Reducing the burden of tuberculosis and sepsis in Gabon

Clinical and epidemiological investigations for improved control

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ter verkrijging van de graad van doctor aan de Universiteit van Amsterdam op gezag van de Rector Magnificus prof dr. ir. K.I.J. Maex
ten overstaan van een door het College voor Promoties ingestelde commissie, in het openbaar te verdedigen in de Agnietenkapel op donderdag 28 Juni 2023, te 16.00 uur

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Faculteit der Geneeskunde

“ Ìhòhò dodo làgbàdo ńwọ ilẹ̀; tó bá jáde tán, ló ńdi onígba aṣọ.”
Yorouba proverb, Adebo Adetola

English translation and meaning: The maize seed is sown unclad but bursts forth from the ground with multiple coverings. Nothing lasts forever; keep your faith in your dreams alive.

Traduction et signification : La graine de maïs est semée nue mais jaillit du sol avec de multiples revêtements. Rien ne dure éternellement ; Garde foi en tes rêves.

La connaissance est le seul bien précieux dont le partage ne fait qu’en augmenter la valeur (Ayinla Omou Akin)

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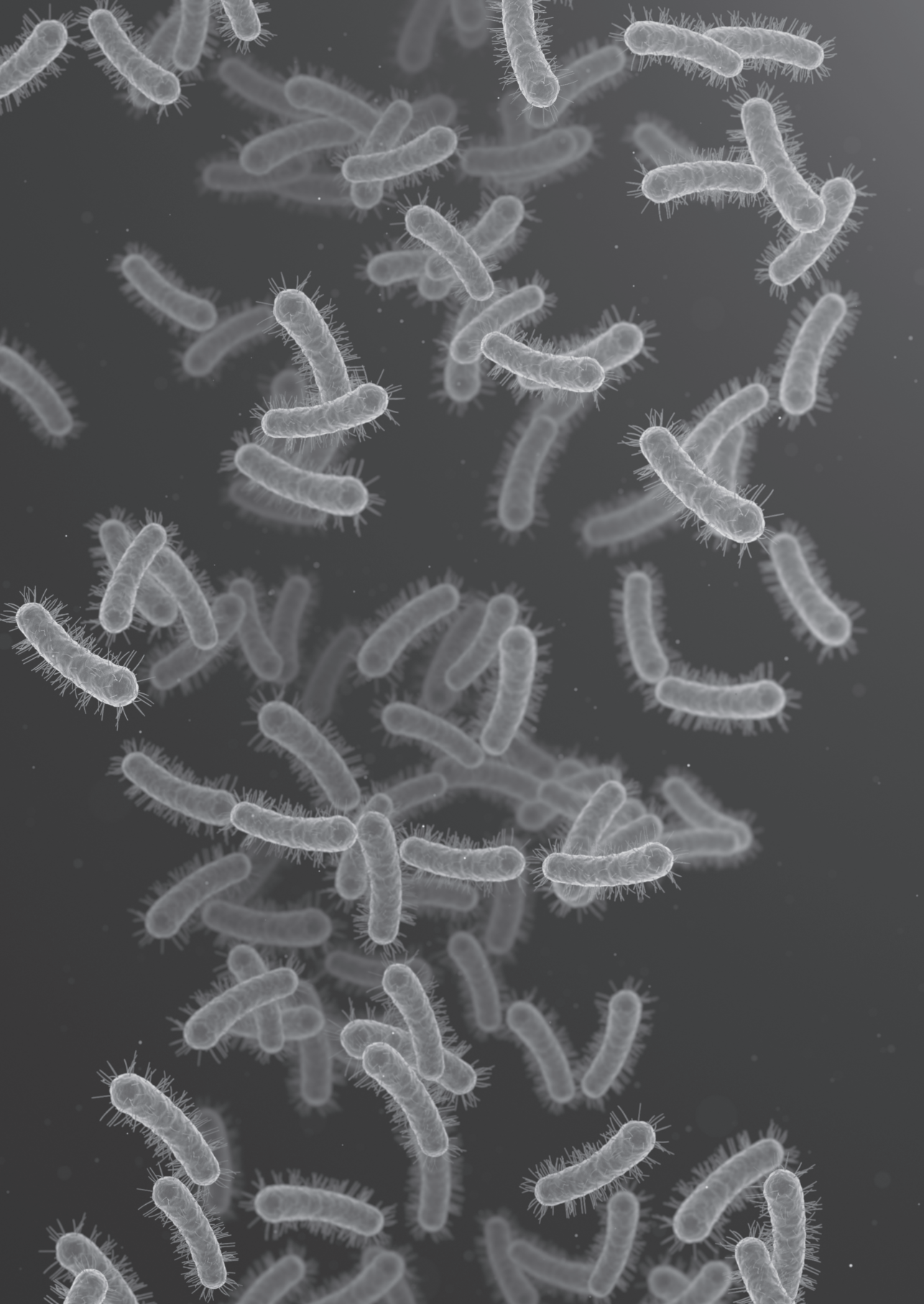


Chapter 1

General Introduction and Outline

Background

Tuberculosis (TB) and sepsis are global health threats [1, 2]. Each year, an estimated 1.5 and 11 million people died of tuberculosis and sepsis [1, 3]. Most tuberculosis and sepsis cases occur in Low and Middle-Income Countries (LMICs) [3, 4]. Gabon is a sub-Saharan MIC, with 2.17 million inhabitants (2020 estimation) listed in the top 30 tuberculosis/HIV high-burden countries [4] by the World Health Organization (WHO). Its TB epidemiological profile is characterised by, a high rate of treatment interruption or discontinuation, a low treatment success rate and a relatively high rate of mortality [5,6]. In a previous study, the most common reasons reported for treatment discontinuation or default were non-affordability of transportation costs, forgetting drug intake, side effects and long duration of cough before diagnosis [6]. Following that, the health authorities readjusted the tuberculosis control guideline and control activities (including decentralising treatment management and health workers' training). However, tuberculosis remains a major public health issue in Gabon. This is likely because some factors known to be contributing to the TB burden are under-investigated and poorly controlled. On this list of contributors, delays in the diagnosis of drug-resistant tuberculosis and non-communicable diseases comorbidities (NCDs-TB) feature prominently [7,8]. Earlier diagnoses of non-communicable diseases such as diabetes improve tuberculosis treatment outcomes [9–12].

On the other hand, some studies showed that *Mycobacterium tuberculosis* is one of the frequent aetiologies of sepsis and it is associated with a higher risk of death in sub-Saharan hospitalised adult patients [13–15]. Sepsis is a life-threatening complication of infection. It is one of the neglected silent killers in Gabon [16]. This is likely due to the low awareness of many health workers and the absence of a sepsis data reporting system. The studies in this thesis highlight the areas requiring urgent actions for reducing the burden of tuberculosis and sepsis in Gabon.

Tuberculosis

History of tuberculosis

Documentation of the first cases of tuberculosis (TB) dates back to 8000 before Christ and was found in the spinal cords of Egyptian mummies [17]. In 1679, a Dutch researcher, Franciscus Sylvius, provided the first anatomical-pathological description of TB [18]. In 1877, Robert Koch developed a staining technique to visualise *Mycobacterium tuberculosis* (Mtb) and described the transmission of tuberculosis through droplets released while coughing [19, 20]. The first antibiotic agent effective against TB was streptomycin developed by Selman Waksman in 1943 [21]. However, its toxicity profile and the necessity to inject it deep into the muscle made it inconvenient for a longer treatment duration. In

1950, isoniazid was developed and showed good bactericidal properties, rendering it a favoured first-line agent against TB [22]. Rifampicin was developed and marketed some years later (1968), by Dow-Lepetit Research Laboratories (Milan, Italy), and become with isoniazid, the keys antibiotics for treating tuberculosis [22].

Epidemiology of tuberculosis

The global number of TB cases has remained stable since the beginning of the 21st century [23]. People infected with Mtb have a 5–10% lifetime risk of falling ill with TB [24]. The WHO 2021 global TB report estimated that 10 million people developed TB worldwide [1]. One-out-of-four new TB cases reported worldwide occurred in the WHO African Region [1] (Figure 1). Undernutrition, HIV infection, alcohol use disorders, smoking, and diabetes are associated with many new cases of TB [24]. Delays in diagnosis and comorbidities are the main cause of death in TB patients [25,26]. The epidemiological transition led to an increased prevalence of NCDs (including diabetes and cardiovascular diseases) in LMICs, where the burden of infectious diseases, such as tuberculosis, remains high. In many LMICs, the true dimensions of the TB and NCDs comorbidity problem have not yet been fully understood, and more data is needed [27].

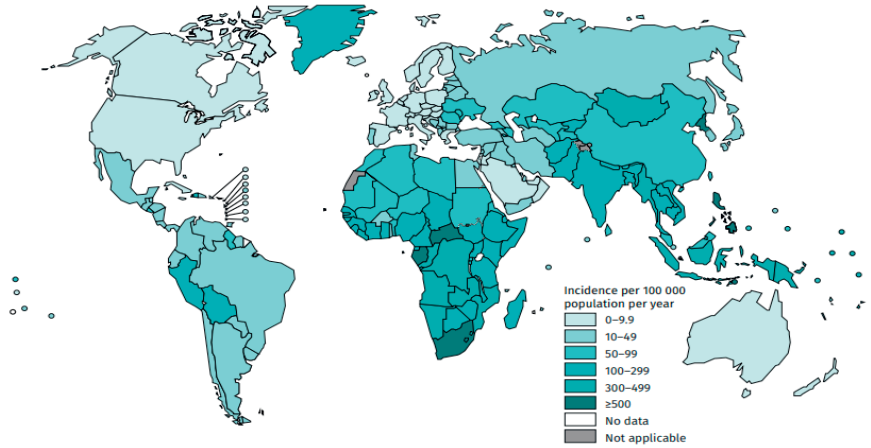


Figure 1: Estimated TB incidence rates, in 2020.(WHO, TB global report 2021)

One of the other challenges facing LMICs is the multidrug-resistant TB (MDR-TB) crisis. Only one in three people with drug-resistant TB accessed treatment in 2020 [24]. WHO estimated the TB incidence in Gabon at 527 per 100,000 inhabitants in 2020 [28], which is amongst the highest worldwide. Bélard and collaborators, in 2016, reported a worrying situation of drug-resistant tuberculosis in the Moyen-Ogooué region where the prevalence of MDR-TB in new patients and previously treated patients was 4% and 31%, respectively [6,29]. Before this thesis, the real national burden of drug-resistant tuberculosis was not known.

