinated young people, only 5 patients (2,1%) reported breathing difficulty, and possible signs of moderate disease, though no one required hospital admission. This high prevalence of asymptomatic carriers accounts, among other factors, for the high transmissibility rate of the Omicron variant, strengthening the need for surveillance and immunization policies, mostly among high-vulnerable populations [29].

No significant differences were found in SARS-CoV-2 seroprevalence between YPLHIV and those without. The relationship between HIV and SARS-CoV-2 co-infection is still uncertain. A study conducted in South Africa after the second wave found a prevalence of 53.2% in YPLHIV with a viral load < 1000 copies/ml and 35.9% in those with a viral load > 1000 copies/ml [30]. The literature is conflicting regarding both the prevalence and severity of COVID-19 in YPLHIV, an increased risk of severe COVID-19 and death, while others found no difference [31]. Our study found no difference concerning symptoms or disease severity between YPLHIV and the others. The mild symptoms and high asymptomatic rate in our HIV-positive cohort may be explained by the characteristics of the sample: young age, low rate of comorbidities and exclusion of those with advanced disease; all these factors were reported to be associated with a better COVID-19 outcome in YPLHIV [30, 32]. Moreover, Omicron infection seems to be related to a high rate of asymptomatic infection, even in HIV-positive people [24].

These differences can result from the combination of several factors in different ways. Co-infection and clinical outcomes are related to individual characteristics, stage of disease, availability and adherence to antiretroviral treatment, personal perception of risk, epidemiological scenario, and use of the correct preventive measures [31]. All these factors may vary geographically and over time, making it difficult to understand their mutual relationship.

Regarding preventive measures, we found a very high knowledge and awareness, over 90%, especially for wearing masks and washing hands, confirming results obtained by a national survey during the first year of the pandemic [33]. Despite the end of the state of emergency, which was declared in Mozambique in March 2022, it is crucial to continue to maintain a high level of adherence to preventive measures, especially in healthcare settings where the risk is increased, having shown high effectiveness in countering the spread of the virus [34].

This study has some limitations. Firstly, no data on HIV viral load and treatment adherence were collected, preventing stratified analyses based on disease status. Furthermore, the number and reason for people excluded based on the inclusion/exclusion criteria was not collected (STROBE checklist in the Additional file). Secondly, the reported COVID-19 symptoms may be affected by recall bias, underestimating them, and SARS-CoV-2 specificity may be difficult to ascertain due to the low execution of the COVID-19 test in this setting. Finally, preventive measures were only investigated in terms of knowledge and awareness, but actual adherence could not be determined.

Conclusions

The present study contributes to providing data on the seroprevalence of SARS-CoV-2 in Mozambique, which is scarcely documented. Specifically, the SARS-CoV-2 seroprevalence in young people was 46.8% as of November 2022. No differences were observed in the odds of testing positive for SARS-CoV-2 antibodies based on HIV serostatus. A higher risk of contracting the infection was associated with being a student and having COVID-19-related symptoms. This finding supports the role of schools in the spread of infection, even in a setting as little explored as sub-Saharan Africa. Symptoms of COVID-19 were mostly mild with no differences compared to HIV status, although these results may be influenced by the exclusion of YPLHIV with advanced disease. It is important to continue monitoring the spread of the virus and impact of COVID-19 in the general population but particularly in the more fragile groups such as YPLHIV.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-023-08808-6.

Additional file 1. Patient questionnaire.

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Authors' contributions

In this study RB was responsible for data analysis and made substantial contribution to data interpretation and original writing. VC conceptualized the study and contributed to original writing. AZ made substantial contributions to original writing and data interpretation. DG was responsible for data collection and contributed to original writing. NR and CDC conceptualized and design the study. AM and FC contributed to data collection and interpretation. DD and FT reviewed the study critically and contributed to data interpretation. KC, HGDA and GP reviewed the study critically. CG supervised and reviewed the study critically.

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Availability of data and materials
The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was approved by the Interinstitutional Bioethics Committee for Health (Comité Interinstitucional de Bioética para Saúde - CIBS), Sofala, on the 29th of August 2022 (protocol number 002/CIBIS/2022). All participants provided written informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Division of Pediatric Infectious Diseases, Department of Women's and Children's Health, University of Padua, Padua, Italy. [2]Doctors with Africa CUAMM Mozambique, Beira, Mozambique. [3]Department of Diagnostics and Public Health, University of Verona, Strada Le Grazie, Verona 8 – 37134, Italy. [4]Department of Translational Research and of New Surgical and Medical Technologies, University of Pisa, Pisa, Italy. [5]Department of Infectious-Tropical Diseases and Microbiology, IRCCS Sacro Cuore Don Calabria Hospital, Verona, Italy. [6]Faculdade de Ciências de Saúde, Universidade Católica de Moçambique, Beira, Mozambique. [7]UNICEF Mozambique, Maputo, Mozambique. [8]Operational Research Unit, Doctors with Africa CUAMM, Padua, Italy.

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Publisher's Note

Active close contact investigation of tuberculosis through computer-aided detection and stool Xpert MTB/RIF among people living in Oromia Region, Ethiopia (CADOOL Study): protocol for a prospective, cross-sectional study

PAPER

Authors
Segala F.V., Nigussa W., Guido G., Kenate B., Facci E., Tsegaye A., Gulo B., Manenti F., Bobosha K., Cotugno S., Asmare A.B., Cavallin F., Tilahun M., Miccio M., Abdissa A., Putoto G., Saracino A., Di Gennaro F.

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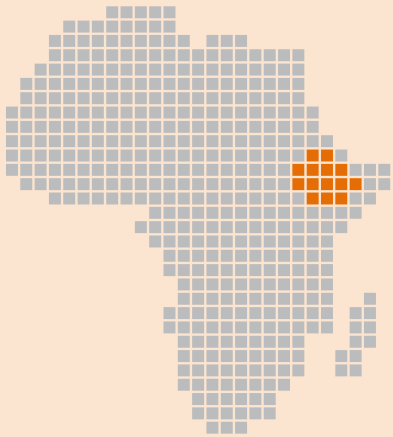

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Active close contact investigation of tuberculosis through computer-aided detection and stool Xpert MTB/RIF among people living in Oromia Region, Ethiopia (CADOOL Study): protocol for a prospective, cross-sectional study

Francesco Vladimiro Segala ,[1] Worku Nigussa,[2] Giacomo Guido ,[3] Birhanu Kenate,[4] Enzo Facci,[2] Ademe Tsegaye,[5] Berhanu Gulo,[2] Fabio Manenti,[6] Kidist Bobosha,[7] Sergio Cotugno,[1] Azmach Biset Asmare,[2] Francesco Cavallin,[8] Melaku Tilahun,[9] Maddalena Miccio,[2] Alemseged Abdissa,[9] Giovanni Putoto,[6] Annalisa Saracino,[1] Francesco Di Gennaro[1]

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For numbered affiliations see end of article.

Correspondence to
Dr Giacomo Guido;
giacguido@gmail.com

ABSTRACT

Introduction Pulmonary tuberculosis (TB) is an infectious disease with high incidence in low-income countries (LICs); it remains one of the infectious diseases with the highest mortality in the world, especially in LICs. It is crucial to recognise and diagnose TB as soon as possible, but microbiological tests on sputum are not always sensitive enough. New methods for an early diagnosis of TB are needed. In this study, we will investigate the role of two different tests to detect TB in Ethiopia (where the prevalence of TB is high): molecular search for TB in stool samples with Xpert assay and detection of pulmonary TB signs on chest X-rays with CAD4TB technology.

Methods and analysis A prospective diagnostic test accuracy study during TB active contact investigation will be conducted. In the referral hospital in Southwest Shoa Zone, Oromia Region, Ethiopia, patients with pulmonary TB and a sputum sample positive for *Mycobacterium tuberculosis* and household contacts of at least 4 years of age will be enrolled, with a target sample size of 231 patients. Trained staff will label household contacts as 'possible TB' cases or not according to their symptoms; when TB is possible, a stool Xpert and computer-aided detection on chest X-ray will be performed, alongside standard diagnostic methods, assessing the diagnostic accuracy of CAD4TB compared with Xpert MTB/RIF during TB contact investigation and the accuracy of stool Xpert compared with sputum Xpert.

Ethics and dissemination This study has been approved by the Oromia Health Bureau Research Ethics Committee (ref no BFO/MBTFH/1-16/100023). All information obtained will be kept confidential. Selected investigators will have access to data, while international partners will sign a dedicated data protection agreement. Eligible participants will receive brief information about the study before being asked to participate and they will provide written informed consent. Results will be disseminated through peer-reviewed journals.

Trial registration number NCT05818059.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The prospective design of a diagnostic test accuracy study allows for the collection of more accurate and complete data.
⇒ Study instruments are based on validated tools.
⇒ Involvement of tuberculosis (TB) close contacts.
⇒ Reference standard is a molecular TB test rather than culture.
⇒ The investigation of the diagnostic accuracy within strata may be limited by the sample size and the number of TB cases in each stratum.

INTRODUCTION

Tuberculosis global burden and epidemiology

Before the advent of COVID-19, tuberculosis (TB) was the leading cause of death from a single infectious agent and the 13th cause of death from all causes.[1] TB is caused by a bacterium, *Mycobacterium tuberculosis* (MTB) that, although it commonly affects the lungs, can cause disease throughout the body and with a broad spectrum of clinical manifestations.[2]

Despite being a preventable and treatable disease, TB infects roughly 25% of the world population, causing an estimated 1.4 million deaths among HIV-negative people (95% uncertainty interval (UI): 1.3 to 1.5 million) and 187 000 deaths (95% UI: 158 000 to 218 000) among people living with HIV.[3] Globally, an estimated 10.6 million people fell ill with TB only in 2021, increasing from the 10.1 million cases estimated for 2020, thus reversing a long-lasting decreasing trend. TB is a disease of poverty, as 87% of all incident

cases of TB were registered in the 30 high-burden countries, mainly low-income countries from WHO regions of South-East Asia and Africa. In this regard, the relationship between TB burden and commonly used indicators of underdevelopment is well established. Widely recognised TB determinants include gross domestic product and prevalence of undernourishment, the latter alone being accountable for an estimated 2 million new TB cases in 2021.[3] Other risk factors for TB include HIV infection, diabetes, smoking habits and alcohol use disorders, all conditions which are highly prevalent among vulnerable populations. Hence, in the context of the COVID-19 pandemic and of the global food crisis triggered by both the war in Ukraine[4] and climate change,[5] it is likely that overall efforts towards TB eradication will be heavily affected.

As reported by the WHO, the immediate consequence of the COVID-19 pandemic was a large fall in the number of newly reported TB cases and an estimated increase in incident cases of rifampicin-resistant TB, all indicators that represent a relevant drawback in the pursuit of the 2025 End TB Milestones.[6] These gaps in TB diagnosis include both people who are diagnosed but not reported to local public health authorities and people who are not diagnosed and thus have not entered into care.

Chest X-ray and computer-aided detection for TB

Detection of radiographic abnormalities through chest X-rays (CXRs) is the preferred tool recommended by the WHO for the screening of TB in general and high-risk populations.[7] Pooled data show that CXR set as 'any abnormality', has sensitivity and specificity of, respectively, 94% and 89%, whereas when set at detection for abnormalities 'suggestive of TB', sensitivity and specificity are, respectively, 85% and 96%. Along with screening, CXR is used as the preferred diagnostic tool for triaging people presenting to emergency department with signs or symptoms suggestive of TB.

Limitations of CXR-based screening implementation are the need for radiological equipment, not always available in resource-limited settings and the need to expose subjects to a small amount of ionising radiation. Radiation exposure may increase the risk of cancer, especially in vulnerable populations such as children—who have a longer life expectancy and have more time to develop radiation-associated side effects—and pregnant women. However, when good practices are observed, CXR exposes the patient to an average of 0.1 mSv, which is the amount of radiation that is commonly received from the environment in the course of 10 days.[8] Also, another major limitation to the use of CXR as a screening tool for TB is the fact that, in high-burden countries, health personnel trained to interpret radiography images are not always available, and that intrareader and inter-reader accuracy is highly variable.[9]

In recent years, computer-aided detection (CAD), artificial intelligence-based software, has been developed with the aim to offer automated interpretation of digital CXR images. In broad terms, CAD programmes produce a numerical score that interprets CXR alterations in order to quantify the probability of TB. When diagnostic accuracy is assessed against bacteriologically confirmed TB, CAD software sensitivity ranges from 90% to 92%, and specificity ranges from 23% to 66%, thus fulfilling the minimal sensitivity required by the WHO for a screening test. These diagnostic performances were confirmed by several prospective studies conducted in low-income and middle-income countries,[9 10] systematic reviews[11 12] and one patient-level meta-analysis,[13] thus leading to the endorsement of CAD technologies by current WHO-consolidated TB guidelines for the screening of individuals aged 15 years or older belonging to selected high-risk populations.[7]

Among the CAD software packages commercially available, CAD4TB platform V.6 (Delft Imaging Systems, the Netherlands), developed using deep learning technologies—a type of machine learning technology based on artificial neural networks—releases results in few seconds and was designed to work on patients from 4 years of age. In a recent study conducted by Murphy *et al*,[14] when compared with a microbiological Xpert reference standard, CAD4TB V.7 has been shown to have both high efficiency and cost-effectiveness in high-burden settings, being able to process 132 images per day at the cost of less than US$6 per person. Even if the technology is validated for use in individuals aged 4 years or older, very few data exist on the clinical utility of this technology among children.

Xpert MTB/RIF on stool samples

Since mortality of untreated TB approaches 50%, and cure rates associated are high,[3] overall disease burden is strictly dependent on diagnostic capacity. In sub-Saharan Africa, microbiological diagnosis of TB is generally based on Xpert MTB/RIF (Cepheid, USA), an automated, PCR-based assay able to detect mycobacterial DNA on respiratory samples. However, in those settings, good-quality sputum samples are often difficult to obtain, leading clinicians to rely on more invasive procedures for diagnosis, such as nasogastric aspirates, sputum induction and pleural or abdominal aspirates, that are both painful and not routinely available in low-resource settings. MTB detection on respiratory samples is further challenged by extrapulmonary TB,[15] smear-negative pulmonary TB (PTB) and paucibacillary TB,[16] and sputum sample collection may put healthcare workers at risk of infection due to exposure to MTB-infected aerosols.[17]

In recent years, attention has been attracted by Xpert MTB/RIF on stool samples, since mycobacteria-containing sputum may be swallowed and then be available for molecular testing. Similarly to Xpert on sputum samples, stool Xpert is able to detect both the presence of mycobacterial DNA and mutations associated with rifampin resistance. Two meta-analyses conducted in 2019 have demonstrated that both Xpert and Xpert Ultra might be used to detect MTB bacilli with high

specificity.[18 19] On a practical standpoint, several techniques have been proposed to process stool samples for GeneXpert testing. In 2021, de Haas *et al*[20] validated a simple, one-step, gravity-based method that requires the same laboratory equipment used for sputum samples and provides valid results without needing for bead-beating, dilution and filtration steps. Details of this procedure have been illustrated in a dedicated handbook.[21]

The use of Xpert MTB/RIF on stool samples has been introduced in the 2020 WHO guidelines as a possible initial diagnostic test for children with signs and symptoms of PTB.[22] However, this recommendation is based on low certainty of evidence. Due to a lack of available evidence, no recommendation has been issued so far about the use of Xpert on stool samples in the adult population.

Justification for the study

Ethiopia is listed among the 30 high-burden countries both for TB and for HIV/TB, transitioning out, in the last Global Tuberculosis Report,[3] from the list of the high-burden countries for multidrug-resistant or rifampicin-resistant TB. Annual TB incidence is 132 cases per 100 000 people (95% CI 92 to 178), with a case fatality ratio of 15% and most of the cases attributable to undernourishment.[23]

As in most of low-resource, high-burden countries, provider-initiated contact investigation is rarely carried out in Ethiopia,[24] although contact tracing and evaluation of all persons who have been in contact with an active case of TB are recommended by the latest national guidelines.[25] The WHO recently updated its screening guidelines, putting emphasis on the importance of active, provider-initiated screening of at-risk populations, especially households of index patients with TB.[26] Epidemiological data about active TB among household contacts are limited but, when reported, prevalence rates are high.[27] Also, a meta-analysis conducted by Gamtesa *et al*[28] found that healthcare-seeking behaviour in Ethiopia is low even in patients showing signs and symptoms of TB.

Provider-initiated screening of selected, high-risk populations is a key strategy in the fight towards TB eradication. According to the WHO, this approach should entail systematic identification of people with possible TB disease with tests, examinations or other procedures that can be applied rapidly. In this context, data about the clinical impact of the use of CAD technologies in Ethiopia are lacking. Also, data about diagnostic performances of, respectively, CAD software and stool Xpert MTB/RIF in the paediatric population and adult population are needed.

Objectives of the research project

General objective

To assess the role of CAD and stool Xpert MTB/RIF in improving the diagnostic process during TB active contact investigation in Ethiopia.

Primary objective

To assess the diagnostic accuracy of CAD4TB compared with sputum and stool Xpert MTB/RIF during TB contact investigation.

Secondary objectives

- To assess the diagnostic accuracy of stool Xpert compared with sputum Xpert in adult population.
- To assess the diagnostic accuracy of CAD4TB within strata (paediatric/adult subjects, HIV status, subjects, sex, smear status, history of TB, malnutrition status, smoking status) against sputum and stool Xpert.
- To provide an estimation of TB prevalence among contacts.

Additional objectives

- To assess if the identification of positive cases can be increased when information from CAD4TB is available to the clinician.
- To assess the occurrence of cases inappropriately labelled by the attending physician as 'possible TB' with and without the information provided by CAD4TB.
- To compare physician self-confidence in identifying possible TB cases based on whether CAD4TB information was available or not.
- To compare CAD4TB score and clinician's confidence on his/her identification of a 'possible case' of TB when not using CAD4TB.
- To assess the association between CAD4TB score and clinician's identification of a 'possible case' of TB when information from CAD4TB is available.
- Identify barriers to healthcare access among TB household contacts.

METHODS AND ANALYSIS

Study design

A prospective diagnostic test accuracy study will be conducted during TB active contact investigation.

Study setting

The study will be carried out in St Luke Catholic Hospital, Wolisso, Ethiopia.

St Luke Catholic Hospital is the referral hospital in Southwest Shoa Zone, Oromia Region, between Addis Ababa and Jimma covering 400 km distance. St Luke Catholic Hospital serves a population from a catchment area of roughly 1.4 million people. As of today, the hospital bed capacity is 208, while mean outpatient department visits are 350 patients per day.[29]

Routine TB screening in St Luke Catholic Hospital is based on patient-initiated pathway with assessment of signs and symptoms suggestive of TB. Possible TB cases are identified through a clinical visit that may include CXR evaluation. When performed, CXR images are evaluated by on-duty clinicians in digital format.

Eligibility criteria

Eligibility and inclusion criteria

All patients diagnosed with PTB and at least one sputum sample positive for acid-fast bacilli on sputum smear or MTB on sputum Xpert or smear will be eligible for inclusion as index cases. Index cases will be recruited both among hospitalised patients and patients followed in outpatient department clinics for completion of TB treatment.

All household contacts of at least 4 years of age will be eligible for inclusion if they lived in the same dwelling as the index patient during the 2 months prior to the diagnosis of the index patient. Pregnant women are eligible for the inclusion but to minimise radiation exposure risk to the fetus, CXR will not be offered.

Exclusion criteria

Household contacts already receiving treatment for active or latent TB will be excluded from the study.

Criteria for withdrawal or discontinuation

Participants can withdraw from the study at any time without the need of a rationale and without compromising their future medical care. All participants will receive the same standard of care.

Procedures before the study

CAD4TB cloud demo sessions

Few weeks before project implementation, clinicians working in Wolisso Hospital will be trained for the use of 'CAD4TB cloud' software (V.6) by partners from Delft Imaging Systems, the Netherlands. Demo sessions will be held through online meetings and will include supervised exercise and skill acquisition testing. Demo sessions will provide a basic introduction and information about interpretation and performance. Furthermore, during demo sessions, a brief CAD4TB cloud manual will be provided.

Stool Xpert MTB/RIF procedure

Prior to the start of data collection, an expert microbiologist will provide full training on the procedures for stool sample processing with Xpert MTB/RIF to St Luke Catholic Hospital laboratory staff. This experienced microbiologist will then be available, in case of need, for the whole duration of the study.

Research training

Before protocol implementation, local research assistants will be identified and specific training meetings will be organised in Wolisso. Training meetings will (1) allow research assistants to settle quickly and become productive and efficient members of data collection; (2) reinforce understanding of the theoretical background behind the research protocol, including the review of local[25] and international TB guidelines[8 15 22]; (3) ensure full understanding of all protocol procedures and design; (4) enhance teamwork within the involved facilities; (5) ensure understanding of data collection platforms and how to use them; (6) strengthen the importance of data protection and consent acquisition; and (7) provide information about principles of research ethics.

Procedures during the study

Close contact recruitment

Close contacts will be identified via administration of a screening questionnaire to index cases. Close contacts will be defined as all people living in the same dwelling of the index case or living in close contact with the index case for the period of infectivity, that is, from up to 2 months before TB diagnosis. To minimise recruitment losses, close contacts will be approached by research assistants and will be offered transportation to St Luke Catholic Hospital to enter the screening programme. Once in the hospital and prior to study entry, all close contacts will be asked for informed consent to be enrolled in the study.

Sequence randomisation

After enrolment, each subject will be assessed according to sequence AB (assessment by clinician #1 without CAD and assessment by clinician #2 with CAD) or sequence BA (assessment by clinician #1 with CAD and assessment by clinician #2 without CAD). Allocation to sequence AB or sequence BA will be performed through randomisation (see the Allocation section).

Close contact screening

St Luke Catholic Hospital is provided with a digital radiograph system capable of delivering digital CXR and compatible with the CAD4TB cloud system. Once enrolled, all patients will be screened for the presence of any CXR abnormality and any symptom suggestive of TB, that is:

- Cough of any duration.
- Haemoptysis.
- Fever.
- Poor weight gain or weight loss.
- Night sweats.
- Chest pain.
- Shortness of breath.

Chest radiography will be performed only by posteroanterior imaging, following the procedures detailed by local and international guidelines in order to minimise radiation exposure.[29–31] Images will be then uploaded on the CAD4TB cloud system. The CAD4TB system starts with a quick inspection of the X-ray image. To detect possible TB-related abnormalities, CAD4TB relies on state-of-the-art machine learning techniques based on deep learning technology. The output of CAD4TB is a score between 0 and 100 (0=normal, 100=very abnormal) indicating the likelihood that the person on the image has TB. Besides the abnormality score, a heatmap indicating the position of the potential TB abnormalities is produced. This heatmap is shown as a colour overlay on top of the original CXR.

A participant will be labelled as 'possible TB' case according to the clinical judgement of the attending physician. Labelling will be informed by all available

data coming from symptom assessment and radiological abnormalities detected with or without CAD use. During assessment of 'possible TB' cases, clinicians will be asked to grade their level of confidence over the likelihood of TB on a 5-point Likert scale. However, all contacts, both 'possible TB cases' and people who tested negative at initial screening, will be referred for microbiological testing.

Microbiological diagnosis with Xpert MTB/RIF on stool and sputum samples

All contacts will be referred for microbiological diagnosis of TB. Patients will be asked to provide sputum for smear microscopy and Xpert MTB/RIF and stool sample for testing with Xpert MTB/RIF.

The Xpert MTB/RIF assay is an automated cartridge-based, real-time test that can detect both MTB DNA and polymorphisms associated with resistance to rifampicin in less than 2 hours, and it is listed among the WHO-endorsed automated platforms for molecular diagnosis.

For the purposes of the present study, stool samples will be processed according to the one-step technique developed by de Haas *et al*.[20] Sputum samples will be processed for Xpert and smear microscopy according to routine local procedures and Ethiopian national guidelines.[25]

Follow-up of screening negative participants

All participants who will result negative to screening by symptoms and/or CXR abnormalities (with or without CAD) and to sputum/stool Xpert will be reassessed at 6, 12 and 18 months post-exposure. This is done primarily for ethical reasons, on the assumption that the first 2 years after TB exposure are at greatest risk of active disease.

A graphical representation of study procedures is provided in figure 1.

Other study variables

Other variables that will be collected are as follows: demographics, HIV status, malnutrition status, history of TB, smoking status and questionnaire about perceived barriers towards access to care.

Criteria for discontinuing or modifying allocated procedures

The participants will not be exposed to any harm or different benefits caused by the study procedures; hence, there are no reasons for discontinuing the study for safety or ethical reasons.

Strategies to improve adherence to intervention protocols

Face-to-face adherence reminder sessions for healthcare staff will occur regularly during the study period. This session will remind them of the purpose of the study and focus on the importance of following study guidelines.

Outcomes

Primary outcome measure

The common accuracy metrics (sensitivity, specificity, positive and negative predictive values) when assessing the accuracy of CAD4TB compared with Xpert MTB/RIF.

Secondary outcome measures

- The concordance between stool Xpert and sputum Xpert.
- The common accuracy metrics (sensitivity, specificity, positive and negative predictive values) when assessing the accuracy of stool Xpert compared with sputum Xpert.
- The common accuracy metrics (sensitivity, specificity, positive and negative predictive values) when assessing the accuracy of CAD4TB compared with Xpert MTB/RIF within the strata.

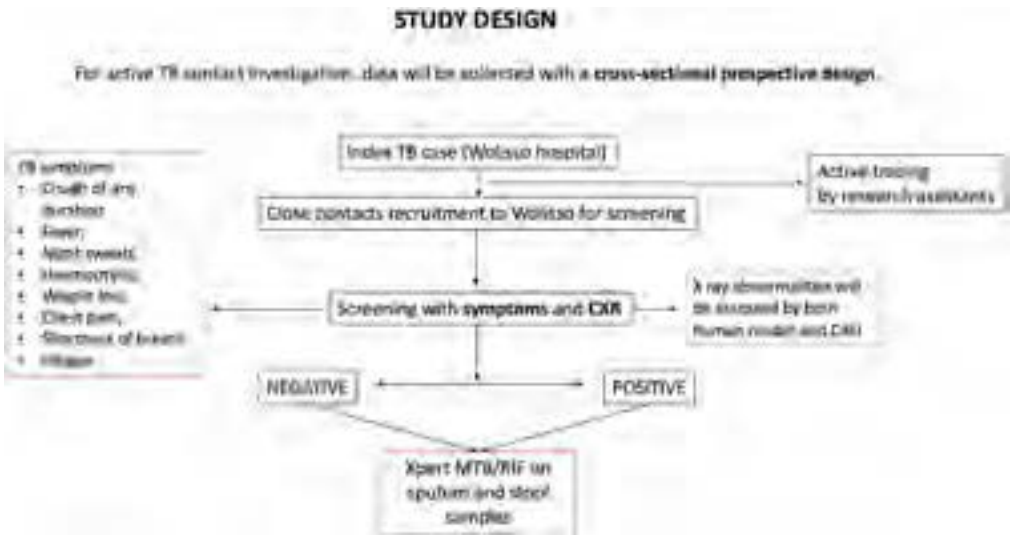

Figure 1 Study design and procedures. CAD, computer-aided detection; CXR, chest X-ray; TB, tuberculosis.

- The incidence of new TB cases among participants during the study period.

Additional outcome measures

- The additional positive cases when information from CAD4TB is available to the clinician.
- The false-positive cases when information from CAD is available to the clinician.
- The number and type of discordant cases in CAD4TB versus clinician CXR evaluation.
- The association between CAD4TB score and clinician's confidence on his/her assessment when CAD4TB information is not available.
- The association between CAD4TB score and clinician's identification of a 'possible case' of TB when information from CAD4TB is available.

Sample size

We assume to confirm TB diagnosis in 90% of possible TB cases when using current standard assessment (without CAD4TB). Around 34 subjects are needed to be 95% confident that our estimate is within 10% of the true value in the population. As we expect to identify a possible TB case in 15% of TB contacts, then 231 TB contacts need to be enrolled in the study.

Allocation

After enrolment, each subject will be assessed according to sequence AB or sequence BA. Allocation to sequence AB or BA will be performed using a computer-generated random assignment list (with a 1:1 ratio), and assignments will be included in sealed opaque envelopes sequentially numbered.

Clinicians cannot be blinded to the assessment method (with or without CAD) and cannot be blinded to the further assessment (referral for microbiological diagnosis with stool and sputum Xpert) due to care process. However, the statistician will be blinded to the assessment during data analysis.

Data collection

Data will be collected using structured questionnaires and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at Catholic University of the Sacred Heart, Rome, Italy.[32 33] REDCap is a secure, web-based software platform designed to support data capture for research studies, providing (1) an intuitive interface for validated data capture; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages; and (4) procedures for data integration and interoperability with external sources.

Statistical analysis

Categorical data will be summarised using absolute and relative frequencies. Numerical data will be summarised using mean and SD, or median and IQR. Estimates will be reported with 95% CIs. In accuracy investigation, the standard measures will be calculated (sensitivity, specificity, positive predictive value, negative predictive value). Concordance between stool GeneXpert and sputum GeneXpert will be assessed using Cohen's kappa and Gwet's AC1. Association between numerical data will be evaluated using Pearson's or Spearman's correlation coefficient. Additional comparisons between subgroups may be performed using Student's t-test, Mann-Whitney test, χ^2 test or Fisher's test, as appropriate. A sensitivity analysis including only subjects with available data from GeneXpert on sputum will be considered. Statistical significance will be set at 5%. The statistical analysis will be carried out using R V.4.2 (R Foundation for Statistical Computing, Vienna, Austria).

Interim analyses

Interim assessments are planned at 3, 6 and 12 months from data collection start. The analyses will assess the number of participants, the proportion of participants among eligible subjects and the proportion of possible TB cases among the participants. The purpose is to check if the magnitude of participants and TB cases is in agreement with those expected during the study design. Adjustments to sample size and duration of enrolment period may be made according to the indications from the interim assessments.

There are no stopping guidelines for harm and/or futility as none are expected.

Biological specimens

Stool

Stool samples will be handled and processed as described on the SOS stoolbox guide (KNCV Tuberculosis Foundation).[21]

Sputum

A volume of 5–10 mL is adequate and there is no advantage in collecting a larger volume. The sample should contain recently discharged material from the bronchial tree with minimal saliva content. Samples will be handled as per local routine laboratory procedures and will not be stored for research purposes.

Project time frame

- Submission of the protocol proposal to Ethics Committee: January 2023.
- Ethics Committee approval: March–April 2023.
- Research assistant's inception and training meeting: March–April 2023.
- CAD4TB demo session: March–April 2023.
- Enrolment and data collection: April 2023–December 2024 (duration of data collection will be reassessed after interim analysis results).
- Data entry and cleaning: April 2023–December 2024 (duration of data collection will be reassessed after interim analysis results).
- Interim analysis: June 2023, September 2023, April 2024.

- Study coordination and progress monitoring: April 2023–December 2024 (duration of data collection will be reassessed after interim analysis results).
- Final data analysis: December 2024 (duration of data collection will be reassessed after interim analysis results).
- Dissemination of study findings: December 2024–January 2025 (duration of data collection will be reassessed after interim analysis results).

Patient and public involvement

The development of the research question and outcome measures were informed by patients. Patients were not involved in protocol development, nor involved in study design, recruitment or conduct of the study. Results will not be disseminated directly to study participants; the burden of the intervention was not assessed by patients.

ETHICS AND DISSEMINATION

Research ethics approval

Approval to carry out this study was received from the Oromia Health Bureau Research Ethics Committee (reference number BFO/MBTFH/1-16/100023).

Any modifications to the protocol which may impact on the conduct of the study, potential benefit of the patient or may affect patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures or significant administrative aspects, will require a formal amendment to the protocol and approval by the Institutional Review Board (IRB).

Administrative changes of the protocol are minor corrections and/or clarifications that have no effect on the way the study is to be conducted. These changes will be documented in a memorandum and notified to the IRB.

Confidentiality and protection of data

All information obtained will be kept confidential. Selected investigators will have access to the data. All records containing personal identifiers will be stored separately from study records identified by a code number. All case report forms and the study database will only include the study number. The database will be protected by a password and will benefit of the security features provided by REDCap.[32] International partners will sign a dedicated Data Protection Agreement. All study-related information will be stored securely at the study site. All electronic data will be secured with password-protected access systems. No information that reveals the identity of any patient will be released or published without consent.

Consent

Eligible subjects will receive brief information about the study before being asked to participate. Management of eligible subjects who decline their participation in the study will not be affected. Eligible subjects will not receive any incentives aiming at promoting the participation. Participants will provide written informed consent and will have the right to withdraw from the study at any time. All information obtained will be kept confidential.

Dissemination

The results of this study will be disseminated by publication in peer-reviewed journals and be presented at relevant conferences. The results will be shared with the community members and other relevant stakeholders and institutions through conferences and seminars.

Authorship eligibility guidelines

The guidelines for authorship of major, international, peer-reviewed journals will be used to establish authorship of collaborative publications.[34]

Author affiliations
[1]Department of Precision and Regenerative Medicine and Ionian Area (DiMePRe-J), University of Bari Aldo Moro, Bari, Italy
[2]St Luke Catholic Hospital, Wolisso, Ethiopia
[3]University of Bari Aldo Moro, Bari, Italy
[4]Health Research Team, Oromia Regional Health Bureau, Addis Ababa, Ethiopia
[5]Doctors with Africa CUAMM, Addis Ababa Coordination Office, Addis Ababa, Ethiopia
[6]Doctors with Africa CUAMM, Padua, Italy
[7]Mycobacterial Diseases Research, Armauer Hansen Research Institute, Addis Ababa, Ethiopia
[8]Biostatistics, University of Padova, Padua, Italy
[9]Armauer Hansen Research Institute, Addis Ababa, Ethiopia

Twitter Melaku Tilahun @mtilahun600

Contributors FVS was involved in conceptualisation, creation of figure 1, writing and original draft preparation. WN was involved in validation and reviewing the paper. GG was involved in writing, reviewing and editing of the paper. BK was involved in validation of the paper. EF was involved in reading and reviewing the paper. AT was involved in reading and reviewing the paper. BG was involved in reading and reviewing the paper. FM was involved in writing, reviewing and editing of the paper. KB was involved in reading and reviewing the paper. SC was involved in writing, reviewing and editing of the paper. ABA was involved in reading and reviewing the paper and in validation of the paper. FC was involved in methodology, writing and original draft preparation. MT was involved in validation of the paper. MM was involved in validation of the paper. AA was involved in reading and reviewing the paper. GP was involved in conceptualisation and reviewing of the paper. AS was involved in writing, original draft preparation and reviewing and editing of the paper. FDG was involved in conceptualisation, writing, original draft preparation and reviewing and editing of the paper.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

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ORCID iDs
Francesco Vladimiro Segala http://orcid.org/0000-0001-5276-2603
Giacomo Guido http://orcid.org/0009-0004-8783-7221

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Incidence and burden of long COVID in Africa: a systematic review and meta-analysis

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Authors
Frallonardo L., Segala F.V., Chhaganlal K.D., Yelshazly M., Novara R., Cotugno S., Guido G., Papagni R., Colpani A., De Vito A., Barbagallo M., Madeddu G., Babudieri S., Lochoro P., Ictho J., Putoto G., Veronese N., Saracino A., Di Gennaro F.

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Incidence and burden of long COVID in Africa: a systematic review and meta-analysis

Luisa Frallonardo[1], Francesco Vladimiro Segala[1], Kajal D. Chhaganlal[2], Mohmaoud Yelshazly[2], Roberta Novara[1], Sergio Cotugno[1], Giacomo Guido[1]✉, Roberta Papagni[1], Agnese Colpani[3], Andrea De Vito[3], Mario Barbagallo[5], Giordano Madeddu[3], Sergio Babudieri[3], Peter Lochoro[4], Jerry Ictho[4], Giovanni Putoto[6], Nicola Veronese[5], Annalisa Saracino[1] & Francesco Di Gennaro[1]

Long COVID, also known as "post-acute sequelae of COVID-19," affects at least 65 million individuals worldwide with a wide spectrum of symptoms that may last weeks, months, or permanently. Its epidemiology and burden in Africa are unclear. This meta-analysis examines long-term COVID-19 effects in the WHO African Region. A systematic search in several databases was carried out up to 12 February 2023 including observational studies from African countries reporting the cumulative incidence of long COVID signs and symptoms. Only studies conducted in African countries were included. Several sensitivity and meta-regression analyses were performed. Among 1547 papers initially screened, 25 were included, consisting of 29,213 participants. The incidence of any long COVID symptomatology was 48.6% (95% CI 37.4–59.8) as psychiatric conditions were the most frequent, particularly post-traumatic stress disorder reaching a cumulative incidence of 25% (95% CI 21.1–30.4). Higher age ($p = 0.027$) and hospitalization ($p = 0.05$) were associated with a higher frequency of long COVID. Long COVID poses a significant burden in Africa, particularly concerning psychiatric conditions. The study recommends identifying at-risk people and defining treatment strategies and recommendations for African long-COVID patients. High-quality studies addressing this condition in African setting are urgently needed.

In October 2021, the World Health Organization (WHO) provided a consensus definition of long COVID as a condition lasting at least two months in individuals diagnosed with confirmed or presumptive acute SARS-CoV2 infection three months before[1]. The global incidence of long COVID is around 10% of affected people, with approximately 65 million cases worldwide[2]. Systematic reviews demonstrated its impact in terms of disability, activity impairment, cognitive function and overall quality of life[3,4], with a global pooled prevalence of quality of life impairment ranging from 38 to 63%[5]. However, in low-income countries, the estimates of its incidence vary greatly due to a significant number of hidden infections (i.e., asymptomatic or undisclosed) and difficulties in accessing testing[6]. Up to June 2023, 9.5 million cases of COVID-19 have been recorded across the 47 countries of the WHO Afro Region, with more than 175.000 deaths[7] but, despite the administration of 1084.5 million doses among 1137.4 million doses received, fewer than 51.8% of the people are fully vaccinated[8].

Risk factors for the occurrence of signs and symptoms of long COVID are older age, comorbidities, anti-SARS-CoV2 vaccination status, hospitalization and progression towards severe acute COVID-19[9]. Along with reducing the risk of progression towards severe or critical COVID-19, vaccination against SARS-CoV2 correlates with a lower incidence and severity of post-COVID conditions[9–13]. Nevertheless, even with the increasing evidence available, the understanding of the impact of this condition in low- and middle-income countries (LMICs) remains uncertain, and there is a notable lack of knowledge regarding the epidemiology and burden of post-acute sequelae of COVID-19 in Africa. Consequently, the objective of this systematic review and meta-analysis is to comprehensively examine the occurrence of post-acute sequelae of COVID-19 in the African continent.

[1]Clinic of Infectious Diseases, Department of Precision and Regenerative Medicine and Ionian Area (DiMePRe-J), University of Bari "Aldo Moro", 70124 Bari, Italy. [2]Department of Research, Faculty of Health Sciences, Universidade Catolica de Mocambique, Beira, Mozambique. [3]Unit of Infectious and Tropical Diseases, Department of Medicine, Surgery and Pharmacy, University of Sassari, Sassari, Italy. [4]Doctors with Africa, CUAMM, Kampala, Uganda. [5]Geriatrics Section, Department of Internal Medicine, University of Palermo, Palermo, Italy. [6]Operational Research Unit, Doctors with Africa CUAMM, Padua, Italy. ✉email: giacguido@gmail.com

Additionally, we aim to evaluate the burden of this condition in terms of prevalent symptoms and risk factors, in order to advocate for well-structured initiatives that facilitate appropriate care for affected individuals. By undertaking this investigation, we hope to enhance the understanding and management of post-acute sequelae of COVID-19 in Africa.

Materials and methods

Protocol registration

This study was conducted following the recommendations in the Cochrane handbook for systematic literature reviews to conduct the screening and selection of studies[14]. This systematic review and meta-analysis was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, updated version to 2021[15]. The protocol has been registered in Prospero (Number Registration n°CRD42023397445).