Sepsis

History

Sepsis was not clearly defined until the 20th century, because of the lack of knowledge of its pathophysiology [30]. In 1914, Hugo Schottmüller attempted a modern definition suggesting that "sepsis is an invasion from a portal of entry into the bloodstream causing severe illness" [31]. Many studies have been performed to understand the role of the

Table 1. Definitions of sepsis over time, from 1991 to 2016,(adapted from Gül et al. Changing Definitions of Sepsis[38])

DEFINITIONS OF SEPSIS		
Sepsis 1 (ACCP 1991) **Systemic inflammatory response syndrome (SIRS):** Temperature >38°C or <36°C; heart rate > 90 beats per min; respiratory rate > 20 breaths per min or PaCO2 < 32 mmHg; and white blood cell count > 12,000/cu mm, <4000/cu mm, or >10% immature (band) forms **Sepsis**: infection + Two or more of the SIRS criteria **Severe sepsis**: Sepsis associated with organ dysfunction, hypoperfusion, or hypotension; hypoperfusion and perfusion abnormalities. Septic shock: Sepsis-induced, with hypotension despite adequate fluid resuscitation along with the presence of perfusion abnormalities	**Sepsis 2 (ACCP 2001)** Infection: Documented or suspected and some of the following: **General parameters:** Fever (core temperature > 38.3°C); hypothermia (core temperature < 36°C); heart rate > 90 beats per min tachypnoea: respiratory rate > 30 breaths per min; altered mental status; significant oedema **Inflammatory parameters:** Leucocytosis (white blood cell count > 12,000/μL); leukopenia (white blood cell count < 4000/μL); normal white blood cell count with > 10% immature forms; **Hemodynamic parameters:** Arterial hypotension (systolic blood pressure < 90 mmHg, Mean arterial pressure (MAP) < 70 mmHg, or a systolic blood pressure decrease > 40 mmHg in adults **Organ dysfunction parameters:** Arterial hypoxemia (PaO2/FIO2 < 300); acute oliguria; creatinine increase 0.5 mg dL–1; coagulation abnormalities (international normalised ratio > 1.5 or activated partial thromboplastin time > 60 s); thrombocytopenia (platelet count < 100,000 μL–1) Hyperbilirubinemia (plasma total bilirubin > 4 mg dL–1 or 70 mmol L–1) **Tissue perfusion parameters:** Hyperlactatemia (>3 mmol L–1); decreased capillary refill or mottling	**Sepsis 3 (ESICM, 2016)** Sepsis is a life-threatening organ dysfunction caused by the dysregulated host response to infection. **Clinical criteria for sepsis**: Suspected or documented infection and an acute increase of 2 SOFA points The task force considered that positive qSOFA (quick SOFA) criteria should also prompt consideration of possible infection in patients not previously recognised as infected. **Septic shock** sepsis with persisting hypotension, requiring vasopressor therapy to elevate MAP 65 mmHg and lactate > 2 mmol L–1 (18 mg dL–1) despite adequate fluid resuscitation

host immune response in the onset and manifestations of sepsis [32, 33]. These studies demonstrated that sepsis is a consequence of a dysregulated physiological response to infection by injuring its tissues and organs. Due to serious difficulties in recognising, treating, and studying sepsis, the need for more precise terminology became evident both for clinicians and researchers. Many consensus definitions have been suggested and improved from 1991 to 2016 (Table 1). The first one (1991, Sepsis1) was developed by the American College of Chest Physicians and the Society of Critical Care Medicine(ACCP) which defined the systemic inflammatory response syndrome (SIRS), sepsis(at least two criteria of SIRS plus infection), severe sepsis, and septic shock [34]. It was revised modestly in 2001 (Sepsis 2), to expand the list of signs and symptoms of sepsis to reflect clinical bedside experience without changing the definitions [35]. These definitions have been used for a long time and improved clinical recognition and management of sepsis and septic shock [30]. However, the SIRS score leads to overdiagnosis of sepsis [36]. In February 2016, the European Society of Intensive Care Medicine (ESICM) published new consensus definitions of sepsis and related clinical criteria (Sepsis 3). The most significant changes were the abandonment of the terms SIRS and severe sepsis. The new definition of sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection [37].

Epidemiology of sepsis

In 2020, the estimated worldwide incidence of sepsis was 48.9 million [39]. The meta-analysis reported by Fleischmann-Struzek and colleagues on the global incidence of sepsis reported a pooled incidence of 189 cases per 100 000 persons [40]. The burden of sepsis among people living in LMICs would be higher than those in high-income countries (HICs) [39, 41]. The true global burden of sepsis is underestimated because most of the data are derived from HICs. Many reasons explain the limited reports on the epidemiology, management, and outcomes of sepsis in LMICs. Firstly, sepsis is often misdiagnosed or fails to be documented in the clinical notes. Secondly, many LMICs do not have contextualised guidelines for diagnosis and report of sepsis. Finally, the low awareness and limited resources contribute significantly to the absence of sepsis as the top priority of many LMICs' health systems. It is, therefore imperative to address this through improving awareness, capacity building, research, and the introduction of practical clinical guidelines [42].

Sepsis can be caused by all types of pathogens, including bacteria, fungi, viruses, and parasites [43]. There is no national data related to sepsis in Gabon. However, studies from the Lambaréné region(Albert Schweitzer Referral Hospital) suggest its association with a higher risk of death in both the emergency department and medicine ward [44, 45]. In the cohort of patients recruited for one year (2012-2013), the incidence of sepsis in the Albert Schweitzer referral Hospital (HAS) was 28% [44].

Diagnosis of sepsis

Sepsis symptoms and signs can be subtle and easily mistaken for manifestations of other disorders. Typically, the common symptoms and signs are fever or hypothermia and shivering, tachycardia, tachypnoea, altered mentation, extreme body pain or discomfort, and other specific signs of the causative infection. However, these signs are not specific to sepsis and call for further investigations to identify any signs of organ dysfunction. Organ dysfunction is defined in terms of a change in baseline sequential organ failure assessment score (SOFA). SOFA is a composite score based on six different individual scores; one for each of the respiratory, cardiovascular, hepatic, coagulation, renal, and neurological systems (Table 2). Each system scores from 0 to 4, with an increasing score reflecting worsening organ dysfunction [46]. However, SOFA components can be unfamiliar and require laboratory assessments not typically obtained routinely outside the intensive care unit. Therefore, a bedside clinical score termed quick SOFA (qSOFA), has been developed, consisting of altered mentation, respiratory rate of 22/min or greater, or systolic blood pressure of 100 mm Hg or less (Table 3). The qSOFA is performed to identify adult patients outside of the intensive care unit who are more likely to have poor outcomes of sepsis. It is used to prompt clinicians to further investigate organ dysfunction, initiate or escalate therapy as appropriate, and consider referral to critical care or increase the frequency of monitoring if such actions have not already been undertaken [37]. However, the performance of qSOFA as compared with SIRS in the early detection of patients suspected of sepsis is questionable and likely depends on the setting [47–50]. A further study from the LMICs setting is needed to contextualise the application of these scores.

Table 2. Sequential [Sepsis-Related] Organ Failure Assessment (SOFA) score (adapted from Vincent et al. [46])

Score	0-point	1 point
Respiratory rate ≥22 / min	No	Yes
Altered mental status (Glasgow score, <15)	No	Yes
Systolic blood pressure ≤ 100 mmHg	No	Yes

qSOFA≥ 2 indicate that patient has a greater risk of a poor outcome

Study site

The studies were performed at the Centre de Recherches Médicales de Lamabaréné (CERMEL) [51], Gabon (Figure 2a). Gabon is a country located in the central African region (Figure 2b) and has a wealth of natural resources, as much of its land mass is covered by primary rainforest. It shares borders with Cameroon, Equatorial Guinea, and the Republic of Congo on the Atlantic Ocean. More than 59% of residents live in Libreville(the capital city), the country's capital, and Port Gentil, the country's economic powerhouse [52].

Table 3. qSOFA (Quick SOFA) criterion

System /Score	0	1	2	3	4
Respiratory					
PaO2 / FiO2, mmHg	≥400	<400	<300	<200 with respiratory support	<100 with respiratory support
Coagulation					
Platelet count × 103 / mm3	≥ 150	< 150	< 100	< 50	< 20
Liver					
Bilirubin, mg / dL	<1.2	1.2-1.9	2.0-5.9	6.0-11.9	>12.0
Cardiovascular	MAP * ≥70 mm Hg	MAP <70 mm Hg	Dopamine <5 or	Dopamine 5.1-15	Dopamine>15
			dobutamine (all doses)	or epinephrine ≤0.1	epinephrine >0.1
				or norepinephrine ≤0.1	or norepinephrine >0.1
Central Nervous System					< 6
Glasgow Coma Scale	15	13-14	10-12	6-9	
Renal					>5.0
Creatine, mg/dL	<1.2	1.2-1.9	2.0-3.4	3.5-4.9	
Or					
Urine Output				< 500	< 200

Catecholamine doses are given as μg/kg/min for at least 1 hour. FiO2, a fraction of inspired oxygen; MAP, mean arterial pressure; PO2, partial pressure of oxygen.
*MAP = Diastolic blood pressure + 1/3 (Systolic blood pressure – Diastolic blood pressure)
SOFA score ≥ 2 indicates organ dysfunction

CERMEL is in Lambaréné in the Moyen Ogooué province. Lambaréné is 240 kilometres from Libreville, the capital city. Lambaréné holds two referral hospitals, Albert Schweitzer Hospital and Georges Rawiri regional Hospital (Figure 2c-d). Infectious diseases (including HIV, tuberculosis, malaria, and sepsis) are the first causes of hospitalisation in the two hospitals [44]. The two referral hospitals together have approximately 70,000 people in catchments. However, patients come from all other areas of the country. CERMEL, holding the national tuberculosis referral laboratory, is located at the Albert Schweitzer Hospital. CERMEL is the former medical research unit of the Albert Schweitzer Hospital established in 1981 [51].

Rationale and outline of this thesis

Despite current efforts, both tuberculosis and sepsis remain major public health issues in Gabon [28,43]. Both diseases require early diagnosis and good management (including co-morbidity). We hypothesised that there are significant contributors to the burden of tuberculosis and sepsis in Gabon that are not explored or controlled.

Regarding tuberculosis, current epidemiological data shows a low treatment success rate [28]. This remains unchanged for several years despite the actions taken [6]. Co-morbidities such as diabetes have been reported to be one of the factors associated with the high burden of tuberculosis in many LMICs settings [53,54]. This is an aspect of the tuberculosis epidemiological profile that has not yet been explored in Gabon.

Resistance to anti-tuberculosis drugs is a consequence of poor treatment adherence. Gabon is classified as a Middle-Income Country and receives very little external support for TB control. The major portion of the cost of tuberculosis treatment and related fees (except for drug procurement) is to be paid by patients. This causes a delay in consulting health care facilities, treatment discontinuation and a high rate of loss to follow-up. Highlighting the growing incidence of drug-resistant TB in Gabon would alert the need to take urgent and adapted control actions to change the trend.

The high rate (17%) of death due to sepsis reported by the retrospective studies and routine data from the emergency department of Lambaréné referral hospital (HAS) [44], calls for attention. It is well established that the first three hours are crucial to increase the chance of survival of patients with sepsis. This requires good awareness from the practitioner for initiating appropriate actions (Surviving sepsis campaign: international guidelines for the management of sepsis and septic shock 2021) [55]. We hypothesised that the health workers in Lambaréné are not sufficiently aware of the international guideline for the diagnosis and management of sepsis; furthermore, we investigated the performances of fours scores: Quick Sequential Organ Failure Assessment(qSOFA), Systemic Inflammatory Response Syndrome Criteria (SIRS), Universal Vital Assessment

(UVA), and Modified Early Warning Score(MEWS), in predicting sepsis in Lambaréné adult patients with infection.

Considering all the above, it appears that the co-morbidity of non-communicable diseases and tuberculosis, the resistance to anti-tuberculosis drugs, and awareness of health workers about sepsis are among areas that need to be investigated to suggest new actions to reduce the burden of tuberculosis and sepsis in Gabon.

Part 1: Non-communicable disease in tuberculosis patients in Gabon,

examines the NCDs burden in tuberculosis patients in Gabon. **Chapter 2** studies non-communicable disease comorbidity and associated factors in tuberculosis patients. **Chapter 3** reports the effect of smoking on the epidemiological, mycobacteriological, and clinical characteristics of pulmonary tuberculosis.

Part 2: Drug-resistant tuberculosis in Gabon,

addresses the urgency of the until the very recently unrecognised massive burden of drug-resistant tuberculosis (DR-TB) in Gabon. **Chapter 4** reports a trends-over-eight years analysis of national drug-resistant TB data and the resistance patterns, while **Chapter 5** is a study on the implementation of a short regimen for multidrug-resistant tuberculosis treatment in Gabon.

Part 3: Improving sepsis diagnosis and awareness,

discusses the problem of sepsis, which for a long has been neglected as a topic of high relevance for LMICs. **Chapter 6** is a systematic review and meta-analysis of tuberculosis sepsis clinical features and epidemiology in HIV-negative patients. **Chapter 7** is a study assessing the performances of the qSOFA, SIRS, UVA, and MEWS to predict mortality in patients with suspected infection in Gabon, while **Chapter 8** is a systematic review and meta-analysis comparing the different scores for diagnosis and mortality prediction of adults with sepsis in Low-and-Middle-Income Countries. **Chapter 9** describes the knowledge of health workers relating to sepsis awareness and management in Lambaréné. **Chapter 10** is a qualitative study on the learning lessons from engagement with Gabon's health policy stakeholders on recognising sepsis as a health priority.

REFERENCES

1. World Health Organization. Global tuberculosis report 2021. Geneva: WHO; 2021. http://apps.who.int/iris. Accessed 09 May 2022.
2. World Health Organization. Sepsis. Geneva: WHO.2018. https://www.who.int/news-room/fact-sheets/detail/sepsis. Accessed 28 Apr 2022.
3. World Health Organization calls for global action on sepsis - cause of 1 in 5 deaths worldwide. Geneva: WHO.2020. https://www.who.int/news/item/08-09-2020-who-calls-for-global-action-on-sepsis-cause-of-1-in-5-deaths-worldwide. Accessed 19 May 2022.
4. World Health Organization. Global lists of high-burden countries for TB, multidrug/rifampicin-resistant TB (MDR/RR-TB) and TB/HIV, 2021–2025. Geneva: World Health Organization; 2021. http://apps.who.int/bookorders. Accessed 19 Jan 2022.
5. What causes the most deaths, in Gabon? Institute for Health Metrics and Evaluation; 2015. https://www.healthdata.org/gabon. Accessed 08 Feb 2021
6. Bélard S, Remppis J, Bootsma S, Janssen S, Kombila DU, Beyeme JO, et al. Tuberculosis Treatment Outcome and Drug Resistance in Lambaréné, Gabon: A Prospective Cohort Study. Am J Trop Med Hyg. 2016;95:472–80.
7. Castañeda-Hernández DM, Rodriguez-Morales AJ. Epidemiological Burden of Tuberculosis in Developing Countries. IntechOpen; 2013;15:318-339
8. Martins-Melo FR, Bezerra JMT, Barbosa DS, Carneiro M, Andrade KB, Ribeiro ALP, et al. The burden of tuberculosis and attributable risk factors in Brazil, 1990–2017: results from the Global Burden of Disease Study 2017. Popul Health Metr. 2020;18 (Suppl 1):10.
9. Faurholt-Jepsen D, Range N, PrayGod G, Jeremiah K, Faurholt-Jepsen M, Aabye MG, et al. Diabetes is a strong predictor of mortality during tuberculosis treatment: a prospective cohort study among tuberculosis patients from Mwanza, Tanzania. Trop Med Int Health. 2013;18:822–9.
10. Viswanathan V, Vigneswari A, Selvan K, Satyavani K, Rajeswari R, Kapur A. Effect of diabetes on treatment outcome of smear-positive pulmonary tuberculosis—A report from South India. J Diabetes Complications. 2014; 28:162–5.
11. Cavanaugh J, Viney K, Kienene T, Harley D, Kelly PM, Sleigh A, et al. Effect of diabetes on tuberculosis presentation and outcomes in Kiribati. Trop Med Int Health. 2015 May; 20(5): 643–649
12. Kornfeld H, Sahukar SB, Procter-Gray E, Kumar NP, West K, Kane K, et al. Impact of Diabetes and Low Body Mass Index on Tuberculosis Treatment Outcomes. CID 2020: 71(9):e392-e398
13. Lewis JM, Feasey NA, Rylance J. Aetiology and outcomes of sepsis in adults in sub-Saharan Africa: a systematic review and meta-analysis. Crit Care Lond Engl. 2019;23(1):212.
14. Jacob ST, Pavlinac PB, Nakiyingi L, Banura P, Baeten JM, Morgan K, et al. Mycobacterium tuberculosis Bacteremia in a Cohort of HIV-Infected Patients Hospitalised with Severe Sepsis in Uganda–High Frequency, Low Clinical Sand Derivation of a Clinical Prediction Score. PLOS ONE. 2013;8:e70305.
15. Barr DA, Lewis JM, Feasey N, Schutz C, Kerkhoff AD, Jacob ST, et al. Mycobacterium tuberculosis bloodstream infection prevalence, diagnosis, and mortality risk in seriously ill adults with HIV: a systematic review and meta-analysis of individual patient data. Lancet Infect Dis. 2020;20:742–52.

16. Ranjit S, Kissoon N. Challenges and Solutions in translating sepsis guidelines into practice in resource-limited settings. Transl Pediatr. 2021;10:2646–65.

17. Zink AR, Sola C, Reischl U, Grabner W, Rastogi N, Wolf H, et al. Characterisation of Mycobacterium tuberculosis Complex DNAs from Egyptian Mummies by Spoligotyping. J Clin Microbiol. 2003;41:359–67.

18. H. Herzog B. History of Tuberculosis. Respiration. 1998;65:5–15.

19. Daniel TM. The history of tuberculosis. Respir Med. 2006;100:1862–70.

20. Blevins SM, Bronze MS. Robert Koch and the 'golden age' of bacteriology. Int J Infect Dis. 2010; 14:e744–51.

21. Schatz A, Bugle E, Waksman SA. Streptomycin, a Substance Exhibiting Antibiotic Activity Against Gram-Positive and Gram-Negative Bacteria. Proc Soc Exp Biol Med. 1944;55:66–9.

22. Prabhu R, Singh V. The History of Tuberculosis: Past, Present, and Future. Adv Microbiol. 2019;09:931–42.

23. Glaziou P, Floyd K, Raviglione M. Global Epidemiology of Tuberculosis. Semin Respir Crit Care Med. 2018;39:271–85.

24. Word Health Organization. Tuberculosis. WHO.Geneva.2021 https://www.who.int/news-room/fact-sheets/detail/tuberculosis. Accessed 8 Apr 2022.

25. Word Health Organization. Tuberculosis deaths rise for the first time in more than a decade due to the COVID-19 pandemic. WHO. Geneva. 2021 https://www.who.int/news/item/14-10-2021-tuberculosis-deaths-rise-for-the-first-time-in-more-than-a-decade-due-to-the-covid-19-pandemic. Accessed 8 Apr 2022.

26. Simonovska L, Trajcevska M, Mitreski V, Simonovska I. The causes of death among patients with tuberculosis. Eur Respir J. 2015;37:46- 59.

27. Creswell J, Raviglione M, Ottmani S, Migliori GB, Uplekar M, Blanc L, et al. Tuberculosis and non-communicable diseases: neglected links and missed opportunities. Eur Respir J. 2011; 37:1269–82.

28. Word Health Organization. Tuberculosis Country Profile. WHO. Geneva; 2020. https://worldhealthorg.shinyapps.io/tb_profiles/?_inputs_&entity_type=%22country%22&lan=%22EN%22&iso2=%22GA%22. Accessed 08 Feb 2021.

29. Bélard S, Janssen S, Osbak KK, Adegnika AA, Ondounda M, Grobusch MP. Limited access to drugs for resistant tuberculosis: a call to action. J Public Health Oxf Engl. 2015;37:691–3.