Research question

The research question for this systematic review is: "What is the incidence of long COVID signs and symptoms in Africa?" To guide the identification of adequate keywords to build search strategies to search bibliographic databases, the research question was framed into the PICO(S) (Participants, Intervention, Comparison, Outcome, Study design) format: (P) laboratory confirmed and/or clinically diagnosed COVID-19: long COVID was defined as the presence of signs and/or symptoms cannot be explained by other medical conditions; (I): none; (C) none; (O) incidence of signs and symptoms of long COVID in African countries; (S) observational studies.

Information sources and search strategies

We searched Medline (via Ovid) and Web of Science from database inception to 08 February 2023. The search for individual studies in these bibliographic databases was supplemented by a manual search of references included in relevant systematic reviews already published regarding this topic.

Considering the main PICOS elements, we built the following search strategy for Medline: "(Africa OR Angola OR Algeria OR Benin OR Botswana OR Burkina Faso OR Burundi OR Cameroon OR Cape Verde OR Chad OR Central African Republic OR Comoros OR Ivory Coast OR Congo OR Egypt OR Eritrea OR Ethiopia OR Gabon OR Gambia OR Ghana OR Djibouti OR Guinea OR Kenya OR Lesotho OR Liberia OR Libya OR Madagascar OR Malawi OR Mali OR Mauritania OR Mauritius OR Morocco OR Mozambique OR Namibia OR Niger OR Nigeria OR Rwanda OR "São Tomé and Príncipe" OR Senegal OR Seychelles OR Sierra Leone OR Somalia OR South Africa OR Sudan OR eSwatini OR Tanzania OR Togo OR Tunisia OR Uganda OR Zambia OR Zimbabwe) AND ("COVID-19" OR "Novel Coronavirus–Infected Pneumonia" OR "2019 novel coronavirus" OR "2019-nCoV" OR "SARS-CoV-2") AND ("lingering symptoms" OR "persistent symptoms" OR "long-term symptoms" OR "long-term Covid" OR "long-term" OR "long term" OR "long")". Then we adapted the search strategy for Web of Science. The management of potentially eligible references was carried out using the Rayyan website (https://www.rayyan.ai/).

Eligibility criteria

Inclusion criteria comprised the following: (1) observational studies (case–control, cohort, longitudinal studies); (2) studies that investigated the diagnosis of long COVID according to all diagnostic criteria and follow-up time; (3) studies made in Africa from March 2020 to February 2023. Only articles written in English were included. Studies with an unclear follow-up, case series and case reports were excluded.

Study selection

We followed the recommendations reported in the Cochrane handbook for Systematic reviews to select studies that were finally included in this review[14]. The selection of the articles was performed independently by six authors (ADV, RN, LF, AC, BZ, RP), in couples. Consensus meetings were held with all reviewers to discuss the studies for which divergent selection decisions were made. Two additional senior members (FVS, FDG) of the review team were involved, when necessary. The studies selection process involved, first, a selection based on title and/or abstracts, then a selection of studies retrieved from this first step based on the full-text manuscripts.

Data collection and data items

We collected the following information: data regarding the identification of the manuscript (e.g., first author name and affiliation, year of publication, journal name, title of the manuscript), data on the characteristics of the population considered (e.g., sample size, mean age, country, gender, etc.), setting (e.g., hospital, intensive care unit, etc.), method of follow-up visit, follow-up in months, type of diagnosis of COVID-19, number of people vaccinated, hospitalized or admitted in intensive care unit, type of variant, and signs and symptoms recorded during the follow-up period. These data were collected using a standard data extraction form in Microsoft Excel. The data extraction was carried out independently by the six authors, in couples, with one author for each couple extracting the data and the other checking, with the senior authors checking the quality of the data extraction.

Risk of bias evaluation

The Newcastle–Ottawa Scale (NOS) was used to assess the study quality/risk of bias[16]. The NOS assigns a maximum of nine points based on three quality parameters: selection, comparability, and outcome. The evaluation was made by one author and checked by another, independently. The risk of bias was then categorized as high

(< 5 points), moderate (6–7), or low (8–9)[17]. The investigators solved any discrepancies by jointly re-assessing an article (NV and FDG).

Data synthesis and analysis

Signs and symptoms were grouped into anatomical clusters, as proposed in Di Gennaro et al.[18]. The cumulative presence of symptoms and signs and 95% confidence intervals (CIs) were estimated using a meta-analysis, under a random-effect model[19]. Heterogeneity between estimates was assessed using the I^2 statistic. In case of an I^2 over 50% a series of meta-regression analyses (taking as moderators if the participants were hospitalized or admitted to ICU, the percentage of females, and the mean age of the sample size) was conducted. Several sensitivity analyses (hospitalization, admitted to ICU, follow-up mode, and sub-continents) were also run. Moderators and strata were chosen based on clinical judgment. Publication bias was assessed by visually inspecting funnel plots and using Egger bias test, with a p value < 0.05 indicative of possible publication bias[20]. All analyses were performed using "metaprop", a command available in STATA 14.0.

Results

Literature search

The flow-chart of this systematic review is shown in Fig. 1. Overall, we retrieved 1836 papers and, after excluding duplicates, we screened 1547 works based on title and abstracts. We then evaluated the full text of 55 work, finally including 25 papers.

Descriptive characteristics

Altogether, the 25 studies included a total of 29,213 African participants. Supplementary Table 1 shows the main descriptive characteristics of the studies included. The studies were mainly made in Egypt (12/25 = 48%), their mean age was 42 years (range 7–73) and the percentage of females was 59.3%. The principal method for diagnosis COVID-19 was PCR (17/25 = 68%). The follow-up method preferred for assessing long COVID was in person visits (n = 9), followed by online survey (n = 8). The median follow-up time was 3 months (range 0.5–12). Vaccination status was mainly unknown as well as the main COVID-19 variant (Supplementary Table 1).

Risk of bias

The Newcastle–Ottawa Scale (NOS) was used to assess the study quality/risk of bias. The NOS assigns a maximum of 9 points based on three quality parameters: selection, comparability, and outcome. The evaluation was made by one author and checked by another, independently. The risk of bias was then categorized as high (< 5 points), moderate (6–7), or low (8–9)[17] (Supplementary Table 1).

Presence of long COVID symptomatology

As shown in Table 1, among the 25 studies that included 29,213 African participants previously affected by COVID-19 the cumulative incidence of long COVID was 48.6%, overall indicating that about half of the patients included had long COVID.

Psychiatric conditions were the most frequent symptomatology among long COVID signs and symptoms, with post-traumatic stress disorder reaching a cumulative incidence of 25.8% (95% CI 21.1–30.4). Among neurological signs and symptoms, the most frequent was cognitive impairment present in 15% of the participants included. Dyspnea was the most frequent respiratory symptom reported (18.3%) followed by cough (10.7%), while palpitations were more frequent among cardiac symptomatology (Table 1). Of importance, loss of appetite (12.7%) and weight loss (10.4%) were extremely common among gastrointestinal and general signs and symptoms as well as fatigue (35.4%) myalgia (15.5%) (Table 1). Overall, self-reported poor quality of life (25.4%) was extremely frequent.

Meta-regression and sensitivity analyses

Since the heterogeneity observed of any sign and symptom was 99%, we did run several sensitivity and meta-regression analyses. Table 2 shows the main meta-regression analyses of our investigation. Among the moderators considered, every one-year increase in age was associated with a significantly higher probability of 10% in having any sign or symptom of long COVID. Higher mean age explained 21.4% of the heterogeneity observed. Similarly, an increase of 1% of hospitalized people was associated with a higher presence of 0.3% of any long COVID symptomatology during the follow-up (Table 2). This factor explained the 15.8% of heterogeneity observed. Other factors considered, such as higher percentage of females, duration of follow-up or higher percentage of admissions in intensive care units were not able to explain any heterogeneity.

Table 3 reports the sensitivity analyses for the main outcome of our investigation, i.e., presence of any long COVID symptomatology. The presence of long COVID seems not to be dependent on hospitalization or admission in ICU or follow-up mode (p for interaction > 0.05). On the contrary, we observed that long COVID was more frequent in Northern (47.73%) or Southern (48.89%) African countries when compared to Eastern ones (5.06%) (Table 3).

Discussion

To our knowledge, this is the first meta-analysis exploring prevalence, risk factors and symptomatology of long COVID in Africa. Twenty-five studies were included, above 1147 papers initially screened, for a total sample size of 29,213 patients. All the patients had a history of COVID-19 infection, confirmed by positive RT-PCR/

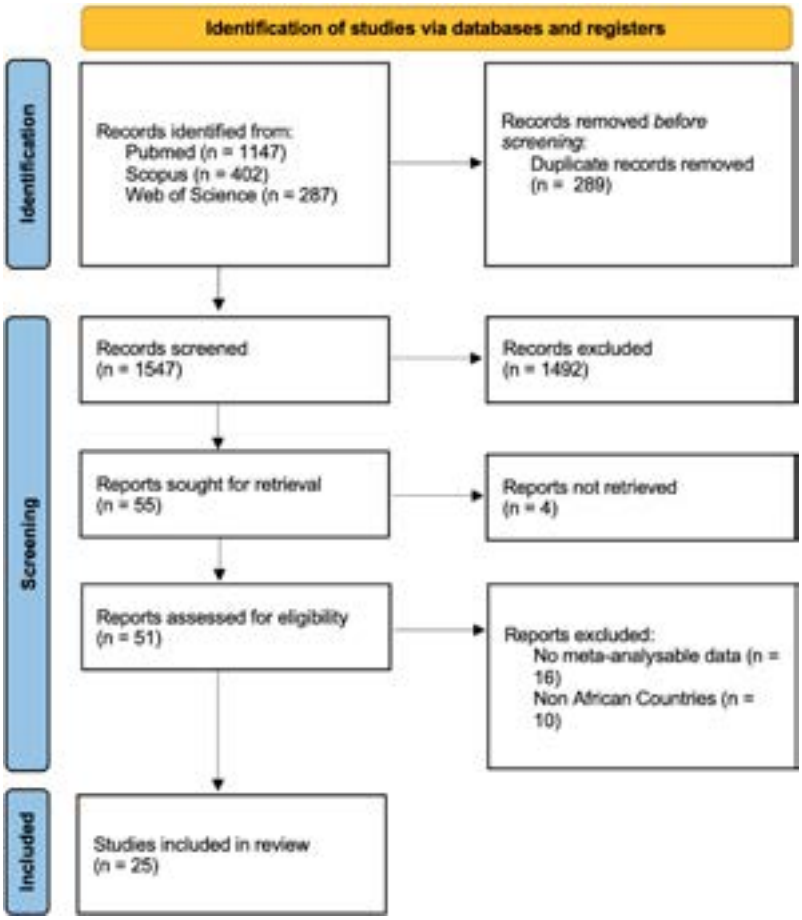

Figure 1. PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources. *Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers). **If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools. *From:* Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. https://doi.org/10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

NAAT (Nucleic Acid Amplification Test or NAAT) on nasopharyngeal swab associated with clinical manifestations and radiological findings.

Nearly 50% of the people included in this meta-analysis exhibited long COVID symptoms. This finding reinforces the critical significance of this emerging condition. In this study, fatigue was the most common symptom (35.4%, 95%CI 25.6–45.2) which represents the most debilitating long COVID symptom, and the first reason patients seek for medical assistance. This is concerning because, in Africa, it has the potential to lead to important impairment in productivity and further loss of economic agency.

In our study, females constituted 59.3% of the total population. However, we did not observe a significant association between gender and the incidence of any specific signs or symptoms of long COVID (Beta coefficient 0.04, *p* value interaction 0.41). These results contradict previous findings suggesting that females may be more susceptible to experiencing long COVID compared to males[18,21]. Notably, significant research has indicated a higher occurrence of general, neurological, and cardiovascular symptoms, predominantly among females rather than males[19–23].

In contrast, consistent with previous studies[24,25,27], our findings support the notion that older age is a prominent factor associated with increased morbidity related to long COVID. Our analysis revealed a significant association between each additional year of age and a 10% higher probability of experiencing any signs or symptoms

System	Number of cohorts	Total sample size	Cumulative incidence	95% CI
Any	**25**	**29,213**	**48.6**	**37.4–59.8**
Neurological				
Headache	14	10,515	12.7	9.8–15.5
Taste disorder (ageusia or dysgeusia)	11	9128	7.1	5.0–9.1
Smell disorder (anosmia)	12	9926	6.7	5.0–8.4
Cognitive impairment	4	2448	15.0	10.2–19.7
Memory deficits	3	2148	7.7	4.3–11.1
Difficulty concentrating	4	5635	10.7	5.5–16.0
Dizziness	9	8782	6.7	4.2–9.2
Tremors	2	812	1.2	0.4–1.9
Seizures	2	4499	0.2	0.05–0.25
Cramps	1	538	2.6	1.6–4.3
Visual impairment	5	6134	7.4	3.7–11.1
Psychiatric				
PTSD	2	341	25.8	21.1–30.4
Depression	10	18,811	18.2	10.9–25.4
Sleep disorders	13	8333	20.3	15.8–24.8
Anxiety	8	3171	24.4	18.0–30.8
Respiratory				
Cough	9	7836	10.7	7.5–13.8
Dyspnea	12	8057	18.3	12.2–24.4
Nasal congestion	2	3700	1.9	1.4–2.3
Voice change	1	115	5.2	2.4–10.9
Mobility issues				
Mobility impairment	2	3700	1.4	1.0–1.8
Mobility decline	2	3700	0.9	0.6–1.2
Heart				
Palpitations	8	5771	11.0	7.4–14.6
Digestive				
Abdominal pain	9	7210	6.1	4.0–8.1
Diarrhea	8	6908	6.2	4.3–8.2
Vomit	5	2626	1.5	0.6–2.3
Loss of appetite	6	4929	12.7	9.0–16.4
Skin				
Rash	6	6400	2.3	1.2–3.3
Hair loss	3	3872	3.5	1.7–5.3
General				
Weight loss	4	2726	10.4	4.2–16.7
Constitutional				
Myalgia	11	7364	15.5	11.1–19.9
Pain	11	8590	11.1	8–14.1
Fever	7	6974	9.9	6.7–13.0
Fatigue	15	10,577	35.4	25.6–45.2
Arthralgia	10	7285	17.3	12.4–22.2
Sore throat	6	1493	5.7	2.4–9.0
Sweats	2	446	4.6	2.7–6.5
Poor QoL	1	174	25.3	19.4–32.2

Table 1. Cumulative incidence of long COVID signs and symptoms in Africa. Data are reported as cumulative incidence with their 95% confidence intervals. *PTSD* post-traumatic stress disorder, *QoL* quality of life. Significant values are in bold.

of long COVID, particularly in the areas of general health, psychiatric well-being, neurological function, and respiratory symptoms. These results indicate that, despite the relatively younger of the African population, advancing age continues to be a crucial risk factor for developing long COVID, even within this specific context.

Moderator	Beta	SE	*p* value	R2
% of females	0.004	0.004	0.41	0.00
Mean age	**0.10**	**0.04**	**0.027**	**21.4**
Duration of the follow-up	0.03	0.02	0.17	5.0
Percentage of hospitalized	**0.003**	**0.001**	**0.048**	**15.8**
Percentage ICU	0.002	0.004	0.64	0.00

Table 2. Meta-regression analysis of any long COVID signs and symptoms. Data are reported as Beta (B) and their standard error and correspondent p-values and adjusted R2. The beta coefficient represents the change in the dependent variable (in this case, the presence of any long COVID signs or symptoms) associated with a one-unit change in the independent variable. Significant values are in bold.

Moderator	Strata	Prevalence	95%CI		*p* for interaction
Hospitalization	Yes	56.38	31.07	81.69	0.57
	No	34.02	0.00	89.33	
	Mixed	47.73	36.77	58.69	
Admitted to ICU	Mixed	51.56	31.88	71.25	0.64
	No	43.44	18.51	68.37	
Follow-up mode	Phone call	45.87	24.36	67.38	0.75
	Outpatient visits	40.81	13.71	67.90	
	Online survey	51.00	19.28	82.71	
	Mixed	62.87	32.03	93.70	
Sub-continents	East	5.06	1.99	12.31	< 0.0001
	Western	17.01	1.11	32.91	
	Southern	48.89	32.83	64.95	
	Northern	47.73	36.77	58.69	

Table 3. Sensitivity analyses for long COVID symptomatology in Africa.

Among people included in the analysis, prevalence of hospitalization and admission to ICU (Intensive Care Unit) was high, respectively 56.38 (95% CI 31.87–81.69) and 51.56 (95% CI 31.88–71.25). Meta-regression showed that percentage of hospitalization reported in each study significantly correlated with between a small increase in the prevalence of any long COVID symptomatology [Beta 0.003 ($p = 0.048$)]. This finding is in line with the meta-analysis conducted by Di Gennaro et al.[18] over a population of 120,970 patients, and suggest that severity of the acute phase may play only a marginal role in the incidence of post-COVID conditions. In our study, the marginal role of acute phase severity was further underscored by the low R-squared value and by sensitivity analyses, that failed in demonstrating a correlation between incidence of long COVID and admission to ICU. However, potential confounders might be, among others, the profound differences between Africa and high-income countries—where most of the evidence about long COVID has been produced—in terms of both ICU access and availability of indicators used to define critical COVID-19, namely the need for high-flow nasal cannula, mechanical ventilation, ECMO or dialysis[26,27].

Furthermore, consistently with other studies[28,29], in the aftermaths of COVID-19 infection, up to a quarter of patients included in this study experienced Mental Health issues such as post-traumatic stress disorder (PTSD) or anxiety. This is concerning, because the additional burden in mental health disorder brought by the COVID-19 pandemic and its chronic consequences meets a health system which is largely unprepared to address mental health conditions. In Fact, a survey conducted by the WHO in 2014 revealed that only 55% of African countries had implemented independent mental health policies[30]. Furthermore, the region had a ratio of 1.4 mental health workers per 100,000 people, against a global average of 9.0 per 100,000, with a rate of patients visiting mental health facilities as low as 14 per 100,000—versus a mean of 1051 per 100,000 recorded for other regions[31]. These findings highlight the pressing need for immediate policy implementation and reallocation of resources to address this severely underestimated public health issue.

The results obtained about prevalence and key risk factors of long COVID occurrence might be useful and have serious implications for low-middle income countries of WHO African region, which have resource constrained health care systems. The evidence generated by this study will help the national public health response and strategy to reduce the impact of long COVID on quality of life, mental health and work ability. Many challenges have been enlightened in determining the prevalence of this condition in these settings, consequently the strategy might consist of improving the knowledge and the skills of health care workers in managing patients with any signs and symptoms of long COVID, updating clinical guidelines and implementing comprehensive healthcare services, particularly in major public healthcare facilities. Furthermore, it will be needed a widespread creation of supplementary community-based centers with qualified personnel where patients affected by this

syndrome and with poor quality of life can acquire awareness about this condition and can be addressed to the rehabilitation process.

Several limitations should be acknowledged. First, although a close correlation with certain predisposing diseases or conditions has been established in several cohort studies and meta-analyses, we were not able to determine the impact of comorbidities and severe acute COVID-19 illness on the occurrence of long-term COVID syndrome. This was due to the high heterogeneity and fragmentation of the data collected in the included studies. Second, it is important to note that out of the 25 studies included in the analysis, only 7 were conducted in the WHO AFRO Region, while the remaining studies focused on North Africa. This disparity underscores the pressing need to generate high-quality evidence specifically within the Sub-Saharan African context. Third, it is crucial to acknowledge that the data regarding vaccination status and the specific COVID-19 variants were largely unknown, thereby hindering the ability to determine the influence of vaccination status on the incidence of long COVID across multiple waves.

Fourth, only English-language articles were considered in our meta-analysis and systematic review. Non-English publications, particularly Arabic publications, constitute a significant proportion of African medical literature, isolating African healthcare professionals from the most recent research. This language barrier also limits our knowledge and the reported data regarding long-term COVID symptoms in Africa.

Conclusions

Long COVID is a major public health issue due to its prevalence in patients tested positive to SARS-COV-2 and the lack of effective therapeutic strategies. Low-middle-income countries do not generally have social safety nets, and the impact of chronic sequelae on the workforce and on families' livelihoods remain a concern. In these countries, health care systems that need to also establish post-acute care services where physical, cognitive, and mental health disabilities will be recognized. More long-term, perspective studies are needed to understand the real long-term impact on quality of life and workforce activity and to develop optimal therapeutic and prevention strategies.

Data availability

The study specific summary data included in the meta-analysis can be obtained from the corresponding authors at giacguido@gmail.com.

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Author contributions

R.N., G.G., R.P., S.C., A.C., A.D.V., S.B., F.V.S., F.D.G. researched and chose articles concerning pharmacological intervention for the treatment of COVID 19 in pregnancy. N.V. dealt with the statistical analysis and solved the discrepancies in the choice of the articles. R.N., L.F, F.D.G., F.V.S., N.V. wrote the manuscript. F.V.S., L.F. and N.V prepared tables. All authors reviewed the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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Correspondence and requests for materials should be addressed to G.G.

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Impact of the COVID-19 pandemic on malaria in pregnancy indicators in Northern Uganda: a joinpoint regression analysis

POSTER AND ORAL PRESENTATION

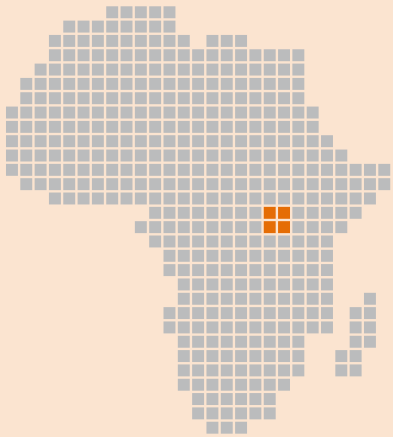
Conference
30th Conference on Retroviruses and Opportunistic Infections (CROI)

Location
Seattle, USA

Presentation date
19 - 22 February 2023

Authors
Di Gennaro F. et al.

Focus country
Uganda



Impact of the COVID-19 pandemic on maternal and malaria services in thirty health facilities in northern Uganda: an interrupted time series analysis

POSTER AND ORAL PRESENTATION

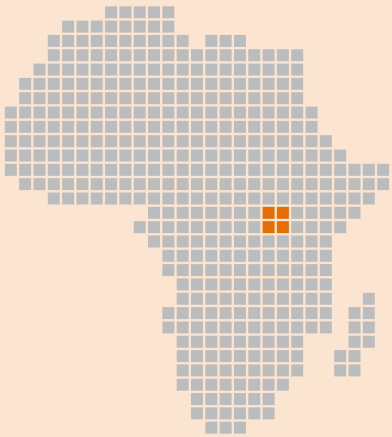
Conference
European Congress of Clinical Microbiology and Infectious Diseases

Location
Copenhagen, Denmark

Presentation date
15 - 18 April 2023

Authors
Segala F. et al.

Focus country
Uganda



Active close contact investigation of tuberculosis through computer-aided detection and stool Xpert MTB/RIF among people living in Oromia Region, Ethiopia (CADOOL Study): preliminary data

POSTER AND ORAL PRESENTATION

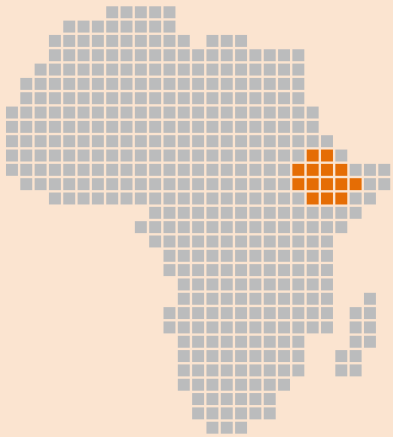
Conference
Emerging issues in Infectious Diseases Congress

Location
Bari, Italy

Presentation date
13 - 14 November 2023

Authors
Cotugno S. et al.

Focus country
Ethiopia



Measuring preparedness to infectious diseases among 2124 households exposed to climate disasters in Mozambique: a cross-sectional study

POSTER AND ORAL PRESENTATION

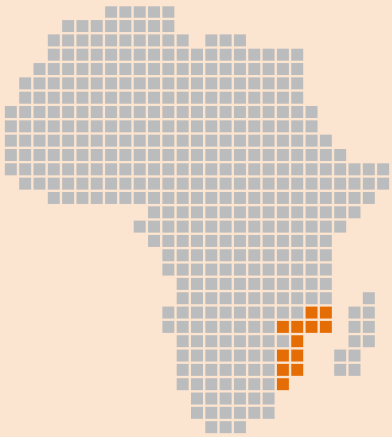
Conference
3rd International Conference on Public Health in Africa (CPHIA 2023)

Location
Lusaka, Zambia

Presentation date
27 - 30 November 2023

Authors
Occa E. et al.

Focus country
Mozambique



Measuring preparedness to infectious diseases among 2124 households exposed to climate disasters in Mozambique: a cross-sectional study

POSTER AND ORAL PRESENTATION

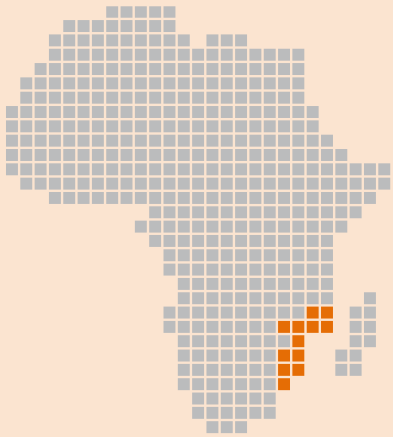
Conference
13th European Congress on Tropical Medicine and International Health (ECTMIH)

Location
Utrecht, Netherlands

Presentation date
20 - 23 November 2023

Authors
Segala F. et al.

Focus country
Mozambique



COVID Perceptions among Pregnant Women Living in a Malaria Hyperendemic Rural Region in Uganda: A Cross-Sectional Study

POSTER AND ORAL PRESENTATION

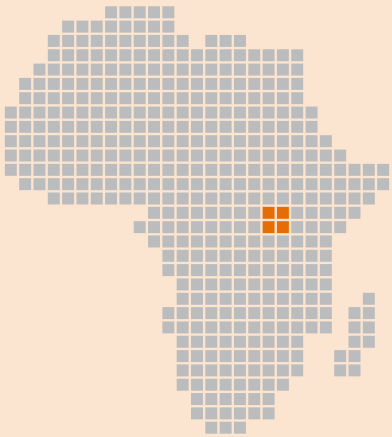
Conference
13th European Congress on Tropical Medicine and International Health (ECTMIH)

Location
Utrecht, Netherlands

Presentation date
20 - 23 November 2023

Authors
Segala F. et al.

Focus country
Uganda



Barriers to Care, Mental Health Status and Impact of COVID-19 Pandemic on Adolescents and Young Adults Living with HIV in Shinyanga Region, Tanzania

POSTER AND ORAL PRESENTATION

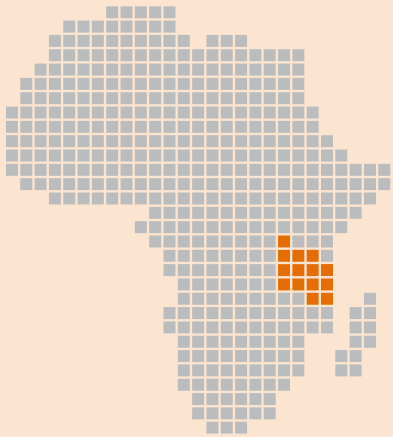
Conference
13th European Congress on Tropical Medicine and International Health (ECTMIH)

Location
Utrecht, Netherlands

Presentation date
20 - 23 November 2023

Authors
Ntanguligwa C. A. et al.

Focus country
Tanzania



Measuring preparedness to infectious diseases among 2124 households exposed to climate disasters in Mozambique: a cross-sectional study

POSTER AND ORAL PRESENTATION

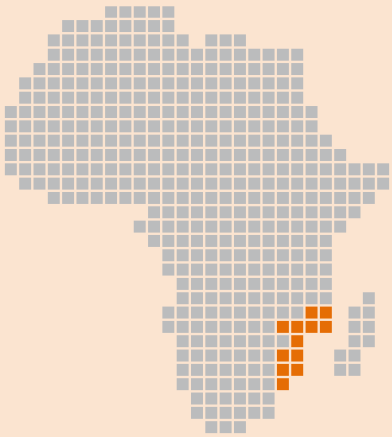
Conference
XXII Congress SIMIT (Italian Society Infectious and Tropical Diseases)

Location
Firenze, Italy

Presentation date
4 - 6 December 2023

Authors
Di Gennaro F. et al.

Focus country
Mozambique



Chronic diseases

Wandering spleen: An unsuspected presentation at a general hospital in Uganda

PAPER

Authors
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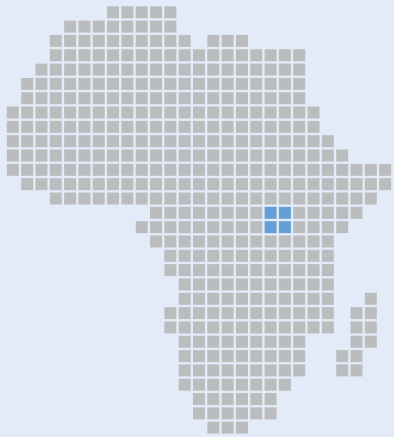

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Case report

Wandering spleen: An unsuspected presentation at a general hospital in Uganda

Luca Salvador [a,c,*], Lino Agaba [b], Benjamin Mukisa [b], James Amone [b], Jimmy Odaga [a,b]

[a] Operational Research Unit, Doctors with Africa CUAMM Uganda, P.O. BOX 7214, Kampala, Uganda
[b] St. John's XXIII Hospital Aber, Jaber 21310, Uganda
[c] Department of Surgical, Oncological and Gastroenterological Sciences, University of Padova, Via Giustiniani 2, 35128 Padova, Italy

ARTICLE INFO

Keywords:
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ABSTRACT

Introduction and importance: Wandering spleen is an uncommon condition marked by splenic hypermobility due to laxity or underdevelopment of the supporting splenic ligaments. Patients may be asymptomatic, have a palpable mass in the abdomen, or exhibit acute, long-lasting, or sporadic symptoms as a result of the spleen's pedicle torsion. The management should be determined by the spleen's vitality.

Case presentation: We report a case of a 29-year-old male who presented with a 5-year history of progressive abdominal swelling, surgically managed as an intrabdominal tumor at a general hospital in Uganda, with a postoperative confirmation of a wandering spleen.

Clinical discussion: Wandering spleen is a rare condition both in high- and low-income countries. Clinical presentations vary from an asymptomatic abdominal mass to acute abdominal pain due to vascular pedicle torsion leading to splenic infarction. When possible, splenopexy is the procedure of choice, especially in children and in tropical countries, to avoid post-splenectomy sepsis. Splenectomy is the definitive treatment for spleen fracture, spleen infarction, or symptoms that recur after splenopexy.

Conclusion: Wandering spleen is a rare differential diagnosis of intrabdominal tumor that must be considered in patients with a palpable abdominal mass with or without acute or chronic abdominal pain. Though a CT scan is the best method to confirm the diagnosis, the radiologist's and surgeon's experience and keenness seem very vital in making the correct diagnosis.

Intraoperative complete abdominal exploration by the surgeon is essential to confirm the radiological findings, to enhance the diagnosis, and to make the best treatment decision.

1. Introduction

Usually situated in the left upper quadrant of the abdomen, the spleen is maintained in place by four principal ligaments: the gastrosplenic ligament, the colicosplenic ligament, the phrenosplenic ligament, and the splenorenal ligament [1].

Wandering spleen is an uncommon condition marked by splenic hypermobility brought on by underdevelopment or acquired laxity of the supporting splenic ligaments, and it seems to be more common in women of reproductive age [2]. A number of factors contribute to the etiology of the wandering spleen, including congenital abnormalities in the dorsal mesogastrium's development, failure of the dorsal mesogastrium to fuse to the posterior abdominal wall during the second month of embryonic development (resulting in an abnormally long splenic pedicle), and absence or malformation of the normal splenic suspensory ligaments (gastrosplenic and splenorenal ligaments) that normally attach the spleen to its normal position [3]. In addition, a wandering spleen may be related to infectious mononucleosis, splenomegaly, malaria, Hodgkin disease, Gaucher disease, and prior pregnancy as acquired factors [4].

Because of this abnormal anatomical condition, the vascular pedicle is usually elongated and mobile, allowing its torsion and leading to splenic infarction [3,5].

Symptoms are therefore related to organ compression or to vascular pedicle torsion.

On clinical examination, patients may present with an asymptomatic palpable mobile mass, a mass with abdominal pain, or an acute abdomen. Chronic intermittent abdominal pain, gastric compression or

* Corresponding author at: Operational Research Unit, Doctors with Africa CUAMM Uganda, P.O. BOX 7214, Kampala, Uganda.
E-mail address: lucasalvador91@yahoo.it (L. Salvador).

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distension, and acute pancreatitis may also occur [6,7].

In this case study, a 29-year-old male was diagnosed with an epigastric solid tumor after complaining of a 5-year history of progressive abdominal swelling and pain and presenting to the emergency department of a general hospital in Uganda.

The work has been reported in line with SCARE criteria [8].

2. Ethic statement

Written informed consent was obtained from the patient for the publication of this case report and any accompanying images.

3. Case report

A 29-year-old male presented to the emergency ward of our institute with a 5-year history of a slowly increasing epigastric swelling and a 1-month history of postprandial fullness and epigastric pain. He reported normal bowel movements, no blood in the stool, no vomiting, no fever, and no weight loss. His past medical history was unremarkable.

Physical examination revealed normal vitals: temperature 36.8, pulse 74 beats/min, and bp 110/80 mmHg.

Abdominal examination revealed a palpable, firm, ballotable, non-tender, non-fluctuant, and approximately 15 × 12 cm in diameter epigastric mass.

A malaria blood smear and HIV test were negative, and a complete blood count showed normal parameters.

An abdominal CT scan with i.v. contrast enhancement was performed which confirmed an epigastric solid mass measuring 20 × 15cm, highly vascularized with internal calcification (Fig. 1), liver and spleen reported as normal without any other abnormal findings.

He was then admitted to the surgical ward with the diagnosis of a solid intrabdominal tumor and for further management.

At exploratory laparotomy, the immediate finding was a highly vascularized lobulated mass utterly fused into the greater omentum. All the feeder vessels were clamped, ligated, and transected with en-bloc removal of the mass. Further exploration of the abdominal cavity revealed the absence of the spleen in the left upper quadrant, contrary to the CT report.

Macroscopic examination of the excised tumor section was highly suspicious of splenic tissue, (Fig. 2) hence a tissue biopsy was taken for histopathological evaluation.

The postoperative recovery was uneventful. On the fifth post-operative day, the patient received a dose of prophylactic pneumococcal vaccine and was discharged. At 1-month post-operative review he was in good health.

The final histopathology examination showed splenic tissue, confirming the hypothesis of a wandering spleen.

4. Discussion

With a frequency of less than 0.25 % in patients who need splenectomy, a wandering spleen is a rare condition [9]. In Uganda, only 11 cases have been reported in literature [10].

Patients with a wandering spleen typically present with an abdominal mass, nonspecific gastrointestinal problems, or acute abdomen [3,6,7,9]. While symptoms may go unnoticed for extended periods of time, complications are linked to vascular pedicle torsion and splenic infarction or to other abdominal organ compression. Among them are pancreatitis, intestinal blockage, duodenal and gastric volvulus, and compression [3,6,10].

In our case, the patient presented with a progressive abdominal mass, intermittent mild abdominal pain, and postprandial fullness.

The preferred diagnostic method is an i.v. contrast-enhanced CT scan, and the most distinguishing feature is the lack of the spleen in its normal location and the presence of an ectopic mass in the pelvis or abdomen [7]. In our case, the CT report showed a solid epigastric intrabdominal tumor with a normal spleen. However, this was contrary to the intraoperative exploration finding of a missing spleen in the left upper quadrant after en-bloc tumor excision.

If the spleen is not infarcted, splenopexy is the preferred treatment. Nevertheless, a splenectomy is required if there is torsion with infarction [11]. In our case, the lack of accuracy of the CT diagnosis, the fixity of the mass in the greater omentum and lesser sac with a very unclear vascular pedicle, and the rarity of the anatomical condition prompted a straightforward tumor excision. Only further intraoperative exploration revealed the absence of the spleen, and histopathological examination confirmed the diagnosis of a wandering spleen.

Following a splenectomy, prophylactic vaccinations against post-splenectomy sepsis syndrome should be administered [12]. In our case, the patient received the prophylactic pneumococcal vaccine on the fifth postoperative day, the day of discharge.

5. Conclusions

Wandering spleen is a rare differential diagnosis of intrabdominal tumor that must be considered if a patient presents with a palpable abdominal mass. Though CT scan is the best method of diagnosis, the surgeon's and radiologist's experience and keenness in interpreting CT images seem very vital in making the correct diagnosis.

In our low-income setting, abdominal CT scans are rarely performed, mostly because patients cannot afford the expensive cost of the exam and there is not a radiologist in our hospital to discuss cases with. CT scans performed in our hospital are reported telematically by a radiologist in Kampala.

The diagnosis and characterization of intraddominal masses in our

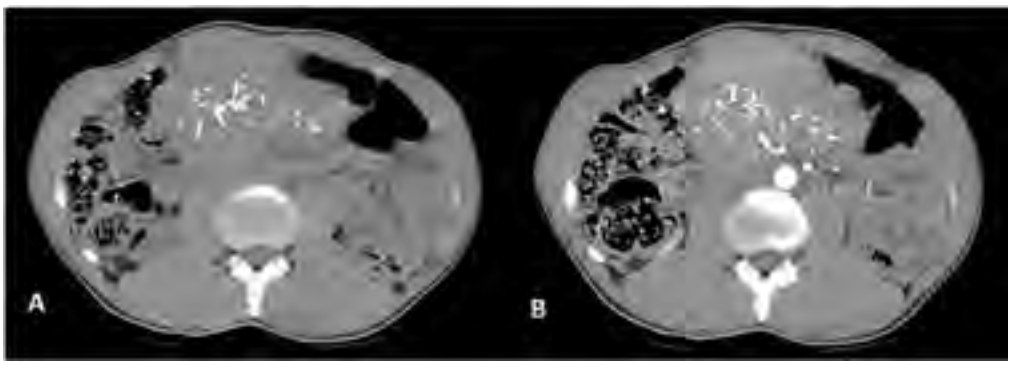

Fig. 1. I.V. enhanced CT scan showing a solid epigastric mass highly vascularized with internal calcification. A) non-contrast B) contrast arterial phase

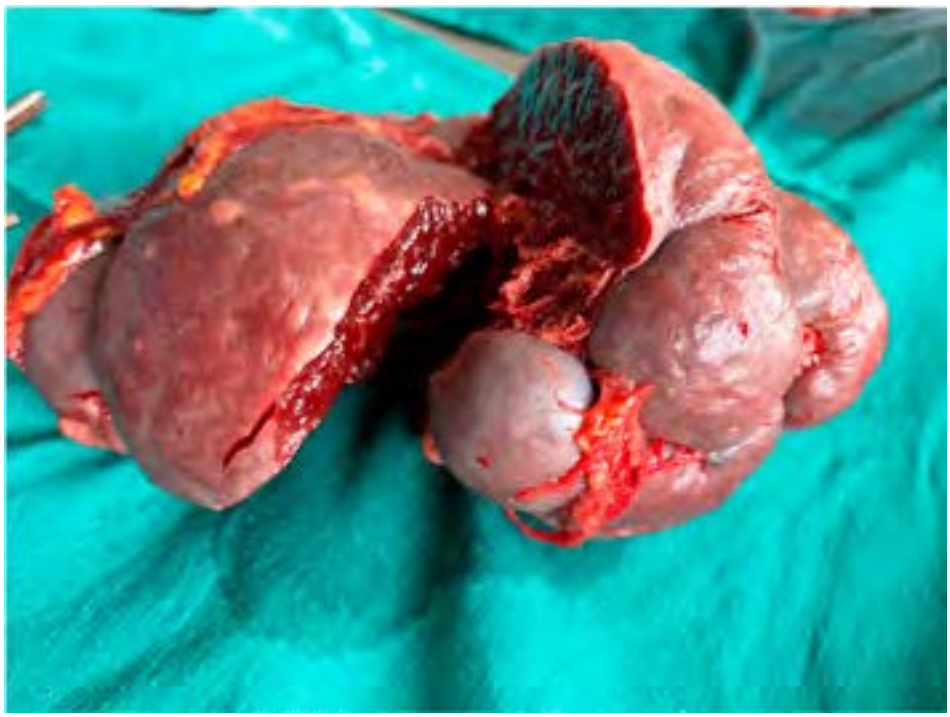

Fig. 2. Specimen

setting are mostly clinical and ultrasound based. The presence of advanced diagnostic instruments, like a CT scan, is a great resource, but it must also be accompanied by a staff prepared for its interpretation.