30. Gotts JE, Matthay MA. Sepsis: pathophysiology and clinical management. BMJ 2016;353:i1585

31. Gyawali B, Ramakrishna K, Dhamoon AS. Sepsis: The evolution in definition, pathophysiology, and management. SAGE Open Med. 2019;7:1-13.

32. Chen X, Yin Y, Zhang J. Sepsis and immune response. World J Emerg Med. 2011;2:88–92.

33. Wiersinga WJ, Leopold SJ, Cranendonk DR, van der Poll T. Host innate immune responses to sepsis. Virulence. 2014;5:36–44.

34. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest. 1992;101:1644–55.

35. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Crit Care Med. 2003;31:1250–6.

36. Vincent J-L, Opal SM, Marshall JC, Tracey KJ. Sepsis definitions: time for change. Lancet Lond Engl. 2013;381:774–5.

37. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315: 801–10.

38. Gül F, Arslantaş MK, Cinel İ, Kumar A. Changing Definitions of Sepsis. Turk J Anaesthesiol Reanim. 2017;45:129–38.

39. Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievlan DR, et al. Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study. The Lancet. 2020;395:200–11.

40. Fleischmann-Struzek C, Mellhammar L, Rose N, Cassini A, Rudd KE, Schlattmann P, et al. Incidence and mortality of hospital- and ICU-treated sepsis: results from an updated and expanded systematic review and meta-analysis. Intensive Care Med. 2020;46:1552–62.

41. Finfer S, Machado FR. The Global Epidemiology of Sepsis. Does It Matter That We Know So Little? Am J Respir Crit Care Med. 2016;193:228–30.

42. Otu A, Elston J, Nsutebu E. Sepsis in Africa: practical steps to stem the tide. Pan Afr Med J. 2015;21:323.

43. Kwizera A, Urayeneza O, Mujyarugamba P, Baelani I, Meier J, Mer M, et al. Epidemiology and Outcome of Sepsis in Adults and Children in a Rural, Sub-Sahara African Setting. Crit Care Explor. 2021;3:e0592.

44. Huson MAM, Kalkman R, Stolp SM, Janssen S, Alabi AS, Beyeme JO, et al. The impact of HIV on presentation and outcome of bacterial sepsis and other causes of acute febrile illness in Gabon. Infection. 2015;43:443–51.

45. Huson MAM, Kalkman R, Grobusch MP, van der Poll T. Predictive value of the qSOFA score in patients with suspected infection in a resource-limited setting in Gabon. Travel Med Infect Dis. 2017;15:76–7.

46. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med. 1996;22:707–10.

47. Raith EP, Udy AA, Bailey M, McGloughlin S, MacIsaac C, Bellomo R, et al. Prognostic Accuracy of the SOFA Score, SIRS Criteria, and qSOFA Score for In-Hospital Mortality Among Adults With Suspected Infection Admitted to the Intensive Care Unit. JAMA. 2017;317:290–300.

48. Seymour CW, Liu VX, Iwashyna TJ, Brunkhorst FM, Rea TD, Scherag A, et al. Assessment of Clinical Criteria for Sepsis: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315:762–74.

49. Tusgul S, Carron P-N, Yersin B, Calandra T, Dami F. Low sensitivity of qSOFA, SIRS criteria and sepsis definition to identify infected patients at risk of complication in the prehospital setting and at the emergency department triage. Scand J Trauma Resusc Emerg Med. 2017; 25:108.

50. Abdullah SMOB, Sørensen RH, Dessau RBC, Sattar SMRU, Wiese L, Nielsen FE. Prognostic accuracy of qSOFA in predicting 28-day mortality among infected patients in an emergency department: a prospective validation study. Emerg Med J EMJ. 2019;36:722–8.

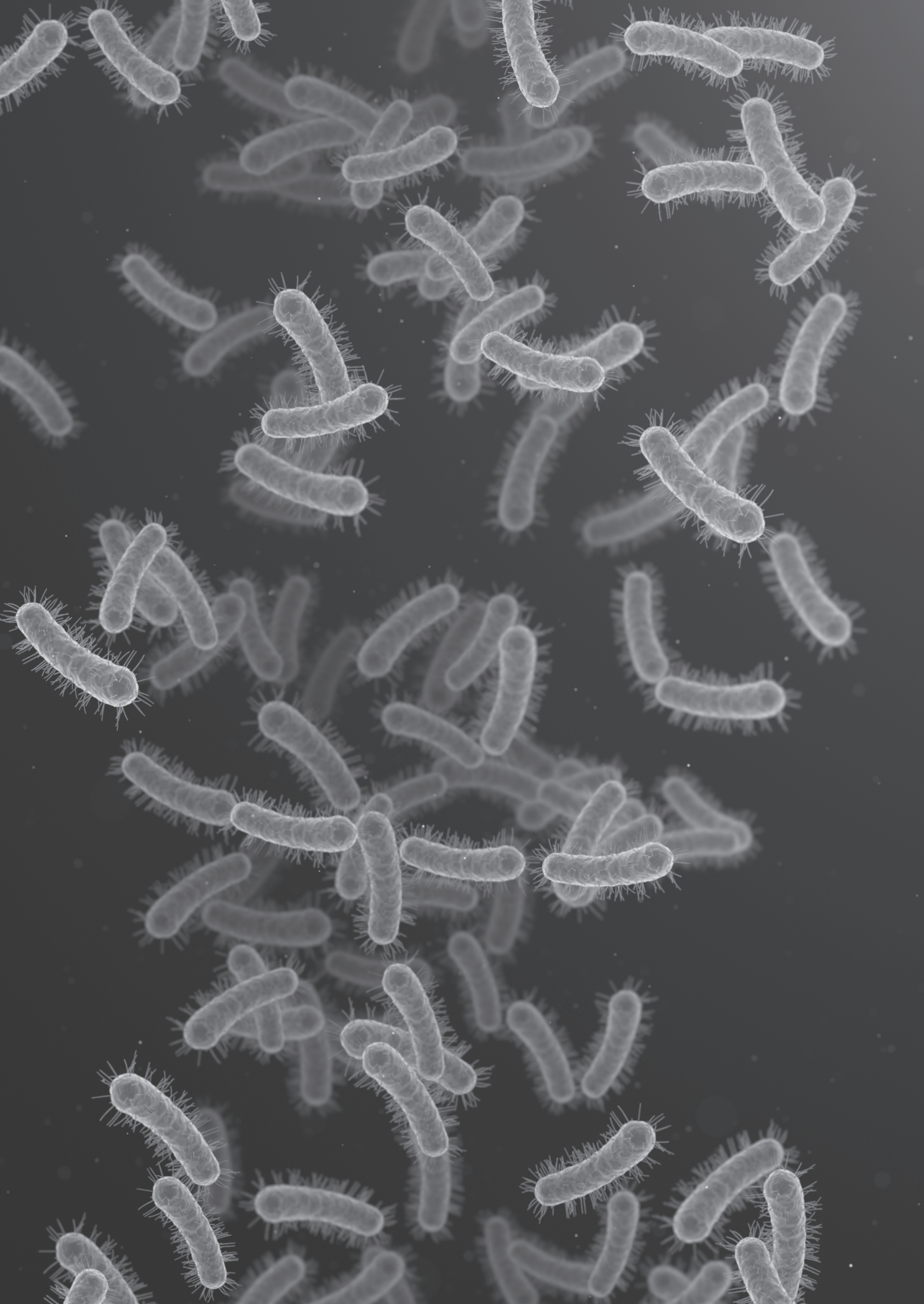
51. Ramharter M, Agnandji ST, Adegnika AA, Lell B, Mombo-Ngoma G, Grobusch MP, et al. Development of sustainable research excellence with a global perspective on infectious diseases: Centre de Recherches Médicales de Lambaréné (CERMEL), Gabon. Wien Klin Wochenschr. 2021;133:500–8.

52. Gabon population Data.net. PopulationData.net. https://www.populationdata.net/pays/gabon/. Accessed 08 Feb 2021

53. Gautam S, Shrestha N, Mahato S, Nguyen TPA, Mishra SR, Berg-Beckhoff G. Diabetes among tuberculosis patients and its impact on tuberculosis treatment in South Asia: a systematic review and meta-analysis. Sci Rep. 2021;11:2113.

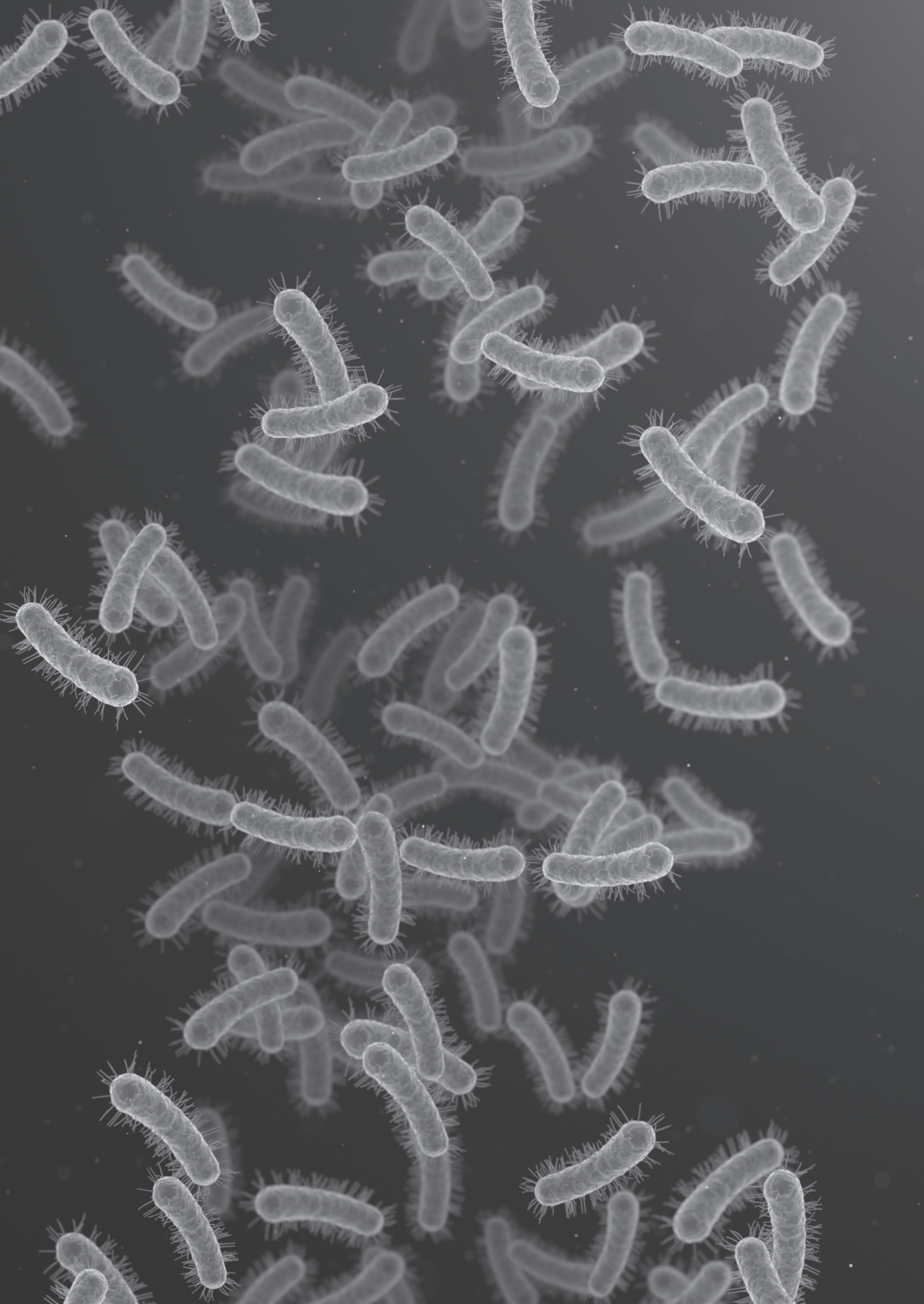
54. Liu Q, Li W, Xue M, Chen Y, Du X, Wang C, et al. Diabetes mellitus and the risk of multidrug resistant tuberculosis: a meta-analysis. Sci Rep. 2017;7:1090.

55. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med. 2021;47:1181–247.



Part 1

Non-communicable disease in tuberculosis patients in Gabon



Chapter 2

Non-communicable disease co-morbidity and associated factors in tuberculosis patients: A cross-sectional study in Gabon

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SUMMARY

Background: There are only limited data from resource-limited settings available on the prevalence of non-communicable diseases and associated risk factors of tuberculosis patients. This study investigated non-communicable disease co-morbidity in tuberculosis patients from Moyen Ogooué Province, Gabon.

Methods: All patients aged 18 years or older consulting for tuberculosis (TB) symptoms in Gabon's Moyen Ogooué province and neighbouring provinces from November 2018 to November 2020 were screened for diabetes mellitus, hypertension, and risk factors thereof (obesity, dyslipidaemia, smoking and alcohol consumption). Logistic regression was performed to identify factors associated with TB-diabetes and TB-hypertension co-morbidities.

Findings: Of 583 patients included, 227 (39%) were diagnosed with tuberculosis. In tuberculosis-confirmed patients, the prevalence of hypertension and diabetes were 16.3% and 12.8%, respectively. The prevalence of diabetes was twice as high in tuberculosis patients compared to non-tuberculosis patients. Factors independently associated with hypertension-tuberculosis co-morbidity were age >55 years (aOR=8.5, 95% CI 2.43, 32.6), age 45–54 years (aOR=4.9, 95%CI 1.3–19.8), and moderate alcohol consumption (aOR=2.4; 95% CI 1.02- 5.9), respectively. For diabetes-tuberculosis co-morbidity, age >55 years was positively (aOR=9.13; 95% CI 2.4–39.15), and moderate alcohol consumption inversely associated (aOR=0.26, 95% CI 0.08- 0.73). One-hundred-and-four (46%) of the tuberculosis patients had at least either dyslipidaemia, hypertension, diabetes, or obesity with a majority of newly-diagnosed hypertension and diabetes.

Interpretation: Integration of screening of non-communicable diseases and their risk factors during TB assessment for early diagnosis, treatment initiation and chronic care management for better health outcomes should be implemented in all tuberculosis healthcare facilities.

Funding: This study was supported by WHO AFRO/TDR/EDCTP (2019/893,805) and Deutsches Zentrum fu€r Infektiologie (DZIF/ TTU 02.812).

Keywords: Tuberculosis; Co-morbidity; Diabetes; Hypertension; Obesity; Non-communicable diseases

Research in context

Evidence before this study

We searched PubMed and Google Scholar for studies published before November 2018 assessing the integrated care for non-communicable diseases (NCDs), amongst tuberculosis patients, to identify the burden of NCDs and tuberculosis co-morbidity in the Gabon and Central Africa region. Applying the search terms 'integrated care', 'point-of-care', 'tuberculosis', 'non-communicable diseases', 'diabetes mellitus, 'hypertension', and 'obesity 'without language restrictions did not identify studies integrating point-of-care testing for both blood glucose and cholesterol into a facility-based standard of care for tuberculosis in Gabon.

Added value of this study

The present study indicates a high prevalence of hypertension, diabetes and NCD risk factors, and co-morbidity in adult tuberculosis patients and controls in Moyen Ogooué region, Gabon. Diabetes prevalence was about twice as high in tuberculosis patients. Overall, almost half of the tuberculosis patients had at least either dyslipidaemia, hypertension, diabetes, or obesity with the majority of them with newly-diagnosed hypertension and diabetes. Factors associated with tuberculosis-diabetes and tuberculosis-hypertension co-morbidities were age older than 55 years and alcohol consumption.

Implications of all the available evidence

The high prevalence of hypertension, diabetes co-morbidities and risk factors thereof in tuberculosis patients indicates a systematic screening for NCDs and NCD risk factors should be integrated into tuberculosis care. Integrated chronic disease care of tuberculosis patients would improve early diagnosis, treatment initiation and management of co-morbidities for better health outcomes.

INTRODUCTION

Low- and middle-income countries (LMICs) are experiencing an increasing double burden of communicable and non-communicable diseases (NCDs), with a limited capacity of the health system to address non-communicable diseases in addition to endemic communicable diseases such as tuberculosis (TB) or human immunodeficiency virus (HIV) [1,2]. Current reports show growing evidence of links between communicable diseases and NCDs, or risk factors thereof [3,4], such as tobacco use, physical inactivity, unhealthy diet, the harmful use of alcohol, and cardio-metabolic risk factors such as high blood pressure, overweight/obesity, and dyslipidaemia [5]. Models of TB/HIV co-management such as 'two diseases, one patient' have improved early TB diagnosis and treatment amongst people with HIV infection, and improved clinical outcomes for both diseases [6]. This concept could also be applied to non-communicable co-morbidities and tuberculosis. Clinicians receiving patients with suspected TB will need to acknowledge that they may be dealing with multiple diseases, of which some might be beyond their core expertise area, in a single patient. Integrated screening and management could improve early diagnosis and health outcomes for both conditions [7]. Some studies have reported NCD screening in tuberculosis patients [7-9]; however, they focused mainly on diabetes. The burden of other frequently-occurring NCDs or risk factors in patients with tuberculosis remains under-investigated. The absence of investigation of NCD co- and multi-morbidity amongst patients with TB may impact negatively the success of TB control programmes [6,10]. Two-way screening and integrated service management can help with TB control programmes by improving early diagnosis, treatment, and treatment outcomes. There is inadequate evidence, so far, on the feasibility and effectiveness of the screening and integrated management of NCDs in TB-suspected patients in resource-limited settings. Gabon is a high-burden TB country [11,12], with an estimated incidence of 521 TB cases per 100,000 inhabitants reported by the World Health Organization (WHO) in 2019 [13]. Around 31% of deaths in Gabon are caused by NCDs [14]. It is expected that in the coming years, Gabon will face the challenge of dealing with a continuously high burden of communicable diseases, while also needing to address the increasing burden of NCDs [15]. The primary objective of this study was to determine the prevalence of NCDs (diabetes mellitus, hypertension) and risk factors (obesity, dyslipidaemia and smoking) in tuberculosis patients. The secondary objective of the study was to investigate factors associated with tuberculosis, TB-diabetes and TB-hypertension co-morbidities, and to assess the feasibility of integrating screening for non-communicable diseases and their risk factors into routine tuberculosis care.

METHODS

The Strengthening Reporting of Observational Studies in Epidemiology (STROBE) guideline [16] was applied to report this study.

Study design and setting

A cross-sectional study was performed from November 2018 to November 2020 amongst patients consulting for tuberculosis symptoms. The study was conducted across Gabon's Moyen Ogooué province and neighbouring provinces. Gabon (population of 2.17 million in 2020) is one of three African countries, together with South Africa (58.56 million) and Lesotho (2.13 million), with a tuberculosis incidence of >500/100,000 (521/100,000) [13]. The tuberculosis mortality rate is estimated at 110 per 100,000 population [13]. The WHO estimated that 10% of Gabon's population is at risk of death due to NCDs by 2025 [14]. The Centre de Recherches Médicales de Lambaréné (CERMEL) tuberculosis laboratory serves the Moyen-Ogooué region, with a catchment area of approximately 170.000 inhabitants, and constitutes the national reference tuberculosis laboratory. In addition, patients from different parts of the country are regularly referred for consultation to CERMEL as a clinical research centre [17-19] with its TB laboratory having evolved into the National DR-TB reference laboratory, providing support for the diagnosis of tuberculosis, patients management, and drafting and implementation of tuberculosis guidelines.

Data collection and study procedures

All patients consulting for tuberculosis signs and symptoms referred to CERMEL's tuberculosis laboratory were invited to participate. Patients were from all the health facilities in Moyen Ogooué region and surroundings: (1) in- and outpatient departments of the Albert Schweitzer Hospital (HAS); (2) in- and outpatient departments of Georges Rawiri Regional Hospital (CHRGR); (3) the local outpatient HIV clinic (Centre de Traitement Ambulatoire [CTA]); (4) the local outpatient TB clinic (Base d'épidémiologie [BELE]); 5) CERMEL; (6) the Centre de Santé de Bifoun; (7) Centre de Santé de Ndjolé; (8) Centre de Santé de Fougamou, and nearby primary healthcare facilities from Ngounié, Nyanga, Estuaire and Ogooué-Maritime provinces. CERMEL thus represents all ports of entry for TB patients into the local and regional healthcare system. All adults (≥18 years) with a presumable TB diagnosis who attended the CERMEL tuberculosis laboratory, or who were hospitalised in one of the Lambaréné Hospitals, were screened. Patients who were unable to provide informed consent were excluded. Once agreed to participate, written consent was obtained from the participant, and a structured questionnaire addressing sociodemographic, smoking, alcohol consumption behaviours and clinical information was administered by the study nurses. The physical examination was performed by a

research physician. All patients provided two sputum samples (one at consultation and one early the next morning) as suggested by the national tuberculosis control programme and reported by Adegbite et al [20].