In conclusion, with the rarity of the condition and the limited CT scan exposure of most surgeons in the developing world, a complete surgical exploration of the abdomen before tumor removal is mandatory to reach a definitive diagnosis and make the best surgical decision.

Consent and Ethical approval.

Written informed consent was obtained from the patient for the publication of this case report and any accompanying images. The ethical approval has been exempted by our institution, considering that the case was written using retrospective and anonymous data.

Registration of research studies

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Provenance and peer review

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Guarantor

Luca Salvador, Jimmy Odaga.

CRediT authorship contribution statement

LA, BM: data collection and interpretation.

JA: data analysis and final revision.

LS, JO: data interpretation, writing paper and final revision.

Declaration of competing interest

N/A

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Diabetic Kidney Disease: a comparison of selected cohorts of patients from low and middle-income countries

PAPER

Authors
Mattiotti M., Capelli I., Ribichini D., Vetrano D., Vicennati V., Cianciolo G., Aiello V., Righini M., Bazzanini N., Mutalemwa K., Rehema I., Ndile E.,, Pagotto U., Azzimonti G., La Manna G.

Published in
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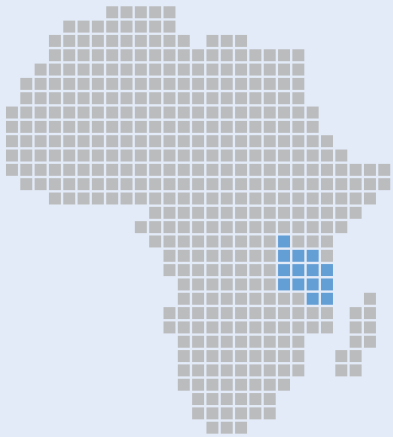
https://doi.org/10.1016/j.ekir.2023.02.430

Topic
Chronic diseases

Focus country
Tanzania



mL/min/1.73m^2 sustained for 30 days, initiation of chronic dialysis or kidney transplantation, or cardiovascular or renal death. *proact* 2 is an endpoint driven trial with 80% power to detect a hazard ratio of 0.6 for the primary outcome. Key secondary outcomes will include time to these individual components as well as annualized change in eGFR and change from baseline in UACR.

Results:

Conclusions: - *proact*2 is a global Phase 3 randomized controlled trial that will evaluate the safety and efficacy of REACT on major kidney disease endpoints, among participants with type 2 diabetes and moderate-severe CKD.

- This trial is part of a comprehensive phase 3 development program with an estimated start date of June 2023.

- REACT, a novel autologous cell therapy composed of SRC, has the potential to directly improve kidney function with a goal to prevent kidney failure.

Conflict of interest

Potential conflict of interest:

ProKidney

WCN23-0428

RENAL AUTOLOGOUS CELL THERAPY (REACT™) FOR DIABETIC CHRONIC KIDNEY DIEASE: PHASE II TRIAL WITH BILATERAL CORTEX INJECTIONS AND RE-DOSING TRIGGERS

Stavas, J[*1], Silva, A[2], Aqeel, A[3], Wooldridge, T[4], Yanover, M[5], Prakash, R[5], Mirkovic, N[1], McKenzie, L[1]

[1]ProKidney, n/a, Raleigh, United States; [2]Boise Kidney and Hypertension Institute, n/a, Meridian, United States; [3]Paragon Health Nephrology, n/a, Kalamazoo, United States; [4]Nephrology and Hypertension Assoc., n/a, Tupelo, United States, [5]Kidney Assoc of Colorado, n/a, Denver, United States

Introduction: Cell-based therapies may repair diseased nephrons and stabilize and enhance kidney function to delay the onset of end-stage kidney disease and improve co-morbidities. REACT™ is a novel product formed of cryopreserved autologous homologous selected renal cells, undergoing phase III clinical trials for diabetic kidney disease (DKD). We describe an open label phase II study to evaluate how patients respond to REACT™ injections in both kidneys and a redosing trigger, as being evaluated in a Phase III blinded data trial (*proact* 1 & 2 trials).

Methods: REGEN 007 is a multi-center Phase II, open label 1:1 randomized controlled trial enrolling up to 50 patients ages 30-80 years with DKD, who have an eGFR of 20 - 50 mL/min/1.73 m^2. Each patient undergoes a percutaneous kidney biopsy and *ex vivo* culture expansion of their selected renal cells. Patients are then randomized to an arm where they receive two REACT™ injections, one in each kidney, three months apart if they meet inclusion criteria, or an arm with an initial single REACT™ dose in one kidney and a 2nd REACT™ dose in the contralateral kidney > 90 days apart, based on a sustained eGFR decline of ≥ 20%, and/or an increase in the urine albumin to creatinine ratio (UACR) from baseline of ≥ 30% and ≥ 30 mg/g. CT-guided bilateral percutaneous renal cortex injections of REACT™ are performed under conscious sedation. Trial design, inclusion and exclusion criteria can be found at the National Clinical Trial Registry (Trial number 05018416).

Results: Thirty-one of the targeted 50 participants have been enrolled with the following characteristics at screening: 64.0% males, 97.0% Non-Hispanic/Latino. Mean age 62.9 years, serum creatinine (sCr) 2.0 mg/dL ±0.50, Cystatin C 2.0 mg/L ±0.40, eGFR (sCr + Cystatin C) 31.2 ml/min/1.72m^2 ±7.88, HgbA1C 7.4% ± 1.14, Hgb 12.9 g/dL ± 1.78, K^+ 4.6 mEq/L ± 0.44, Bicarbonate 20.3 mEq/L ± 3.0, and a median UACR 662 mg/g [SD 705.8]. Percent baseline medications are: Angiotensin Converting Enzyme inhibitors 25.8, Angiotensin Converting Enzyme receptor Blockers 48.4, beta blockers 64.5, diuretics 64.4, glucose lowering agents 100, Sodium glucose Cotransporter 2 inhibitors 32.3, and platelet inhibitors 67.7. Efficacy endpoint is an eGFR slope improvement from first injection to 18 months after last injection. REACT™ and procedure related serious adverse events are expected to be commensurate with ongoing trials and standard of care.

Conclusions: REACT™ cell-based therapy has the potential to effect nephron structure and function by stabilizing or improving DKD progression and its comorbidities. Current phase II and III trials are underway to determine efficacy, safety, renal function-dependent dosing, and time to treatment with bilateral kidney injections of REACT™.

Conflict of interest

Potential conflict of interest:

ProKidney employment for some of the authors

WCN23-0462

DIABETIC KIDNEY DISEASE: A COMPARISON OF SELECTED COHORTS OF PATIENTS FROM LOW-MIDDLE AND HIGH INCOME COUNTRIES

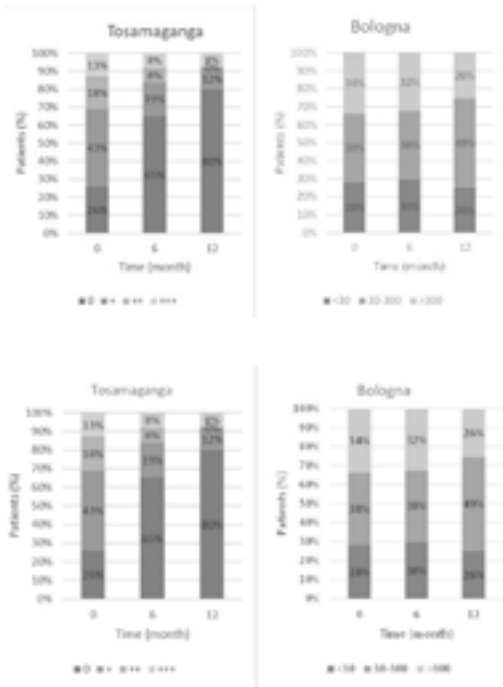
Mattiotti, M[*1,2,3], Capelli, I[1,3], Ribichini, D[4,5], Vetrano, D[1,3], Vicennati, V[4,5], Cianciolo, G[1], Aiello, V[1,3], Righini, M[1,3], Bazzanini, N[2], Mutalemwa, K[2], Rehema, I[2], Ndile, E[2], Pagotto, U[4,5], Azzimonti, G[2], La Manna, G[1,3]

[1]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Nephrology- Dialysis and Renal Transplant Unit, Bologna, Italy; [2]Medici con l'Africa CUAMM Tanzania, Medici con l'Africa CUAMM, Padova, Italy; [3]Alma Mater Studiorum, Alma Mater Studiorum University of Bologna, Bologna, Italy; [4]Alma Mater Studiorum University of Bologna, Department of Medical and Surgical Sciences DIMEC, Bologna, Italy, [5]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Division of Endocrinology and Diabetes Prevention and Care, Bologna, Italy

Introduction: Diabetic kidney disease (DKD) still represents the leading cause of kidney failure worldwide. If compared to other diabetes complications, its prevalence has failed to decline over past decades. The classical paradigma of albuminuric DKD has been replaced by a wider spectrum of nephropathiesphenotypes, maybe unmasked by new therapeutical options and overlapping comorbidity. Poor datas about DKD in Low and Low-Middle Income Countries are available. In our work we compare two cohorts of DKD patients from Tanzania and from Italy.

Methods: 129 patients referring to NCDs Clinic of Tosamaganga (Tanzania) were compared with 235 patients from the Multidisciplinary Diabetological-Nephrological Clinic of Bologna (Italy) for demographical features (age, sex, BMI), complications (retinopathy, diabetic foot, ischemic cardiopathy, heart failure, stroke), blood exams (HbA1c, creatinine, eGFR, microalbuminuria), kidney morphology and therapy at enrollment and at 6-month and 12-month follow up.

Results: Tanzanian patients were younger (60±14 vs 68±12 years, p<0.00001), with an higher prevalence of women (67% vs 26%, p<0.00001) and lower BMI (25,8±5,6 vs 30,2±5,8 kg/m2, p<0.00001) if compared to Italian patients. No significant difference was found for complications screening, except for higher prevalence of ischemic cardiopathy in Italy (30% vs 1%, p<0.00001). A worsen glycemic control could be observed for tanzanian cohort (79,0±10,0 vs 56,9±13,8 mmol/mol, p<0.00001) and higher eGFR (59,8±32,1 vs 52,1±23,6 ml/min, p<0.00001). At enrollment 28% of Tanzanian patients had CKD stage I and 22% CKD stage II, while 26% of Italian patients had CKD stage IIIa and 39% CKD stage IIIb. Both cohorts showed stability during follow up (Figure 1). A sharp reduction of microalbuminuric (43% vs 19% vs 12%) and macroalbuminuric (31% vs 16% vs 8%) patients were observed during follow up of Tanzanians, while Italians shows an increase of microalbuminuric patients at 12-month follow up (38% vs 49%) but a reduction of macroalbuminuric (34% vs 26%) (Figure 2). In the first cohort an increased prescription of ACE-inhibitor was documented (11% vs 41%), in the second of SGLT2-inhibitors (18% vs 48%). Tanzanian patients showed reduced diameter of kidney (right 9,0±1,2 and left 9,6±1,3 cm) if compared to Italian patients (right 10,9±0.9 and left 11.2±1,1 cm, p<0.00001), cortico-medullar differentiation was comparable between cohorts (Tanzania right 1.4±0.3 and left 1.3±0,2, Italy right 1.6±0,4 and left 1.2±0.2 cm) but median height was lower for Tanzanians (157, 142-167 cm) than Italians (171, 155-180 cm).



Conclusions: Two phenotypes of diabetic patients have been highlighted from comparison between Low-Middle and High Income Country: patients from Tosamaganga are mostly female, younger and with normal BMI; italian patients are mainly affected by metabolic syndrome and vascular complications; female are more represented in African cohort, maybe related to cultural reasons; adherence to follow up and compliance to therapy are associated with improved renal outcomes for both population, suggested by stability of eGFR and downgrading of Albuminuria at one year follow up. Improvement of albuminuria in both cohorts suggests a role of nephroprotective strategy (RAASi in Tanzania and SGLT2i in Italy). Ultrasonography adds useful information, but kidney dimension needs to be integrated with anthropometric features.

No conflict of interest

WCN23-0465

SIX MONTHS OUTCOME OF EMPAGLIFLOZIN IN DIABETIC KIDNEY DISEASE PATIENTS IN BANGLADESH

Kar, S[*2], Das Gupta, D[1]

[1]Sylhet M A G Osmani Medical College, Pharmacology, Sylhet, Bangladesh, [2]Sylhet M A G Osmani Medical college, Nephrology, Sylhet, Bangladesh

Introduction: Empagliflozin is a useful drug to combat diabetic kidney disease.There are not enough data on Bangladeshi patients regarding its usefulness.So we studied it on Bangladeshi patients.

Methods: This was a prospective observational study done at outpatient department of Mount Adora Hospital Nayasarak Sylhet , Bangladesh.

We included 27 patients having diabetic kidney disease (DKD) along with diabetic proteinuria, we freshly started Empagliflozin 10 mg daily and followed up for 6 months.One patient had 3 fold rise of baseline creatinine and we discontinued Empagliflozin therapy for that patient. Two patients died in course of study ,one from hypoglycemia and another from myocardial infarction. We could make a follow up of 24 patients for a period of six months.

We used CKD-EPI Creatinine Equation (2021) to measure eGFR.

All the hypertensive patients received ACE inhibitor or ARB.

Results: The mean age of our patients was 54.28 years. Female was 13 (54%). 23 patients had hypertension. 18 (75%) were on insulin therapy. The pre Empagliflozin treatment mean serum creatinine was 1.74mg/dl and after 6 months of Empagliflozin was 1.56 mg/dl (p 0.07). The result is almost significant. The pre Empagliflozin mean eGFR was 46.13 ml/min and after 6 months its was 50.13 ml/min (p 0.13) difference was there but not significant.

The pre Empagliflozin Urine for ACR was 1060.46 mg/gm and after 6 months it lowered down to 481.35 mg/gm (p 0.001) which is significant.

Three patients had urinary tract infection in the six months period and Empaglflozin was paused during that treatment period and restarted again.No major adverse event or hospitalisation happened among these 24 patients.

Although the study population is small but our observation was Empagliflozin is well tolerated in our population.

Conclusions: Empagliflozin is an effective therapy for Diabetic Kidney Disease in Bangladeshi population. Cost is a barrier to this therapy and most our people cannot afford it. Its easy affordability can reduce End Stage Kidney Disease burden in Bangladesh.

No conflict of interest

WCN23-0471

THE ENHANCEMENT OF METALLOTHIONEIN BIND METAL PATHWAY WITH SGLT2 INHIBITORS IN KIDNEY PROXIMAL TUBULES OF ADOLESCENTS WITH TYPE 2 DIABETES USING SINGLE CELL RNA-SEQ DATA

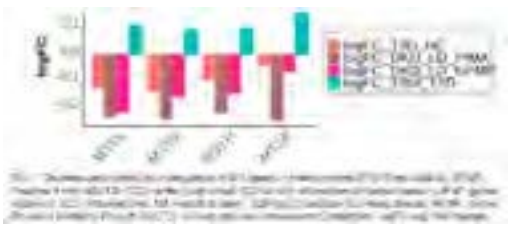
ALAKWAA, F[*1], McCown, P[1], Naik, A[1], Schaub, J[1], Menon, R[1], Otto, E[1], Nair, V[1], Eddy, S[1], Pyle, L[2], Hartman, J[1], Hodgin, J[1], Nelson, R[3], Brosius Division, F[4], Kretzler, M[1], Bjornstad, P[5]

[1]University of Michigan, Internal Medicine, Ann Arbor, United States; [2]University of Colorado School of Medicine, Department of Pediatrics, Aurora, United States; [3]National Institute of Diabetes and Digestive and Kidney Diseases, Chronic Kidney Disease Section, Phoenix, United States; [4]The University of Arizona College of Medicine Tucson, Division of Nephrology, Tucson, United States, [5]University of Colorado School of Medicine, Department of Medicine, Aurora, United States

Introduction: Oxidative stress is the main contributor to diabetic kidney disease (DKD), and SGLT2 inhibitors (SGLT2i) mitigate DKD onset in type 2 diabetes (T2D). An investigation of cell-type specific molecular reprogramming in the kidney with SGLT2i treatment was undertaken in young persons with T2D.

Methods: Single cell RNA sequencing (scRNAseq) profiles of young persons (17±2 years) with T2D, treated with SGLT2i (N=10, T2Di+) or not (N=6, T2Di-), and healthy controls (N=6, HC) were obtained from protocol kidney biopsies. Similarly derived scRNAseq data were available for living donors (N=20, LD), T2D Pima Indians with DKD (N=42) and Kidney Precision Medicine Project (N=12) cohorts. Analysis of scRNAseq data identified differentially expressed genes (DEGs). enrichR enabled pathway enrichment analysis of DEGs.

Results: All participants had normal to elevated GFR by iohexol clearance (185-224 ml/min). A similar occurrence of microalbuminuria (~20%) but lower HbA1c (6.1% vs. 7.3%) were observed in T2Di- compared to T2Di+ at screening. In the proximal tubular (PT) cluster (10,032 cells), 1003 genes elevated in T2Di- vs. HC were suppressed by SGLT2i (T2Di+ vs. T2Di-) while 176 repressed transcripts in T2Di+ were recovered with SGLT2i. Most metabolic pathways increased in T2Di- were suppressed in PT by SGLT2i, except metallothionein and insulin receptor signaling pathways, which were enhanced with SGLT2i exposure ($p<0.05$). Repression of metallothionein in PT could be validated in two independent DKD cohorts (Fig.1).



Conclusions: SGLT2i treatment may rescue metallothionein expression in PT, consistent with a more favorable redox state.

No conflict of interest

Enhancing surgical oncology in Sub-Saharan Africa through international cooperation

PAPER

Authors
Taliente F., Kasalirwe Kisekka P., Ssembuusi J., Kagolo M., Katantazi A., Iacobelli V., Giuliante F.

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European Journal of Surgical Oncology, May 2023

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Topic
Chronic diseases

Focus country
Multi-country

This paper is not available as open access. If you would like to read the entire paper, please go to the web page given and follow the instructions.

The hypertension corner - a new concept to increase hypertension awareness and diagnosis in a poor setting

PAPER

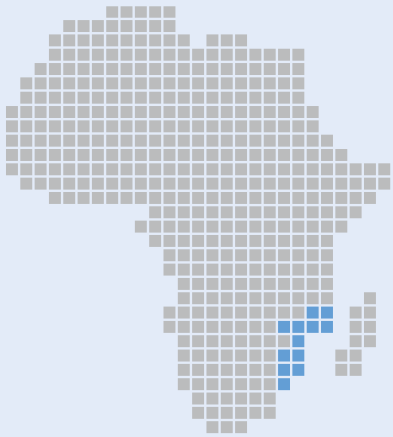
Authors
Massaro P., Ramirez L., Mate C., Gelfi G., Putoto G., Jessen N, Damasceno A.

Published in
Eur J Prev Cardiol,
August 2023

Link
https://doi.org/10.1093/eurjpc/zwad174

Topic
Chronic diseases

Focus country
Mozambique



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Epilepsy care in resources-constrained settings: the nodding syndrome alliance experience in three clinics in Western Equatoria, South Sudan

POSTER PRESENTATIONS

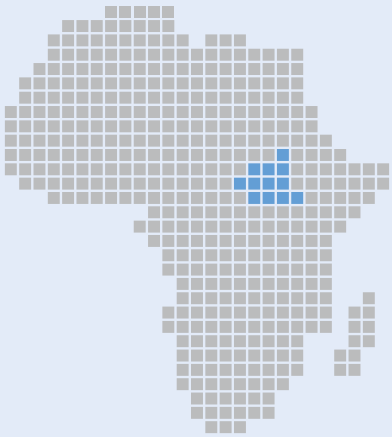
Conference
17th World Congress on Public Health

Location
Rome, Italy

Presentation date
2 - 6 May 2023

Authors
Sgorbissa B. et al.

Focus country
South Sudan



Influence of socioeconomic factors on Blood Pressure Control among Hypertensive Patients in an NCDs Clinic in rural Tanzania

POSTER PRESENTATIONS

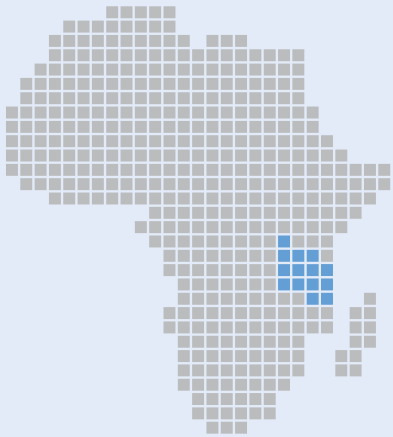
Conference
5th Regional Non-Communicable Disease Scientific Conference

Location
Dar Es Salaam, Tanzania

Presentation date
1 - 3 November 2023

Authors
Ndile E. et al.

Focus country
Tanzania



Paper based integrated management system of Diabetes and Hypertension and on the job training in the HCs could be the key in the management of NCDs

POSTER PRESENTATIONS

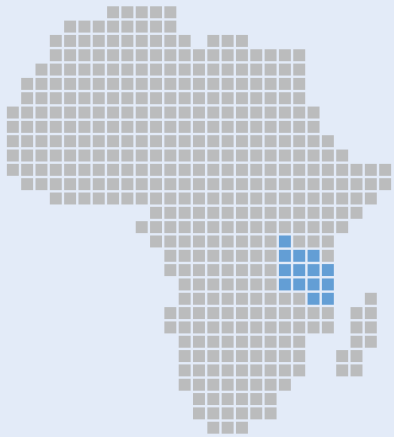
Conference
5th Regional Non-Communicable Disease Scientific Conference

Location
Dar Es Salaam, Tanzania

Presentation date
1 - 3 November 2023

Authors
Mutalemwa K. et al.

Focus country
Tanzania



Nutrition

Incorrect Feeding Practices, Dietary Diversity Determinants and Nutritional Status in Children Aged 6–23 Months: An Observational Study in Rural Angola

PAPER

Authors
Pietravalle A., Dosi A., Inocêncio T.A., Cavallin F., Tomás J., Putoto G., Laforgia N.

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Topic
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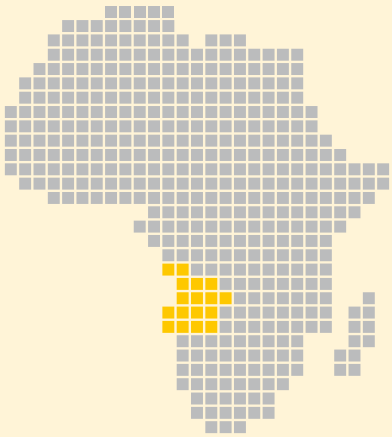
Angola



children

MDPI

Brief Report

Incorrect Feeding Practices, Dietary Diversity Determinants and Nutritional Status in Children Aged 6–23 Months: An Observational Study in Rural Angola

Andrea Pietravalle [1,*], Alessia Dosi [2], Telmo Ambrosio Inocêncio [3], Francesco Cavallin [4], Joaquim Tomás [2], Giovanni Putoto [1] and Nicola Laforgia [5]

[1] Doctors with Africa CUAMM, 35121 Padua, Italy
[2] Doctors with Africa CUAMM, Luanda 56918-000, Angola
[3] Missionary Catholic Hospital of Chiulo, Ombadja 23030, Angola
[4] Independent Statistician, 36020 Solagna, Italy
[5] Section of Neonatology and Neonatal Intensive Care Unit, Interdisciplinary Department of Medicine (DIM), University of Bari "Aldo Moro", 70121 Bari, Italy
* Correspondence: a.pietravalle@cuamm.org

Abstract: Background: More than a quarter of children who are affected by severe acute undernutrition reside in Sub-Saharan Africa. Incorrect feeding practices have a negative impact on a child's health in both the short and the long term, and the interval from conception to two years is the most critical for the development of undernutrition-related complications. These first 1000 days of life also represent an "opportunity window" for early interventions, hence, having a clear insight into dietary habits and the determinants of diet quality is fundamental to improving nutritional counseling practices. Objectives: To investigate incorrect feeding practices, dietary diversity determinants and nutritional status in children aged 6–23 months. Methods: Prospective quali-quantitative observational study conducted at the Missionary Catholic Hospital of Chiulo (Angola) from March to April 2023. Results: Of 250 children, global acute malnutrition affected 25.2% and was associated with starting complementary feeding at <4 months of age ($p = 0.007$) and not achieving the minimum meal frequency ($p < 0.0001$). Minimum dietary diversity was found in 11.2%, minimum meal frequency was experienced by 72.8%, and the minimum acceptable diet was found in 11.2% of participants. The minimum dietary diversity was reached only by households with access to food from five or more major food groups ($p = 0.007$) or the money to buy food from five or more major food groups ($p = 0.008$) and was higher in households where the householder had a higher educational level ($p = 0.002$). Regarding the determinants linked to family traditions and beliefs, the main religion-associated beliefs concerned the impurity of pork ($n = 25$) and fish ($n = 8$), while eggs ($n = 19$) and cow milk ($n = 8$) were the main food types that were deemed harmful for children. Conclusions: Although some factors (economic and religious) may be difficult to overcome, other factors linked to erroneous beliefs (dangerous foods) or incorrect feeding practices (early weaning and an incorrect frequency of meals) can be targeted, to improve the effectiveness of nutritional counseling practices.

Keywords: malnutrition; dietary diversity; incorrect feeding practices

Citation: Pietravalle, A.; Dosi, A.; Inocêncio, T.A.; Cavallin, F.; Tomás, J.; Putoto, G.; Laforgia, N. Incorrect Feeding Practices, Dietary Diversity Determinants and Nutritional Status in Children Aged 6–23 Months: An Observational Study in Rural Angola. *Children* **2023**, *10*, 1878. https://doi.org/10.3390/children10121878

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1. Introduction

The word "malnutrition" may denote undernutrition or overnutrition status, but it usually means undernutrition, which includes acute (wasting), chronic (stunting) and composite forms, according to the degree and timing of nutritional deficiency [1].

According to recent estimates, 13.6 million children under the age of five globally are affected by severe acute undernutrition, and more than a quarter of these live in Sub-Saharan Africa [1].

The early interruption of breastfeeding and the early start of weaning, together with the assumption of a quantitatively and qualitatively poor diet, have a negative impact on a child's health both in both the short (mortality) and the long term (morbidity, mental skill, educational success, work proficiency and income) [2].

The first 1000 days of life (from conception to 2 years) represent the most critical period for the development of undernutrition-related complications, but also represent an "opportunity window" for early intervention [3]. Dietary counseling is a key aspect in the management of malnourished children and should be included in the primary aspects of the treatment strategy but is often absent or inadequate [4]. Understanding dietary habits and the determinants of diet quality is fundamental to improving nutritional counseling practices. Dietary diversity, based on the evaluation of different food groups consumed daily, is a key indicator of diet quality and nutrient adequacy in infants aged 6–23 months [5]. An insight into the burden and role of the determinants of inadequate dietary diversity represents a crucial starting point for the improvement process [6].

This study aimed to investigate the incorrect feeding practices, nutritional status and dietary diversity determinants of children aged 6–23 months, who were admitted to the Missionary Catholic Hospital of Chiulo in Angola.

2. Materials and Methods

This is a prospective quali-quantitative observational study conducted at the Missionary Catholic Hospital of Chiulo from March to April 2023. The Ethics Committee of the Angolan Ministry of Health approved the study (ref. number 6/C.E.M.S./2023). Informed consent was obtained from all subjects involved in the study. All procedures were undertaken according to appropriate guidelines and regulations.

2.1. Setting

The Missionary Catholic Hospital of Chiulo (Cunene province, Angola) is a district hospital implementing the Community Management of Acute Malnutrition program in a rural area of 12,263 km^2 with 345,490 inhabitants (including 60,392 children under 5 years) [4].

Within a network of 36 healthcare facilities implementing the national nutrition program, the hospital acts as a stabilization center for the inpatient care of malnourished children with complications and as outpatient treatment units for the rehabilitation phase after discharge.

2.2. Definitions

Malnutrition is defined by the combination of clinical evaluation and anthropometrical measurements (Weight for Height ratio or Mid-Upper Arm Circumference) according to the classification of the World Health Organization [7]. *Severe Acute Malnutrition* (SAM) is indicated by Weight for Height ratio < 3 Standard Deviation and Mid-Upper Arm Circumference ≤115 mm. *Moderate Acute Malnutrition* (MAM) is indicated by Weight for Height ratio ≥ 3 and <2 Standard Deviations, or a mid-upper arm circumference between >115 and <124 m.

Global acute malnutrition (GAM) is the proportion of children aged 6–59 months, in a given population, with either SAM or MAM [8].

Minimum dietary diversity (MDD) is the proportion of children who ate food and beverages from at least five of these eight different food groups in the day before the evaluation: 1. breast milk; 2. grains, roots, tubers and plantains; 3. pulses, nuts and seeds; 4. dairy products; 5. flesh foods; 6. eggs; 7. vitamin-A rich fruits and vegetables; and 8. other fruits and vegetables [9].

Minimum meal frequency (MMF) is the proportion of children who ate in the day before the evaluation at least: 1. two feedings of solid, semi-solid or soft foods for breastfed infants aged 6–8 months; 2. three feedings of solid, semi-solid or soft foods for breastfed children aged 9–23 months; 3. four feedings of solid, semi-solid or soft foods or milk feeds

for non-breastfed children aged 6–23 months with at least one of the four feeds as a solid, semi-solid or soft feed [9].

Minimum Acceptable Diet (MAD) is the percentage of children who consumed, on the previous day of evaluation, a minimum acceptable diet (achieving both MDD and MMF) [9].

2.3. Patients

All children aged 6–23 months admitted within the study period, were eligible for inclusion.

2.4. Outcome Measures

The outcome measures of the quantitative analysis included GAM, MDD, MMF and MAD. Family traditions and beliefs were included in the qualitative analysis.

2.5. Data Collection

Data were collected and recorded anonymously by using a form that was submitted to caregivers and consulting hospital charts. Data collection included: (a) children's data: age, sex, birth weight, height/length and nutritional status; (b) known risk factors for malnutrition: maternal age, educational status, number of pregnancies, birth weight, duration of exclusive breastfeeding and age of complementary feeding introduction; (c) dietary habits: MDD, MMF and MAD; and (d) known dietary diversity determinants: income, cash availability, socio-economic status, agriculture and agrobiodiversity, gender, household size and family traditions.

2.6. Statistical Analysis

Descriptive analyses were reported as median and interquartile range (IQR) (numerical variables) or absolute frequency and percentage (categorical variables). Associations between categorical variables were assessed using the Chi square test or Fisher's test. All tests were 2-sided and a p of <0.05 was considered statistically significant. Statistical analysis was carried out using R 4.3 (R Foundation for Statistical Computing, Vienna, Austria) [10].

3. Results

The study included 250 children (132 male and 118 female) aged 6–23 months (Table 1). There were 43 with MAM (17.2%) and 20 with SAM (8.0%), yielding a GAM of 25.2%.

Table 1. Child characteristics.

n	**250**
Age (months) (median (IQR))	12 (9–15)
Male/Female	132:118
Weight (kg) (median (IQR))	8.3 (7.0–9.2)
Height/length (cm) (median (IQR))	71 (67–75)
Edema (*n* and %)	
absent	225 (90.0)
+	15 (6.0)
++	10 (84.0)
Nutritional status (*n* and %)	
Normal	187 (74.8)
MAM	43 (17.2)
SAM	20 (8.0)

The known risk factors for malnutrition are summarized in Table 2. GAM was present in 20.6% (18/87) of children who received exclusive breastfeeding at >6 months and in 27.6% (45/163) of those who received exclusive breastfeeding at <6 months (p = 0.29). GAM was

present in 50.0% (12/24) of children who started complementary feeding at <4 months and in 22.6% (51/226) of those who started complementary feeding at >4 months ($p = 0.007$).

Table 2. Known risk factors for malnutrition.

Mothers	
Age (years) (median (IQR))	27 (22–32)
Number of pregnancies (median (IQR))	3 (2–5)
Educational status (*n* and %)	
Never attended school	74 (29.6)
Primary school	79 (31.6)
Secondary school	97 (38.8)
Children	
Birth weight (kg) (median (IQR)) *	3.2 (2.9–4.8)
Mother as primary caregiver (*n* and %)	244 (97.6)
Breastfeeding (*n* and %)	208 (83.2)
Duration of exclusive breastfeeding (*n* and %)	
<6 months	163 (65.2)
>6 months	87 (34.8)
Age of complementary feeding introduction (*n* and %)	
<4 months	24 (9.6)
4–6 months	139 (55.6)
>6 months	87 (34.8)

* Birth weight was available for 120/250 children.

Overall, MDD was present in 11.2% of children (28/250), MMF in 72.8% (182/250) and MAD in 11.2% (28/250). The data on MDD and MAD overlapped. GAM was present in 10.7% (3/28) of children who achieved minimum dietary diversity and in 27.0% (60/222) of those who did not ($p = 0.10$). GAM was present in 12.1% (22/182) of children who achieved minimum meal frequency and in 60.2% (41/68) of those who did not ($p < 0.0001$).

The known determinants of MDD are described in Table 3. MDD was reached only by households with access to food from five or more major food groups ($p = 0.007$) or income to buy food from five or more major food groups ($p = 0.008$). Notably, the data suggested that 197/250 households (78.8%) had access to food from five or more major food groups, but only 28/197 (14.2%) fed them to children; similarly, 198/250 households (79.2%) had the income to buy food from five or more major food groups, but only 28/198 (14.1%) fed them to children. In addition, MDD was higher in households where the householder had a higher educational level (19.3% vs. 5.9%, $p = 0.002$).

Family traditions and religious beliefs cause the elimination of some foods:

- Eggs, because of dumbness ($n = 18$) or diarrhea ($n = 1$);
- Cow milk, because of wounds, according to the Kimbanguist religion ($n = 8$)
- Fish, because it hurt the skin, according to the Kimbanguist religion ($n = 2$), or is harmful for children ($n = 1$);
- Meat ($n = 1$) because it is harmful for children;
- Vegetables ($n = 1$) because they are harmful for children;
- Pork, because it is impure ($n = 25$) (Isaia 66, 17; Levitico 11) (Kimbanguist religion);
- Fish without scales, because it is impure ($n = 8$) (Kimbanguist religion);
- Fish, because it is holy ($n = 1$);
- Meat, because it is holy ($n = 1$).

Table 3. Known determinants of minimum dietary diversity (MDD).

Determinant	*n* (%)	MDD: *n* (%)	*p* Value
Head of household			
Gender:			
Female	50 (20.0)	6 (12.0)	0.99
Male	200 (80.0)	22 (11.0)	
Educational status:			
Never attended/primary school	152 (60.8)	9 (5.9)	0.002
Secondary school	98 (39.2)	19 (19.3)	
Household size			
Family members:			
≤5	107 (42.8)	10 (9.3)	0.54
>5	143 (57.2)	18 (12.6)	
Children < 5 years:			
1–3	249 (99.6)	-	-
>3	1 (0.4)		
Agriculture, agrobiodiversity and livelihood diversity			
Irrigated field:			
No	234 (93.6)	24 (10.2)	0.16
Yes	16 (6.4)	4 (25.0)	
Farm animals:			
No	81 (32.4)	10 (12.3)	0.85
Yes	169 (67.6)	18 (10.6)	
Householder with another job:			
No	89 (35.6)	5/89 (5.6)	0.06
Yes	161 (64.4)	23/161 (14.2)	
Availability of foods			
From ≥5 major food groups:			
No	53 (21.2)	0 (0)	0.007
Yes	197 (78.8)	28 (14.2)	
Income			
Ablility to buy food from =/> major food groups:			
No	52 (20.8)	0/52 (0.0)	0.008
Yes	198 (79.2)	28/198 (14.1)	
Cultural aspect			
Family traditions and beliefs			
No	203 (81.2)	24/203 (11.8)	0.69
Yes	47 (18.8)	4/47 (8.5)	

4. Discussion

Attaining ideal nourishment during the first 2 years of life is critical because it reduces morbidity and mortality, lowers the risk of chronic disease, and fosters better development overall [10]. The WHO and UNICEF recommendations include: beginning breastfeeding within 1 h of birth; exclusive breastfeeding for the first 6 months of life; and the introduction of nutritionally adequate and safe complementary (solid) foods at 6 months, together with continued breastfeeding up to 2 years of age or beyond [11,12].

Breastmilk is a significant source of energy and nutrients in children aged 6–23 months, and exclusive breastfeeding up to 6 months offers several advantages for the infant, with a significant protection against gastrointestinal infections [11]. On the other hand, if complementary foods are not introduced in a timely manner, when the need for energy and nutrients exceeds what is provided by breast milk, growth can be impaired. However, the results of giving semi-solid foods to a still-immature child—jointly with poor food

quality—are equally harmful [12]. Our data suggested an association between GAM and starting complementary feeding before 4 months of life, but no association was found with exclusive breastfeeding for less than 6 months. Of course, the role of other potential confounding factors, and the complex relationship between exclusive breastfeeding and introducing complementary feeding, suggest caution when drawing implications from such findings.

We found that only around one out of ten children achieved the minimum acceptable diet, in agreement with figures from the latest National Demographic and Health survey, which reported a 13% incidence of MAD [13]. Our data show that MMF was significantly associated with lower GAM, while MDD was not. These findings were in broad agreement with a recent study from the same setting, suggesting an association between lower GAM and a higher achievement of both MMF and MDD [14].

In our study, we investigated the prevalence and the role of the different determinants of dietary diversity, on the basis of the detailed classification described in a recent qualitative ethnographic study [15]. As previously suggested [6], we found that children living in a household with higher level of education had more chance of achieving minimum diet diversity, hence highlighting the importance of parental education. As expected, we found that minimum diet diversity could only be achieved when there was access to food from five or more major food groups and enough income to buy these foods. Noteworthily, most households had access to food from five or more major food groups and adequate income, but only a minority of them fed the children with food from five or more major food groups. The possibility that cultural and/or religious beliefs play a role seems not to be the reason, because our data demonstrate that MDD was similar in households with and without family traditions and beliefs. Nonetheless, the qualitative analysis highlighted some religion-associated beliefs on food impurity (mainly regarding pork and fish) and other beliefs about specific foods being harmful for children (mainly regarding eggs and cow milk). These data are in line with findings from similar settings and should be considered when planning educational interventions to improve child nutrition [16].

A recent work underlined sociocultural impacts on food preferences and the role of analyzing cultural food routines when modelling appropriate and successful policy interventions [17]. Overall, we acknowledge that economic and religious constraints may be difficult to overcome, but other factors such as erroneous beliefs (i.e., about dangerous foods) and incorrect feeding practices (early weaning and incorrect meal frequency and composition) may be useful targets to reach with appropriate educational interventions. Specific education on these elements should find a place within the social and behavioral programs, known as "parenting interventions", that focus on enhancing caregivers' knowledge, attitudes, practices and skills, with the final goal of endorsing the best early child development [18].