All patients consulting for tuberculosis signs and symptoms were considered presumptive TB patients. Patients with positive *Mycobacterium tuberculosis* smear microscopy, MTB RIF Xpert, culture or extra-pulmonary TB (EPTB) were considered confirmed TB. A diagnosis of extra-pulmonary confirmed TB was based on positive MTB RIF Xpert/culture, or ultrasound scanning and clinical evidence consistent with active EPTB in the absence of an alternative diagnosis, and the decision of the clinician to treat with a full course of TB chemotherapy.

Fasting capillary blood glucose was determined using rapid blood glucose (RBG) metre strips (ACON, San Diego, CA, USA). A twelve-hour overnight fasting blood sample was collected from all patients before anti-tuberculosis treatment was initiated, to measure glucose, glycosylated haemoglobin (HbA1c), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and total cholesterol (TC). Diagnosis of diabetes was based on the previous medical history of diabetes in the medical file of the patient or on WHO criteria [21] for the classification of glucose tolerance (diabetic: fasting glucose ≥7·0 mmol/L, the HbA1c level (≥6·5%), or random glucose ≥11·1 mmol/L with clinical symptoms). Participants without a medical history of diabetes but with abnormal RBG and normal HbA1c were tested a second time (a week later) assessing plasma glucose to confirm the diagnosis of diabetes mellitus. Blood pressure was measured by a nurse after the subject had rested for at least five minutes, using an automatic digital blood pressure monitor (Spengler, Aix-en-Provence, France). For each patient, two readings were recorded (left and right arm each once) [22,23]. Arterial hypertension was defined as diastolic blood pressure ≥90 mm of Hg and/or a systolic blood pressure ≥ 140 mm Hg, and/or use of any participant-reported antihypertensive drug. Participants without a medical history of hypertension (HT) with uncontrolled blood pressure or high blood glycaemia on screening were invited to come to the clinic two weeks later for confirmation. If the diagnosis was indeed confirmed, they were referred for specialist treatment. Dyslipidaemia was defined by the presence of high total cholesterol (TC ≥240 mg/dL), low-density lipoprotein cholesterol (LDL-C ≥ 160 mg/dL), high triglyceride (TG ≥150 mg/dL), and low high-density lipoprotein cholesterol (HDL-C < 40 mg/dL) [24]. The low-LDL-C level was calculated using the Friedewald formula (LDL=TC HDL-1/5(TG))[25]. All biochemical assessments were performed using Cobas® (Roche, Switzerland) clinical chemistry analysers. Body weight was recorded in kilograms (kg) using an automated scale (Omron Healthcare, Hoofddorp, Netherlands). Height was measured in centimetres using a fixed stadiometer (SECA, Hamburg Germany). Waist circumference was measured in standing position, the inelastic tape placed around the patient's hipbones, keeping the tape snugly around the waist. Body mass index (BMI) was calculated as weight (kg) divided by height (m^2) according to the

WHO international classification (18·5 to 24·9: normal; 25 to 29·9: overweight; above 30: obesity) [26]. Abdominal obesity was categorised as waist circumference (WC) ≥ 90 cm (men) and ≥80 cm (women) [27]. Participants were asked to provide an estimation of the quantity, the type and the rate of alcohol consumption. Harmful alcohol consumption was defined according to the Alcohol Use Disorders Identification Test (AUDIT) score [28]. The AUDIT is a 10-item screening tool developed by the World Health Organization to assess alcohol use, drinking behaviour, and related problems. The possible answers to each question are scored 0, 1, 2, 3 or 4. The range of possible scores is 0 to 40, where 0 indicates a teetotaller who has never had a problem with alcohol. A value of 1 to 7 indicates low-risk consumption according to the guidelines of the World Health Organization. Values of 8 to 15 indicate moderate alcohol use disorder [28]. For this study, we considered only participants with an AUDIT score of 8 and higher as alcohol users. Any past medical history including asthma was collected from medical files, or self-reported by the patients.

Sample size

All TB patients consulting at the study site during the study period were invited to be included in the study. The minimum sample size was 162 tuberculosis patients to be included. The sample size was calculated using Epi StaCalc software [29], based on an expected diabetes prevalence of 12% [30] in tuberculosis patients, at a 95% confidence level and 5% precision.

Statistical analysis

Statistical analyses were performed using RStudio (R Foundation for Statistical Computing, Vienna, Austria) software [31]. The numeric variables were described using the median and the interquartile range. The proportion of diabetes, hypertension, obesity, and smoking in tuberculosis and non-tuberculosis patients were determined and compared using the Chi-square test. Factors associated with hypertension-tuberculosis and diabetes-tuberculosis were investigated using multivariable logistic regression. The multivariable logistic regression model was built by including clinically relevant variables such as sex, age, education, smoking, dyslipidaemia and alcohol, and factors associated with each event (hypertension and diabetes) in univariable analyses, with inclusion criteria of $p<0·2$ added. Adjusted odds ratios (aORs) with 95% confidence intervals (CIs) were reported. Feasibility and effectiveness of the screening approach were measured using the mean cost (in FCFA, USD) of the laboratory test for NCDs diagnosis, the availability of the screening tool for routine care, the number of patients needed to screen (NNS) to get one additional new DM or HT case, and the additional yield of new cases. The NNS was calculated using the Rembold formula [32]. The additional yield of new cases of NCDs was calculated using the formula: (newly diagnosed cases × 100)/ (known cases+ newly diagnosed cases) [30].

Ethics approval and consent to participate

The study protocol was endorsed by CERMEL's institutional Scientific Review Board (SRC) and approved by CERMEL's Institutional Ethics Committee (CEI-018/2018). Written informed consent was obtained from all participants included. The study was conducted in line with the Good Clinical Practice principles of the International Conference on Harmonization and the Declaration of Helsinki.

Role of the funding source

The supporting funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author, Martin P. Grobusch accessed the dataset, and the decision to submit for publication was jointly taken by all authors.

RESULTS

General characteristics

Table 1 summarises the study population characteristics. A total of 583 patients presumably having TB were included in the study, of which 322 (55.2%) were male; the median age was 39 [IQR 29–51] years; and 144 (24.7%) were HIV-positive, amongst whom 49 (34%) were taking HIV antiretroviral combination therapy. A total of 208 (35.7) were underweight. The overall prevalence of hypertension and diabetes were 22.8(133) and 8.7 (51), respectively. Thirty-seven (37/51; 73%) diabetes patients knew their status. Amongst them, only 27% (10/37) had normal glucose levels. A total of 227 (39%) patients were diagnosed with tuberculosis (Figure 1), of which 8 (3.5%) had extrapulmonary tuberculosis, and 14 (6.2%) had multidrug-resistant tuberculosis.

Prevalence of diabetes, hypertension, and NCD risk factors in tuberculosis patients

Twenty-nine (17 with a history of diabetes treatment, nine with repeated fasting glucose ≥7.0 mmol/L, and three with HbA1c≥6.5%) TB patients had diabetes; the prevalence of diabetes was 12.8% (29 /227). Hypertension prevalence in tuberculosis-confirmed patients was 16.3% (37/227), the prevalence of dyslipidaemia was 17.6% (40/227), and the prevalence of obesity (including abdominal obesity or BMI above 30) was 6.2% (14/227) Table 2. summarises the prevalence of diabetes, hypertension, obesity, dyslipidaemia in all of the participants, in a patient with confirmed tuberculosis and those without tuberculosis.

Table 1 Sociodemographic characteristics of TB and non-TB patients (total=583).

Characteristics	All	No Tuberculosis	Tuberculosis
	N = 583(%)	*N = 356 (61%)*	*N = 227 (39%)*
Age group			
18–34 years	195 (33.4)	104 (29.2)	91 (40.1)
35–44 years	181 (31.0)	101 (28.4)	80 (35.2)
45–54 years	81 (13.9)	58 (16.3)	23 (10.1)
≥ 55 years	126 (21.6)	93 (26.1)	33 (14.5)
Sex			
F	261 (44.8)	157 (44.1)	104 (45.8)
M	322 (55.2)	199 (55.9)	123 (54.2)
Area of residence			
Rural	166 (28.5)	93 (26.1)	73 (32.2)
Urban	417 (71.5)	263 (73.9)	154 (67.8)
Educational attainment			
None	54 (9.3)	40 (11.2)	14 (6.2)
Primary	150 (25.7)	99 (27.8)	51 (22.5)
Secondary	344 (59.0)	196 (55.1)	148 (65.2)
University	35 (6.00)	21 (5.9)	14 (6.2)
Incomes			
Monthly fixed	140 (24.0)	96 (27.0)	44 (19.4)
Daily fixed	44 (7.6)	30 (8.4)	14 (6.2)
Occasional	82 (14.1)	57 (16.0)	25 (11.0)
No income	317 (54.4)	173 (48.6)	144 (63.4)
Size of household			
Median [IQR]	5 [3–7]	4 [2–7]	5 [3–7]

IQR: interquartile range.

Prevalence of TB and NCDS risk factors or HIV co-morbidity (occurrence of one or more medical conditions)

A total of 46% (104/227) of tuberculosis patients had at least one co-morbidity or NCD risk factor (including, hypertension, diabetes, dyslipidaemia, and obesity). When taking into account HIV, this prevalence is 65% (147/227). The most-common combination of co-morbidity or NCDs risk factors in TB patients was HIV-hypertension and HIV-dyslipidaemia (Figure 2).