Our study has some limitations. First, the study design limits the generalizability of the results to different settings. Second, the sample size is limited. Third, the available data did not allow for further investigations of some interesting findings, such as the reasons for not properly feeding children despite the availability of food and money, together with the roles of family traditions and beliefs.

5. Conclusions

The present study highlighted specific aspects that should be targeted by interventions aiming at improving the effectiveness of nutritional counseling practices, which represent a fundamental tool for prevention of severe childhood undernutrition.

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Abbreviations

SAM	Severe Acute Malnutrition
MAM	Moderate Acute Malnutrition
GAM	Global Acute Malnutrition
MDD	Minimum Dietary Diversity
MMF	Minimum Meal Frequency
MAD	Minimum Acceptable Diet

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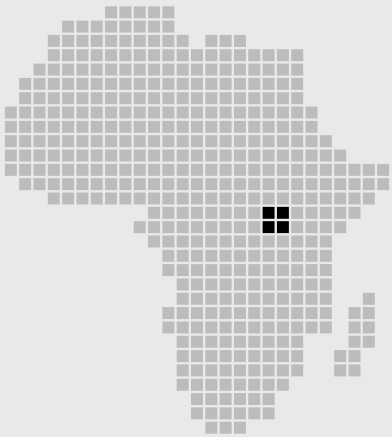

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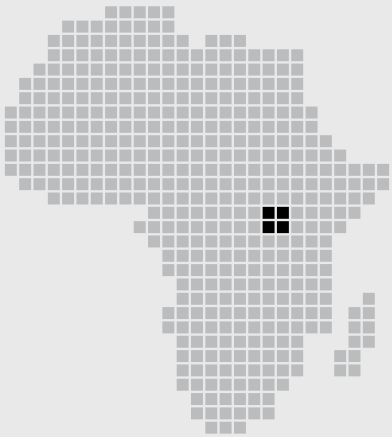

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1. Abdissa Alemseged, Armauer Hansen Research Institute, Addis Ababa, Ethiopia
2. Abdul Ramadhani, Amsterdam UMC, Department University of Amsterdam, Department of Global Health, Amsterdam Institute for Global Health and Development
3. Adetunji Adeniji O, Princess Christian Maternity Hospital, University of Sierra Leone Teaching Hospitals Complex, Freetown, Sierra Leone
4. Agaba Lino, St. John's XXIII Hospital Aber, Jaber 21310, Uganda
5. Agabiirwe Caroline Noel, Programs, UNICEF Uganda
6. Agaro Caroline, Health Office, Oyam District Local Government, Loro, Uganda
7. Agostoni Carlo, ondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Pediatric Area, Milan, Italy, Department of Clinical Sciences and Community Health (DISCCO), University of Milan, Milan, Italy
8. Ahivaldino Zita, Department of Paediatry, Central Hospital of Maputo, Maputo 1113, Mozambique
9. Aiello Valeria, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Nephrology-Dialysis and Renal Transplant Unit, Bologna, Italy, Alma Mater Studiorum, Alma Mater Studiorum University of Bologna, Bologna, Italy
10. Ajelli Marco, Laboratory for Computational Epidemiology and Public Health, Department of Epidemiology and Biostatistics, Indiana University School of Public Health, Bloomington, USA
11. Ally Mussa, Nucleo de Investigacao Operacional de Pemba, Pemba, Mozambique
12. Alupu Monica, Doctors with Africa, CUAMM, Uganda
13. Amone James, St. John's XXIII Hospital Aber, Jaber 21310, Uganda
14. Amongin Dinah, Programs, UNICEF Uganda
15. Amoruso Irene, Hygiene and Public Health Unit, DCTVSP, University of Padua, Italy
16. Amuasi John, Department of Global Health, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana
17. Antunes Mario, Department of Surgery, Central Hospital of Beira, Beira, Mozambique, Catholic University of Mozambique, Beira, Mozambique
18. Aryal Diptesh, Mahidol Oxford Tropical Medicine Research Unit, Bangkok, Thailand, D'Or Institute for Research and Education, Sao Paulo, Brazil, Department of Critical Care, Nepal Intensive Care Research Foundation, Kathmandu, Nepal
19. Ascoli Bartoli Tommaso, National Institute for Infectious Diseases, Lazzaro Spallanzani, IRCCS, Rome, Italy
20. Asmare Azmach Biset, St Luke Catholic Hospital, Wolisso, Ethiopia
21. Atambi Patrobas, Ngokolo Health Centre, Shinyanga, Tanzania
22. Atzori Andrea, Doctors with Africa CUAMM, Italy
23. Azzimonti Gaetano, Doctors with Africa CUAMM, Italy
24. Babudieri Sergio, Unit of Infectious and Tropical Diseases, Department of Medicine, Surgery and Pharmacy, University of Sassari, Sassari, Italy
25. Bah Abdul Karim, Princess Christian Maternity Hospital, University of Sierra Leone Teaching Hospital Complex, Fourah Bay Road, Freetown 00232, Sierra Leone
26. Bah Sarjoh, Princess Christian Maternity Hospital, University of Sierra Leone Teaching Hospitals Complex, Freetown, Sierra Leone
27. Baldovin Tatjana, Hygiene and Public Health Unit, DCTVSP, University of Padova, Italy
28. Balestri Eleonora, Neonatal Intensive Care Unit, AUSL-IRCCS of Reggio Emilia, Reggio Emilia, Italy, Doctors with Africa CUAMM Ethiopia
29. Barbagallo Mario, Geriatric Unit, Department of Internal Medicine and Geriatrics, University of Palermo
30. Bavaro Davide Fiore, Department of Precision and Regenerative Medicine and Ionian Area, Clinic of Infectious Diseases, University of Bari
31. Bazzanini Noemi, Medici con l'Africa CUAMM Tanzania, Medici con l'Africa CUAMM, Padova, Italy
32. Beane Abi, Mahidol-Oxford Tropical Medicine Research Unit (MORU), Mahidol University, Bangkok, Thailand
33. Benoni Roberto, Section of Operational Research, Doctors with Africa-Cuamm, Padova, Italy
34. Bertoldo Alessandro, Zerouno Procreazione, Centro di Medicina, Venezia, Italy
35. Bertoncello Chiara, Hygiene and Public Health Unit, DCTVSP, University of Padova, Italy
36. Biasci Filippo, Doctors with Africa CUAMM Ethiopia
37. Biccard Bruce, Department of Anaesthesia and Perioperative Medicine, University of Cape Town, Cape Town, South Africa
38. Biggeri Mario, ARCO (Action Research for CO-development), PIN Educational and Scientific Services for the University of Florence, Prato, Italy, Department of Economics and Management, University of Florence, Florence, Italy
39. Bingom Christopher, Doctors with Africa, CUAMM, Uganda
40. Bobosha Kidist, Mycobacterial Diseases Research, Armauer Hansen Research Institute, Addis Ababa, Ethiopia
41. Borellini Martina, Department of Woman's and Child's Health, University of Padua, Via Giustiniani, 3, Padua, 35128, Italy, Doctors with Africa CUAMM, Padova
42. Bosco Nsubuga John, Saint Kizito Hospital, Matany, Uganda
43. Boyle Sonia, Princess Christian Maternity Hospital, University of Sierra Leone Teaching Hospitals Complex, Freetown, Sierra Leone
44. Brasili Luca, Doctors with Africa CUAMM,Tanzania
45. Brindicci Gaetano, Clinic of Infectious Diseases, Department of Biomedical Sciences and Human Oncology, University of Bari, Bari, Italy
46. Byabasheija Robert, Programs, UNICEF Uganda
47. Cadorin Simone, Doctors with Africa CUAMM
48. Calia Margherita, Doctors with Africa CUAMM Ethiopia
49. Camporeale Michele, Clinic of Infectious Diseases, Department of Biomedical Sciences and Human Oncology, University of Bari, Bari, Italy
50. Capelli Irene, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Nephrology-Dialysis and Renal Transplant Unit, Bologna, Italy, Alma Mater Studiorum, Alma Mater Studiorum University of Bologna, Bologna, Italy
51. Caracciolo Claudia, Doctors with Africa CUAMM, Italy
52. Carraro Giacomo, Operative Research Unit, Doctors with Africa CUAMM, Rua Fernao Mendes Pinto 165, Ponta Gea, 1363, Beira, Mozambique
53. Casigliani Virginia, Doctors with Africa CUAMM Mozambique, Department of Translational Research and of New Surgical and Medical Technologies, University of Pisa, Pisa, Italy
54. Castellani Chiara, Institut Supérieur des Techniques Médicales (ISTM) Marie-Reine-de-la-Paix de Kenge, Kenge, Democratic Republic of Congo
55. Cavagna Chiara, Doctors with Africa CUAMM, Italy
56. Cavallin Francesco, Independent Statistician, Solagna, Italy
57. Censi Veronica, Doctors with Africa CUAMM, Italy
58. Centomo M , Hygiene and Public Health Unit, DCTVSP, University of Padova, Italy
59. Cianciolo Giuseppe, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Nephrology- Dialysis and Renal Transplant Unit, Bologna, Italy
60. Chambisse Elsa, Médicos com África CUAMM Moçambique
61. Chenene Fernando, Doctors with Africa CUAMM Mozambique

62. Chhaganlal Kajal, Faculdade de Ciências de Saúde, Universidade Católica de Moçambique, Beira, Mozambique
63. Chilundo Josina, Department of Pneumology, Central Hospital of Maputo, Maputo 1113, Mozambique, Faculty of Medicine, Eduardo Mondlane University Maputo, Maputo 1113, Mozambique
64. Chitnis Ketan, UNICEF communication for development
65. Chuau Inusso, UNICEF, Peer Support Volunteers MCO, Mozambique
66. Colpani Agnese, Unit of Infectious and Tropical Diseases, Department of Medicine, Surgery and Pharmacy, University of Sassari, Sassari, Italy
67. Coppola Cristina, Direzione sanitaria aziendale, Asl Bari
68. Costigan Kathleen, Bugisi Health Centre, Shinyanga, Tanzania
69. Cotugno Sergio, Department of Precision and Regenerative Medicine and Ionian Area, Clinic of Infectious Diseases, University of Bari
70. D'Andrea Valeria, Center for Health Emergencies, Bruno Kessler Foundation, Trento
71. D'Argenio Angelo, Clinic of Infectious Diseases, Department of Precision and Regenerative Medicine and Ionian Area (DiMePRe-J), University of Bari Aldo Moro
72. Da Dalt Liviana, Division of Paediatric Emergency Medicine, Department of Women's and Children's Health, University of Padua
73. Dall'Oglio Giovanni, Doctors with Africa, CUAMM, Uganda
74. Dalla Porta Francesca, Medici con l'Africa CUAMM
75. Dalla Zuanna Teresa, Hygiene and Public Health Unit, DCTVSP, University of Paduaa, Italy
76. Damasceno Albertino, Faculty of Medicine, Eduardo Mondlane University, Maputo, Mozambique
77. De Gennaro Francesco, Department of Precision and Regenerative Medicine and Ionian Area, Clinic of Infectious Diseases, University of Bari
78. De Iaco Giuseppina, Department of Precision and Regenerative Medicine and Ionian Area, Clinic of Infectious Diseases, University of Bari
79. De Klerk Josien, Amsterdam Institute of Global Health and Development, Paasheuvelweg 25, 1105 BP, Amsterdam, the Netherlands
80. De Santis Laura, Clinic of Infectious Diseases, Department of Precision and Regenerative Medicine and Ionian Area (DiMePRe-J), University of Bari Aldo Moro
81. De Vita Elda, Department of Precision and Regenerative Medicine and Ionian Area, Clinic of Infectious Diseases, University of Bari
82. De Vito Andrea, Unit of Infectious and Tropical Diseases, Department of Medicine, Surgery and Pharmacy, University of Sassari, Sassari, Italy
83. Di Chiara Costanza, Division of Pediatric Infectious Diseases, Department of Women's and Children's Health, University of Padua, Padua, Italy
84. Di Gennaro Francesco, Clinic of Infectious Diseases, Department of Precision and Regenerative Medicine and Ionian Area (DiMePRe-J), University of Bari Aldo Moro, Operational Research Unit, Doctors with Africa CUAMM
85. Dissanayake Vishmi, Mahidol-Oxford Tropical Medicine Research Unit (MORU), Mahidol University, Bangkok, Thailand
86. Donà Daniele, Division of Pediatric Infectious Diseases, Department of Women's and Children's Health, University of Padua, Padua, Italy
87. Dondorp Arjen, Mahidol Oxford Tropical Medicine Research Unit, Bangkok, Thailand, Amsterdam Institute for Global Health and Development, Amsterdam, The Netherlands, Nuffield Department of Medicine, University of Oxford, Oxford, UK
88. Done Dilanthi Gamage, Nat-Intensive Care Surveillance, Mahidol Oxford Tropical Medicine Research Unit, Colombo, Sri Lanka, Institute of Applied Health Research, University of Birmingham, Birmingham, UK
89. Dos Anjos Helga Guambe, UNICEF Mozambique, Maputo, Mozambique
90. Dosi Alessia, Doctors with Africa CUAMM, Angola
91. Draru Joyce, Nursing, Arua Regional Referral Hospital, Arua, West Nile, Uganda
92. Endrias Tariqua, Neonatal Intensive Care Unit, St Luke Catholic Hospital, Wolisso, Ethiopia
93. Erio Tusajigwe, Amsterdam Institute of Global Health and Development, Paasheuvelweg 25, 1105 BP, Amsterdam, the Netherlands
94. Esiru Godfrey, Doctors with Africa CUAMM, Uganda
95. Facci Enzo, Doctors with Africa CUAMM, Ethiopia
96. Falanga Carmine, ANLAIDS Sezione Lombardia, 20124 Milan, Italy
97. Farina Umberto, Scuola di specializzazione in Igiene e medicina preventiva, Dipartimento di Scienze mediche e chirurgiche, Università di Foggia
98. Ferretti S. Hygiene and Public Health Unit, DCTVSP, University of Padova, Italy
99. Filippi Valeria, Doctors with Africa CUAMM, Ethiopia
100. Fonzo Marco, Hygiene and Public Health Unit, DCTVSP, University of Padua, Italy
101. Forastiere Laura, Department of Biostatistics, Yale School of Public Health, New Haven, CT, USA
102. Forni Guido, Accademia Nazionale dei Lincei, Rome
103. Fortunato Francesca, Scuola di specializzazione in Igiene e medicina preventiva, Dipartimento di Scienze mediche e chirurgiche, Università di Foggia
104. Frallonardo Luísa, Clinic of Infectious Diseases, Department of Precision and Regenerative Medicine and Ionian Area (DiMePRe-J), University of Bari Aldo Moro
105. Galli Margherita, Center for Health Emergencies, Bruno Kessler Foundation, Trento
106. Gatta Alessandra, Operational Research Unit, Doctors with Africa Cuamm, Italy
107. Gelfi Giorgia, Doctors with Africa CUAMM,Mozambique
108. Ghalib Maryam Shamal, General Surgery, Wazir Akbar Khan Hospital, Kabul, Afghanistan
109. Ghelardi Angelo, UNICEF
110. Ghose Aniruddha, Department of Medicine, Chittagong Medical College Hospital, Chattogram, Bangladesh
111. Giannini Dara, Doctors with Africa CUAMM Mozambique
112. Giaquinto Carlo, Division of Pediatric Infectious Diseases, Department of Women's and Children's Health, University of Padua, Padua, Italy
113. Gibson Poppy, School of Education and Social Care, Anglia Ruskin University, Chelmsford, UK
114. Giuliante Felice, Hepatobiliary Surgery Unit, Foundation "Policlinico Universitario A. Gemelli", IRCCS, Catholic University, Rome, Italy
115. Gokhale Krishna, Institute of Applied Health Research, University of Birmingham, Birmingham, UK
116. Gooden Tiffany E, Institute of Applied Health Research, University of Birmingham, Birmingham, UK
117. Guadagno Chiara, Doctors with Africa CUAMM,Tanzania
118. Guido Giacomo, Clinic of Infectious Diseases, Department of Biomedical Sciences and Human Oncology, University of Bari, Bari, Italy
119. Gulo Berhanu, St Luke Catholic Hospital, Wolisso, Ethiopia
120. Guzzetta Giorgio, Center for Health Emergencies, Bruno Kessler Foundation, Trento
121. Hagos Eleni, Doctors with Africa CUAMM, Jinka, South Omo, Ethiopia
122. Haniffa Rashan, Mahidol-Oxford Tropical Medicine Research Unit (MORU), Mahidol University, Bangkok, Thailand