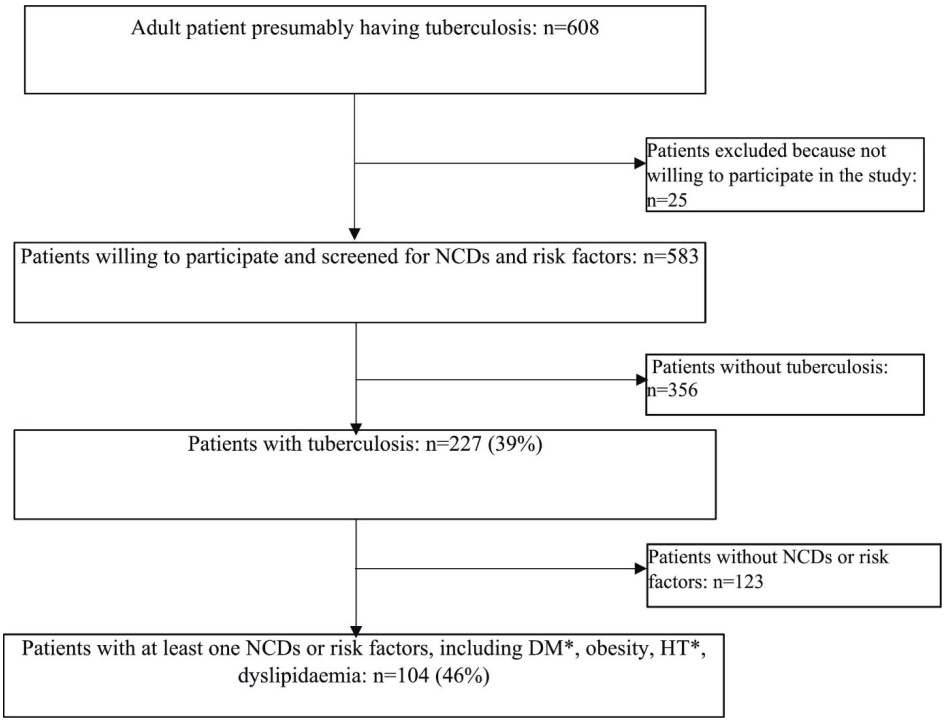

Figure 1 Flow of participants through the screening process.

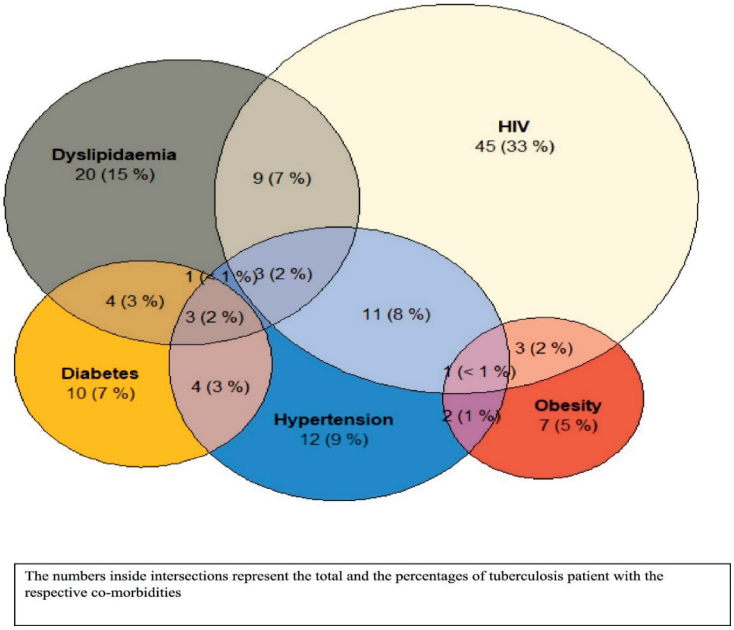

Figure 2. Venn-Euler diagram representing the distribution of participants according to their co-morbidities or NCDs risk factors. The numbers inside intersections represent the total and the percentages of tuberculosis patients with the respective comorbidities.

Table 2. Clinical characteristics in TB and non-TB patients (total=583).

Characteristic	All	No Tuberculosis	Tuberculosis
	N = 583(%)	*N = 356 (61%)*	*N = 227 (39%)*
HIV infection			
Negative	439 (75.3)	291 (81.7)	148 (65.2)
Positive	144 (24.7)	65 (18.3)	79 (34.8)
Medical History of tuberculosis			
No	514 (88.2)	317 (89.0)	197 (86.8)
Yes	69 (11.8)	39 (11.0)	30 (13.2)
Diabetes status			
No-diabetes	532 (91.3)	334 (93.8)	198 (87.2)
Diabetes	51 (8.7)	22 (6.18)	29 (12.8)
Medical History of diabetes			
No	546 (93.7)	342 (95)	204 (83)
Yes	37 (6.3)	20 (5)	17 (7)
Hypertension			
No	450 (77.2)	260 (73.0)	190 (83.7)
Yes	133 (22.8)	96 (27.0)	37 (16.3)
Medical history of hypertension			
No	525 (90)	310 (86.1)	215(94.7)
Yes	58 (10)	46 (12.9)	12 (5.3)
Smoking			
No	365 (62.6)	219 (61.5)	146 (64.4)
Yes currently	41 (7.0)	25 (7.0)	16 (7.0)
Yes, but I quit smoking	177 (30.4)	112 (31.5)	65 (28.6)
Alcohol consumption			
No	358 (61.4)	222 (62.4)	136 (59.9)
Yes	225 (38.6)	134 (37.6)	91 (40.1)
Dyslipidaemia			
No	496 (85.1)	307 (86.2)	189 (83.3)
Yes	87 (14.9)	49 (13.8)	38 (16.7)
Body Mass Index			
Normal BMI	282 (48.4)	176 (49.4)	106 (46.7)
Underweight	208 (35.7)	105 (29.5)	103 (45.4)
Overweight	48 (8.2)	37 (10.4)	11 (4.9)
Obese	45 (7.7)	38 (10.7)	7 (3.1)
Abdominal obesity			
No	532 (91.3)	314 (88.2)	218 (96.0)
Yes	51 (8.8)	42 (11.8)	9 (4)

Factors associated with tuberculosis

Compared to patients 55 years or older, the patients within the age categories of 18–34 years and 35–45 years were more likely to present with tuberculosis (aOR=2·02; 95% CI 1·11–3·75, and aOR=2·09; 95% CI 1·16–3·83, respectively). Other factors associated with tuberculosis in multivariable analysis were diabetes (aOR=4·24; 95% CI 2·17–8·53), HIV infection (aOR=2·31; 95% CI 1·49–3·58), rural residency (aOR=1·54; 95% CI 1·01–2·35) and obesity (aOR=0·28; 95% CI 0.11–0.65), Table 3.

Factors associated with diabetes, and HBP in tuberculosis patients

Age older than 55 years (aOR=6.99; 95%CI 2.10–25.44) and moderate alcohol consumption (aOR=0.27; 95% CI 0.09–0.75) were independently associated with diabetes in multivariable analysis (Table 4). Age older than 55 years (aOR=7.48; 95% CI 2.36–25.80) and 45–54 years (aOR=4.35; 95% CI 1.26–15.49); a family history of diabetes (aOR=3.05; 95% CI 1.08–8.38), moderate alcohol consumption (aOR=2.38; 95% CI 1.01- 5.7) were positively and being underweight (aOR=0.39; 95% CI (0.15–0.94) inversely associated with hypertension (Table 5).

Additional yield of diabetes mellitus, HBP and feasibility of systematic screening of diabetes and NCDs factors in TB patients

In TB patients, the additional yield of diabetes case screening was 41% (12/29); the NNS to detect one new case of diabetes was 13. The additional yield of hypertension cases on screening was 68% (25/37), and the NNS to detect one new case of hypertension was 8.

The feasibility of integrating the routine screening of NCD in TB patients was assessed by using two tools: The cost of NCDs screening and the point-of-care availability of a screening tool. The average cost for a patient without medical insurance is 43,750 FCFA (78.12 USD). Those covered by the medical insurance would pay 13,675 FCFA (24.42 USD). A total of 86% (486/583) of presumptive TB patients had medical insurance and 83% (189/227) of tuberculosis patients were insured. Therefore, screening of NCDs will not significantly induce additional costs for the patients.

Table 3 Univariable and multivariable risks factor associated with tuberculosis.

Dependant: tuberculosis		Univariable or (95%ci, p. value)	Adjusted or (95%ci, p. value)
Age group	≥ 55 years	Ref	Ref
	45–54 years	1.12 (0.59–2.08, $p = 0.73$)	1.15 (0.57–2.31, $p = 0.69$)
	35–44 years	2.23 (1.37–3.69, $p = 0.01$)	2.09 (1.16–3.83, $p = 0.02$)
	18–34 years	2.47 (1.53–4.05, $p<0.001$)	2.02 (1.11–3.75, $p = 0.02$)
Sex	F	Ref	Ref
	M	0.93 (0.67–1.30, $p = 0.68$)	1.06 (0.70–1.63, $p = 0.77$)
Area of living	Urban	Ref	Ref
	Rural	1.34 (0.93–1.93, $p = 0.12$)	1.54 (1.01–2.35, $p = 0.04$)
Education attainment	None	Ref	Ref
	Primary	1.47 (0.75–3.03, $p = 0.28$)	1.05 (0.48–2.34, $p = 0.90$)
	Secondary	2.16 (1.16–4.24, $p = 0.02$)	1.41 (0.67–3.06, $p = 0.37$)
	University	1.90 (0.77–4.78, $p = 0.16$)	1.42 (0.50–4.08, $p = 0.51$)
Income	Monthly fixed income	Ref	Ref
	Daily fixed income	1.02 (0.48–2.08, $p = 0.96$)	0.74 (0.32–1.67, $p = 0.48$)
	Occasional income	0.96 (0.53–1.72, $p = 0.88$)	0.86 (0.43–1.68, $p = 0.65$)
	No income	1.82 (1.20–2.78, $p = 0.01$)	1.57 (0.97–2.58, $p = 0.07$)
Diabetes Status	No	Ref	Ref
	Yes	2.22 (1.25–4.02, $p = 0.01$)	4.24 (2.17–8.53, $p<0.001$)
Hypertension	No	Ref	Ref
	Yes	0.53 (0.34–0.80, $p = 0.01$	0.78 (0.48–1.27, $p = 0.32$)
Smoking	No	Ref	Ref
	Yes currently	0.96 (0.49–1.84, $p = 0.9$)	0.93 (0.42–2.01, $p = 0.86$)
	Yes, but I quit smoking	0.87 (0.60–1.26, $p = 0.46$)	0.79 (0.50–1.24, $p = 0.30$)
Alcohol consumption	No	Ref	Ref
	Yes	1.11 (0.79–1.56, $p = 0.55$)	1.30 (0.88–1.94, $p = 0.19$)
Body Mass Index	Normal	Ref	Ref
	Obese	0.31 (0.12–0.67, $p = 0.01$)	0.28 (0.11–0.65, $p = 0.001$)
	Overweight	0.49 (0.23–0.98, $p = 0.05$)	0.53 (0.23–1.12, $p = 0.11$)
	Underweight	1.63 (1.13–2.35, $p = 0.01$)	1.43 (0.96–2.12, $p = 0.08$)
Dyslipidaemia	No	Ref	Ref
	Yes	1.28 (0.81–2.01, $p = 0.27$)	1.21 (0.73–1.99, $p = 0.45$)
HIV infection	Negative	Ref	Ref
	Positive	2.39 (1.63–3.51, $p<0.001$)	2.31 (1.49–3.58, $p<0.001$)

Table 4 Factors associated with diabetes in tuberculosis patients (29 diabetes cases / in 229 TB cases).