123. Hanciles Eva, Department of Anesthesia and Intensive Care, Connaught Hospital, University of Sierra Leone, Freetown, Sierra Leone
124. Harris Steve, Department of Critical Care, University College London Hospitals NHS Foundation Trust, London, UK
125. Hashmi Madiha, Mahidol Oxford Tropical Medicine Research Unit, Bangkok, Thailand, Department of Critical Care Medicine, Ziauddin University, Karachi, Pakistan
126. Hermans Sabine, Amsterdam UMC, Department University of Amsterdam, Department of Global Health, Amsterdam Institute for Global Health and Development, Amsterdam, the Netherlands
127. Hessebo Tesfayesus Tefera, Jinka General Hospital, Jinka, South Omo, Ethiopia
128. Iacob Giulio, Doctors with Africa, CUAMM, Uganda - Ospedale San Giuseppe Multimedica, Milano
129. Iacobelli Valentina, Doctors with Africa CUAMM, Uganda
130. Ichto Jerry, Doctors with Africa CUAMM, Uganda
131. Inocêncio Telmo Ambrosio, Missionary Catholic Hospital of Chiulo, Ombadja 23030, Angola
132. Janneh Foday Musa, Princess Christian Maternity Hospital, University of Sierra Leone Teaching Hospital Complex, Fourah Bay Road, Freetown 00232, Sierra Leone
133. Jessen Neusa, Faculty of Medicine, Eduardo Mondlane University, Maputo, Mozambique
134. John-Cole Valerie, Princess Christian Maternity Hospital, University of Sierra Leone Teaching Hospitals Complex, Freetown, Sierra Leone
135. Kaddu Ronnie P, Department of Anaesthesia, The Aga Khan University, Nairobi, Kenya
136. Kagolo Moses, Matany Saint Kizito Hospital, Moroto, Uganda
137. Kamara Abibatu, Ministry of Health and Sanitation, Freetown, Sierra Leone
138. Kargbo Henry, Princess Christian Maternity Hospital, University of Sierra Leone Teaching Hospitals Complex, Freetown, Sierra Leone
139. Kasalirwe Kisekka Paul, Doctors with Africa CUAMM, Uganda
140. Katantazi Abdulsalam, Matany Saint Kizito Hospital, Moroto, Uganda
141. Kenate Birhanu, Health Research Team, Oromia Regional Health Bureau, Addis Ababa, Ethiopia
142. Kwizera Arthur, Department of Anaesthesia and Intensive Care Medicine, Makerere University, Kampala, Uganda
143. L'Episcopia Mariangela, Department of Infectious Diseases, Istituto Superiore di Sanità, Rome, Italy
144. La Manna Gaetano, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Nephrology- Dialysis and Renal Transplant Unit, Bologna, Italy, Alma Mater Studiorum, Alma Mater Studiorum University of Bologna, Bologna, Italy
145. La Raja Massimo, Transfusion Medicine Department of Azienda Sanitaria Universitaria Giuliano Isontina (ASU GI), Trieste, Italy, Doctors with Africa CUAMM, Padova
146. La Vecchia Adriano, Department of Clinical Sciences and Community Health (DISCCO), University of Milan, Milan, Italy
147. Laforgia Nicole, Doctors with Africa CUAMM, Bari
148. Laforgia Renato, Doctors with Africa CUAMM, Bari
149. Lamberti-Castronuovo Alessandro, CRIMEDIM - Center for Research and Training in Disaster Medicine, Humanitarian Aid and Global Health, Università del Piemonte Orientale, Novara, Italy
150. Lattanzio Rosanna, Department of Precision and Regenerative Medicine and Ionian Area, Clinic of Infectious Diseases, University of Bari
151. Leluko Dionis Erasto, Tosamaganga Hospital, Iringa, Tanzania
152. Lochoro Peter, Doctors with Africa CUAMM, Uganda
153. Macuácua Sheila, Department of Paediatry, Central Hospital of Maputo, Maputo 1113, Mozambique
154. Madeddu Giordano, Unit of Infectious and Tropical Diseases, Department of Medicine, Surgery and Pharmacy, University of Sassari, Sassari, Italy
155. Maffoni Silvia, Doctors with Africa CUAMM, Iringa, Tanzania, University of Pavia, Italy
156. Maggioni Giuseppe, Department of Medicine, University of Padua, 35128 Padova, Italy
157. Mancini Vincenzo, Università degli Studi di Roma "La Sapienza"
158. Manenti Fabio, Doctors with Africa CUAMM, Italy
159. Mangi Sabina, Tosamaganga Council Designated Hospital, Iringa, Tanzania
160. Manica Mattia, Center for Health Emergencies, Bruno Kessler Foundation, Trento
161. Mantovani Alberto, IRCCS Humanitas Research Hospital,Milan
162. Maokola Werner, National Aids Control Program(NACP), Dodoma, Tanzania
163. Mariani Michele Fabio, Clinic of Infectious Diseases, Department of Biomedical Sciences and Human Oncology, University of Bari, Bari, Italy
164. Marotta Claudia, Doctors with Africa CUAMM, Italy
165. Martelli Giulia, Infectious Diseases Unit, AUSL Romagna, Morgagni Pierantoni Hospital Forlí, Doctors with Africa CUAMM IT, Forlí, Italy
166. Martinelli Domenico, Scuola di specializzazione in Igiene e medicina preventiva, Dipartimento di Scienze mediche e chirurgiche, Università di Foggia
167. Marziano Valentina, Center for Health Emergencies, Bruno Kessler Foundation, Trento
168. Massaro Paulo, Doctors with Africa CUAMM,Mozambique
169. Mat-Nor Mohammed Basri, Department of Intensive Care Anaesthesiology, International Islamic University Malaysia, Kuala Lumpur, Malaysia
170. Mate Celina, Non-Communicable Diseases Department, Ministry of Health, Maputo, Mozambique
171. Mattiotti Maria, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Nephrology- Dialysis and Renal Transplant Unit, Bologna, Italy, Medici con l'Africa CUAMM Tanzania, Alma Mater Studiorum, Alma Mater Studiorum University of Bologna, Bologna, Italy
172. Maziku Donald,Tosamaganga Hospital, Iringa, Tanzania
173. Mbiya Kamunga Adrien, Doctors with Africa CUAMM, Sierra Leone
174. Mealli Fabrizia, Department of Statistics, Computer Science, Applications "G. Parenti", University of Florence, Florence, Italy
175. Merolle Ada, Doctors with Africa CUAMM Mozambique
176. Merler Stefano, Center for Health Emergencies, Bruno Kessler Foundation, Trento
177. Meta Judith, Shinyanga and Simiyu Test & Treat Project, Shinyanga, Tanzania
178. Mfinanga Sayoki, National Institute for Medical Research(NIMR)-Muhimbili centre, Dar es Salaam, Tanzania, Alliance for Africa Health Research, Nairobi, Kenya, School of Public Health, Department of Epidemiology and Statistics, Muhimbili University of Health and Allied Science, Dar es Salaam, Tanzania
179. Mhaluka Lawrence, Tosamaganga Council Designated Hospital, Iringa, Tanzania
180. Miccio Maddalena, St Luke Catholic Hospital, Wolisso, Ethiopia
181. Minardi Maria Letizia, Clinical Infectious Diseases, Department of System Medicine, Tor Vergata University, Rome, Italy
182. Minh Yen Lam, Oxford University Clinical Research Unit, University of Oxford, Ho Chi Minh City, Vietnam
183. Mllacha Peter, Shinyanga Regional Referal Hospital, Shinyanga, Tanzania
184. Mokori Alex, Programs, UNICEF Uganda

185. Montalbetti Francesca, Jinka General Hospital, Jinka, South Omo, Ethiopia
186. Moonesinghe Suneetha Ramani, Department of Targeted Intervention, University College London, London, UK
187. Mortara Milena, Department of Anesthesia and Intensive Care, University of Piemonte Orientale, Novara, Italy, Princess Christian Maternity Hospital, University of Sierra Leone Teaching Hospitals Complex, Freetown, Sierra Leone
188. Moyer Eileen, Amsterdam Institute of Global Health and Development, Paasheuvelweg 25, 1105 BP, Amsterdam, the Netherlands
189. Muhelo Arlindo, Department of Paediatry, Central Hospital of Maputo, Maputo 1113, Mozambique
190. Mukaka Mavuto, Mahidol Oxford Tropical Medicine Research Unit, Bangkok, Thailand, Nuffield Department of Medicine, University of Oxford, Oxford, UK
191. Mukisa Benjamin, St. John's XXIII Hospital Aber, Jaber 21310, Uganda
192. Mulu Dagmawi Awoke, Jinka General Hospital, Jinka, South Omo, Ethiopia
193. Murthy Srinivas, Department of Pediatrics, Faculty of Medicine, University of British Columbia, Vancouver, Canada
194. Mussagi Ana Cristina, Department of Paediatry, Central Hospital of Maputo, Maputo 1113, Mozambique
195. Mutalemwa Katunzi, Doctors with Africa CUAMM, Tanzania
196. Nadia Farah, Department of Intensive Care Anaesthesiology, International Islamic University Malaysia, Kuala Lumpur, Malaysia
197. Nannini Maria, ARCO (Action Research for CO-development), PIN Educational and Scientific Services for the University of Florence, Prato, Italy, Department of Economics and Management, University of Florence, Florence, Italy
198. Ndile Emmanuel, Doctors with Africa CUAMM, Tanzania
199. Ndungutse Amos Hashaka, Programs, UNICEF Uganda
200. Ngole Benedict, Operational Research Unit, African Network for Change, Kampala, Uganda
201. Nicastri Emanuele, National Institute for Infectious Diseases, Lazzaro Spallanzani, IRCCS, Rome, Italy
202. Nieman Nicole Rose, Missionary Sisters of the Sacred Heart, Rome, Italy
203. Nigussa Gamshie Worku, Doctors with Africa CUAMM,Ethiopia
204. Nirantharakumar Krishnarajah, Guido Giacomo, Clinic of Infectious Diseases, Department of Biomedical Sciences and Human Oncology, University of Bari, Bari, Italy
205. Noirjean Silvia, Department of Statistics, Computer Science, Applications "G. Parenti", University of Florence, Florence, Italy
206. Novara Roberta, Clinic of Infectious Diseases, Department of Precision and Regenerative Medicine and Ionian Area (DiMePRe-J), University of Bari Aldo Moro
207. Ntanguligwa Constantine, European Society of Clinical Microbiology and Infectious Diseases (ESCMID)
208. Occa Edoardo, Università degli Studi di Milano - Bicocca
209. Odaga Jimmy, Operational Research Unit, Doctors with Africa CUAMM Kampala, Uganda; St. John's XXIII Hospital Aber, Jaber
210. Ogwal Polycap, Doctors with Africa, CUAMM, Uganda
211. Ogwang Eric, Doctors with Africa, CUAMM, Uganda
212. Ogwang Joseph, Operational Research Unit, St. John's XXIII Hospital Aber, Jaber, Uganda
213. Okori Sam, Aber Hospital, Aber, Uganda
214. Olal Lameck, Operational Research Unit, African Network for Change, Kampala, Uganda
215. Olung Nelson, Operational Research Unit, St. John's XXIII Hospital Aber, Jaber, Uganda
216. Onapa Emmanuel, Operational Research Unit, St. John's XXIII Hospital Aber, Jaber, Uganda
217. Onida Ilaria, Azienda ospedaliero - universitaria di Sassari
218. Orsi Michele, IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano, Milan, Italy
219. Pagotto Uberto, Alma Mater Studiorum University of Bologna, Department of Medical and Surgical Sciences DIMEC, Bologna, Italy, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Division of Endocrinology and Diabetes Prevention and Care, Bologna, Italy
220. Pallara Elisabetta, Clinic of Infectious Diseases, Department of Biomedical Sciences and Human Oncology, University of Bari, Bari, Italy
221. Panaru Hem, Department of Critical Care, Nepal Intensive Care Research Foundation, Kathmandu, Nepal
222. Panico Gianfranco Giorgio, Clinic of Infectious Diseases, Department of Precision and Regenerative Medicine and Ionian Area (DiMePRe-J), University of Bari Aldo Moro
223. Papagni Roberta, Department of Precision and Regenerative Medicine and Ionian Area, Clinic of Infectious Diseases, University of Bari
224. Pari Vrindha, Chennai Critical Care Consultants Private Limited, Chennai, India
225. Parise Nicoletta, Department of Statistical Sciences, University of Padua
226. Parotto Emanuela, Dipartimento di Chirurgia DIDAS, Unità Operativa Complessa (UOC) Istituto Anestesia e Rianimazione, Azienda Ospedale Università, Padua, Italy
227. Patti Giulia, Clinic of Infectious Diseases, Department of Precision and Regenerative Medicine and Ionian Area (DiMePRe-J), University of Bari Aldo Moro
228. Pell Christopher, Amsterdam Institute for Global Health and Development, Amsterdam, The Netherlands
229. Pellegrino Carmen, Clinic of Infectious Diseases, Department of Precision and Regenerative Medicine and Ionian Area (DiMePRe-J), University of Bari Aldo Moro
230. Pereira Snehal Pinto, Department of Targeted Intervention, University College London, London, UK
231. Pietravalle Andrea, Doctors with Africa CUAMM, Italy
232. Pisani Luigi, Operational Research Unit, Doctors With Africa CUAMM, Padua, Italy
233. Pizzol Damiano, Operative Research Unit, Doctors with Africa Cuamm, Beira 1100, Mozambique
234. Poletti Piero, Center for Health Emergencies, Bruno Kessler Foundation, Trento
235. Pozniak Anton, Chelsea and Westminster Hospital NHS Foundation Trust and LSHTM, London, UK
236. Prato Rosa, Scuola di specializzazione in Igiene e medicina preventiva, Dipartimento di Scienze mediche e chirurgiche, Università di Foggia
237. Putoto Giovanni, Doctors with Africa CUAMM, Italy
238. Quaglio Gianluca, Medical Preparedness and Crisis Management Unit (MPCMU), Directorate-General for Personnel, European Parliament, Brussels, Belgium
239. Ragazzoni Luca, CRIMEDIM - Center for Research and Training in Disaster Medicine, Humanitarian Aid and Global Health, Università del Piemonte Orientale, Novara, Italy
240. Raho Lucia, octors with Africa CUAMM, 70123 Bari, Italy
241. Ramirez Lucy, Doctors with Africa CUAMM,Mozambique
242. Rashan Aasiyah, Institute of Health Informatics, University College London, London, UK
243. Rehema Itambu, Doctors with Africa CUAMM, Tanzania
244. Rescigno Maria, IRCCS Humanitas Research Hospital, Milan
245. Resti Carlo, Doctors with Africa CUAMM, Addis Ababa, Ethiopia
246. Reynolds Lindsey, The Ethics Lab, Neuroscience Institute, Department of

Medicine, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa
247. Ribichini Danilo, Alma Mater Studiorum University of Bologna, Department of Medical and Surgical Sciences DIMEC, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Division of Endocrinology and Diabetes Prevention and Care, Bologna, Italy
248. Ricciardi Aurelia, Clinic of Infectious Diseases, Department of Biomedical Sciences and Human Oncology, University of Bari, Bari, Italy
249. Righini Matteo, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Nephrology- Dialysis and Renal Transplant Unit, Bologna, Italy, Alma Mater Studiorum, Alma Mater Studiorum University of Bologna, Bologna, Italy
250. Righy Cassia, National Institute of Infectious Diseases, Oswaldo Cruz Foundation, Rio de Janeiro, Brazil
251. Rinke de Wit Tobias F., Amsterdam UMC, Department University of Amsterdam, Department of Global Health, Amsterdam Institute for Global Health and Development
252. Ronzoni Niccolò, Doctors with Africa CUAMM Mozambique, Department of Infectious-Tropical Diseases and Microbiology, IRCCS Sacro Cuore Don Calabria Hospital, Verona, Italy
253. Rossi Elisa, Doctors with Africa CUAMM,Tanzania
254. Saide Cássimo Manuel, Mozambique
255. Salluh Jorge, D'Or Institute for Research and Education, Sao Paulo, Brazil
256. Salvador Luca, Operational Research Unit, Doctors with Africa CUAMM, Kampala, Uganda; Department of Surgical, Oncological and Gastroenterological Sciences, University of Padova
257. Santini Stefano, Doctors with Africa CUAMM, Italy
258. Saracino Annalisa, Department of Precision and Regenerative Medicine and Ionian Area, Clinic of Infectious Diseases, University of Bari
259. Sarmati Loredana, Clinical Infectious Diseases, Department of System Medicine, Tor Vergata University, Rome, Italy
260. Scapini Ester, Anesthesia and Intensive Care Medicine, University of Bari, Bari, Italy
261. Schiavone Marcella, Doctors with Africa CUAMM, 70123 Bari, Italy
262. Schultz Marcus, Intensive Care Medicine, University of Amsterdam, Amsterdam, The Netherlands
263. Segala Francesco Vladimiro, Department of Precision and Regenerative Medicine and Ionian Area, Clinic of Infectious Diseases, University of Bari
264. Sendagire Cornelius, Uganda Heart Institute, University of Makerere, Makerere, Uganda, D'Or Institute for Research and Education, Sao Paulo, Brazil
265. Sesay Amadu, Princess Christian Maternity Hospital, University of Sierra Leone Teaching Hospital Complex, Fourah Bay Road, Freetown 00232, Sierra Leone
266. Sesay Tom, Ministry of Health and Sanitation, Freetown, Sierra Leone
267. Severini Carlo, Department of Infectious Diseases, Istituto Superiore di Sanità, Rome, Italy
268. Sgorbissa Beatrice, Hygiene and Public Health Unit, DCTVSP, University of Padova, Italy
269. Siaw-frimpong Moses, Department of Anaesthesiology and Intensive care, Komfo Anokye Teaching Hospital, Kumasi, Ghana
270. Smith Lee, Centre for Health, Performance and Wellbeing, Anglia Ruskin University, Cambridge CB1 1PT, UK
271. Somigliana Edgardo, IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano, Milan, Italy
272. Spada Vito, Clinic of Infectious Diseases, Department of Precision and Regenerative Medicine and Ionian Area (DiMePRe-J), University of Bari Aldo Moro
273. Ssembuusi John, Matany Saint Kizito Hospital, Moroto, Uganda
274. Strepparava Maria Grazia, Clinical Psychology Unit, San Gerardo Hospital, Monza, Italy
275. Surenthirakumaran Rajendra, Department of Community and Family Medicine, University of Jaffna, Jaffna, Sri Lanka
276. Susini Maria Chiara, Doctors with Africa CUAMM, Ethiopia
277. Taddei Stefano, University of Pisa, Italy
278. Taliente Francesco, Doctors with Africa CUAMM, Uganda
279. Taylor Williamson, Princess Christian Maternity Hospital, University of Sierra Leone Teaching Hospitals Complex, Freetown, Sierra Leone
280. Teklie Bereket Gebremedhin, Jinka General Hospital, Jinka, South Omo, Ethiopia
281. Thomson David, Department of Anaesthesia and Perioperative Medicine, University of Cape Town, Cape Town, South Africa
282. Thwaites C. Louise, Nuffield Department of Medicine, University of Oxford, Oxford, UK, Oxford University Clinical Research Unit, University of Oxford, Ho Chi Minh City, Vietnam
283. Tilahun Melaku, Armauer Hansen Research Institute, Addis Ababa, Ethiopia
284. Tiru Nitsuh, Princess Christian Maternity Hospital, Freetown, Sierra Leone
285. Tognon Francesca, Doctors with Africa CUAMM, Italy
286. Toitole Kusse Koirita, Doctors with Africa CUAMM, Jinka, South Omo, Ethiopia
287. Tolera Jiksa, Neonatal Intensive Care Unit, St Luke Catholic Hospital, Wolisso, Ethiopia
288. Tolppa Timo, Nat-Intensive Care Surveillance, Mahidol Oxford Tropical Medicine Research Unit, Colombo, Sri Lanka
289. Tomás Joaquim, Doctors with Africa CUAMM, Angola
290. Torelli Giovanni F., Doctors with Africa CUAMM, Dar Es Salaam, Tanzania. Policlinico Umberto I, Rome, Italy
291. Totaro Valentina, Clinic of Infectious Diseases, Department of Precision and Regenerative Medicine and Ionian Area (DiMePRe-J), University of Bari Aldo Moro
292. Trentini Filippo, Center for Health Emergencies, Bruno Kessler Foundation, Trento
293. Trevisanuto Daniele, Department of Woman's and Child's Health, University Hospital of Padua
294. Trifirò Silvia, Doctors with Africa CUAMM, Iringa, Tanzania, Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy
295. Tripathy Swagata, Centre for Inflammation Research, University of Edinburgh, Edinburgh, UK, All India Institute of Medical Sciences, New Delhi, India
296. Tsegaye Ademe, Saint Luke Hospital, Wolisso, Ethiopia
297. Tulone Ottavia, Geriatric Unit, Department of Internal Medicine and Geriatrics, University of Palermo
298. Turay Momoh Sitta, Princess Christian Maternity Hospital, University of Sierra Leone Teaching Hospitals Complex, Freetown, Sierra Leone
299. Udayanga Ishara, Nat-Intensive Care Surveillance, Mahidol Oxford Tropical Medicine Research Unit, Colombo, Sri Lanka
300. Valente Martina, CRIMEDIM - Center for Research and Training in Disaster Medicine, Humanitarian Aid and Global Health, Università del Piemonte Orientale, Novara, Italy
301. Vengadasalam Sutharshan, Teaching Hospital Jaffna, Jaffna, Sri Lanka
302. Veronese Nicola, Geriatric Unit, Department of Internal Medicine and Geriatrics, University of Palermo
303. Vetrano Daniele, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Nephrology- Dialysis and Renal Transplant Unit, Bologna, Italy, Alma Mater Studiorum, Alma Mater Studiorum University of Bologna, Bologna, Italy
304. Vicennati Valentina, Alma Mater Studiorum University of Bologna, Department of Medical and Surgical Sciences DIMEC,

IRCCS Azienda Ospedaliero-Universitaria di Bologna, Division of Endocrinology and Diabetes Prevention and Care, Bologna, Italy
305. Vijayaraghavan Bharath Kumar Tirupakuzhi, Department of Critical Care Medicine, Apollo Hospitals Educational and Research Foundation, Chennai, India
306. Wagstaff Duncan, Department of Anaesthesia and Perioperative Medicine, University of Cape Town, Cape Town, South Africa, Centre for Preoperative Medicine, University College London, London, UK
307. Waweru-Siika Wangari, Department of Anaesthesia, The Aga Khan University, Nairobi, Kenya
308. Yelshazly Mohmaoud, Department of Research, Faculty of Health Sciences, Universidade Catolica de Mocambique, Beira, Mozambique
309. Zainab Bah, Government of Sierra Leone Ministry of Health and Sanitation, Freetown, Western Area, Sierra Leone
310. Zarcone Maurizio, Unità Operativa Complessa di Epidemiologia Clinica con Registro Tumori, Azienda Ospedaliera Universitaria Policlinico "Paolo Giaccone", Palermo, Italy
311. Zardini Agnese, Center for Health Emergencies, Bruno Kessler Foundation, Trento
312. Zin Annachiara, Division of Pediatric Infectious Diseases, Department of Women's and Children's Health, University of Padua, Padua, Italy
313. Zucula Helton, Department of Paediatry, Central Hospital of Maputo, Maputo 1113, Mozambique

“The resources are there if we look for them; so are the research agendas. There are plenty of tools and helpful technologies. Yet those simple but precious ingredients – curiosity and humility – remain necessary even now”.

“Non mancano le risorse se le cerchiamo, neppure le agende di ricerca, se lo vogliamo. Gli strumenti abbondano, la tecnologia aiuta. Tutto vero. Dobbiamo metterci però gli ingredienti di base: curiosità e umiltà”.