		Univariable OR (95%CI, P. Value)	Adjusted OR(95%CI, P. Value)
Age group	18–34 years	Ref	Ref
	35–44 years	1.33 (0.46–3.97, p = 0.59)	1.39 (0.43–4.63, p = 0.58)
	45–54 years	1.14 (0.16–5.15, p = 0.87)	0.47 (0.05–2.80, p = 0.44)
	≥ 55 years	6.86 (2.46–20.52, p<0.001)	6.99 (2.10–25.44, p = 0.002)
Sex	F	Ref	Ref
	M	2.47 (1.08–6.18, p = 0.04)	1.72 (0.57–5.40, p = 0.34)
Income	Monthly fixed income	Ref	Ref
	Daily fixed income	1.80 (0.41–7.07, p = 0.40)	3.72 (0.67–20.50, p = 0.12)
	Occasional income	0.86 (0.21–3.08, p = 0.81)	0.66 (0.12–3.20, p = 0.61)
	No income	0.45 (0.17–1.20, p = 0.09)	0.54 (0.18–1.75, p = 0.28)
Hypertension	No	Ref	Ref
	Yes	1.78 (0.66–4.37, p = 0.22)	1.48 (0.40–4.96, p = 0.53)
Smoking	No	Ref	Ref
	Yes currently	1.25 (0.18–5.07, p = 0.78)	1.06 (0.12–6.38, p = 0.95)
	Yes, but I quit smoking	1.98 (0.85–4.50, p = 0.10)	1.47 (0.51–4.13, p = 0.46)
Alcohol consumption	No	Ref	Ref
	Yes	0.53 (0.21–1.21, p = 0.14)	0.27 (0.09–0.75, p = 0.02)
Body Mass Index	Normal	Ref	Ref
	Obese	1.01 (0.05–6.52, p = 0.99)	0.97 (0.04–9.40, p = 0.97)
	Overweight	1.35 (0.19–5.90, p = 0.71)	1.82 (0.19–11.53, p = 0.55)
	Underweight	0.73 (0.31–1.65, p = 0.44)	0.99 (0.37–2.66, p = 0.98)
Family medical history of diabetes	No	Ref	Ref
	Yes	2.20 (0.80–5.49, p = 0.10)	2.79 (0.81–8.93, p = 0.08)
Dyslipidaemia	No	Ref	Ref
	Yes	0.50 (0.12–1.53, p = 0.27)	0.63 (0.13–2.25, p = 0.51)
HIV infection	Negative	Ref	Ref
	Positive	0.56 (0.21–1.31, p = 0.20)	0.58 (0.19–1.60, p = 0.31)

Table 5 Factors associated with hypertension in tuberculosis patients (37 cases of hypertension/227 TB patients).

		Univariable OR (95%CI, P. Value)	Adjusted OR(95%CI, P. Value)
Age group	18–34 years	Ref	Ref
	35–44 years	1.52 (0.54–4.45, $p = 0.428$)	1.21 (0.40–3.77, $p = 0.74$)
	45–54 years	6.40 (2.02–20.95, $p = 0.002$)	4.35 (1.26–15.49, $p = 0.02$)
	≥ 55 years	7.80 (2.83–23.23, $p<0.001$)	7.48 (2.36–25.80, $p = 0.01$)
Sex	F	Ref	Ref
	M	0.87 (0.43–1.78, $p = 0.70$)	0.48 (0.18–1.23, $p = 0.13$)
Diabetes	No	Ref	Ref
	Yes	1.78 (0.66–4.37, $p = 0.23$)	1.18 (0.34–3.72, $p = 0.78$)
Smoking	No	Ref	Ref
	Yes currently	1.88 (0.49–5.97, $p = 0.31$)	1.20 (0.27–4.81, $p = 0.79$)
	Yes, but I quit smoking	1.15 (0.50–2.49, $p = 0.73$)	0.93 (0.32–2.57, $p = 0.88$)
Alcohol consumption	No	Ref	Ref
	Yes	2.25 (1.11–4.66, $p = 0.02$)	2.38 (1.01–5.73, $p = 0.04$)
Body Mass Index	Normal	Ref	Ref
	Obese	0.60 (0.03–3.77, $p = 0.64$)	0.73 (0.03–5.95, $p = 0.79$)
	Overweight	0.80 (0.12–3.39, $p = 0.78$)	0.68 (0.08–3.81, $p = 0.69$)
	Underweight	0.43 (0.19–0.92, $p = 0.03$)	0.39 (0.15–0.94, $p = 0.04$)
Family medical history of diabetes	No	Ref	Ref
	Yes	2.83 (1.17–6.52, $p = 0.01$)	3.05 (1.08–8.38, $p = 0.03$)
Dyslipidaemia	No	Ref	Ref
	Yes	0.69 (0.22–1.77, $p = 0.47$)	0.78 (0.23–2.27, $p = 0.66$)
HIV infection	Negative	Ref	Ref
	Positive	1.34 (0.64–2.75, $p = 0.42$)	1.37 (0.58–3.22, $p = 0.46$)

DISCUSSION

We found the prevalence of NCDs; DM and hypertension amongst TB patients were 13% and 16%, respectively. The prevalence of DM amongst TB patients in our study is similar to reports from Nigeria (12%) [33] and higher than what was reported from Ethiopia (8.3%) [34], and Uganda (8.5%), respectively. The differences in prevalence across studies might be explained by the diabetes burden in the general population of each country. The differences in dietary habits, behaviours, and methods of DM screening might explain

the variation in the prevalence of DM amongst TB patients in other studies as compared to ours. The proportion of new diabetes cases in TB patients (5.3%,12/227) identified in our study is similar to that reported from Ethiopia (4.9%). The high proportion of newly-diagnosed diabetes cases in our study highlights the magnitude of the problem, low awareness, and the importance of systematically screening for DM, HT and NCD risk factors in general amongst TB patients[7]. As reported previously, in our study, diabetes in tuberculosis patients is associated with older age [35].

Our findings suggest that tuberculosis patients who consumed (moderately, or more) alcohol had lower odds (aOR=0.26; 95% CI (0.08–0.73) to present with diabetes. Data on the association between alcohol consumption and the risk of diabetes are controversial[36].

Several meta-analyses suggest that light and moderate alcohol consumption are associated with a lower risk of diabetes [36- 39]. As in many observational studies, alcohol consumption in our study is based on self-reporting; and the quantities consumed by the patients could not be verified with accuracy; therefore, the findings should be interpreted with caution. In the context of this study, we were mainly interested in the smoking/harmful alcohol use status of the patients. Our previous study in the same study population reported the burden of smoking and alcohol use in TB patients by reporting the quantity smoked or drunk per day [20].

Few studies in LMICs investigated the burden of hypertension in tuberculosis patients. The prevalence of hypertension in TB patients in the present study is similar to the 19% reported by Segafredo et al. from Angola [7]. Older age and alcohol consumption are associated with hypertension in tuberculosis patients in our study; a finding in line with previous reports [35,40]. As reported by other studies [35,41,42] a considerable proportion of our study population did not know their diabetes and hypertension status. The additional case yield from TB patient screening was 41% (12/29) and 68% (25/37) for diabetes and hypertension, respectively. Furthermore, 46% (104/227) of tuberculosis patients had at least one comorbidity (hypertension, diabetes) or NCD risk factor (dyslipidaemia, obesity). A study in Indonesia reported 35.5% of patients with co-morbidities (asthma, diabetes, hypertension, myocardial infarction, kidney disease, neoplasia) in tuberculosis patients [41]. Another study conducted in the Philippines reported that 40% of subjects with co-morbidities among tuberculosis patients [43]. On the one hand, the slight difference in theses proportions compared to our study might be due to the co-morbidity assessment methodology in each study. For example, the study from the Philippines focused on diabetes, severe anaemia, obesity, and under-nutrition. On the other hand, the difference could be explained by the NCDs respective epidemiological peculiarities of the country or continent where the studies have been conducted. We were not able to find any study from sub-Saharan Africa that reported the prevalence of at least two NCDs, or co-morbidities risk factors, in tuberculosis patients. An un-diagnosed

co-morbidity in tuberculosis patients might worsen tuberculosis outcomes, and impact negatively the success of a TB control programme [6].

Our findings stress the utility and feasibility of routine screening for diabetes and other non-communicable diseases in all patients visiting a health care facility irrespective of the primary motif of consultation. Lessons learned from operational research aiming to integrate chronic care using the vertical HIV programmes as the starting point is that those should be implemented for tuberculosis, too [44]. The tests used in our study are widely available and could serve a useful screening function. Given the numbers needed to test to detect a new case for each of the non-communicable diseases, it seems feasible to incorporate routine screening and secondary prevention of common NCDs. Furthermore, the vast majority of tuberculosis patients in our study have medical insurance. Therefore, screening for NCDs would not be expensive for patients. However, systematic screening for non-communicable diseases during TB care would require capacity building and a more inclusive focus on the patient's general health and well-being. In our study, we worked with nurses who are in charge of tuberculosis patient screening in routine activities. Additional screening of NCDs in tuberculosis patients did not seem to be a challenge. All TB care centres in Gabon have the diagnostic tools used in our study at hand (except for HbAc1 measurement); this diabetes point-of-care rapid capillary test could be provided. The nurses and physicians could be trained continuously in the field to provide screening of NCDs. The national tuberculosis control program in many LMICs integrated successfully the screening of HIV in tuberculosis patients. This could be easily extended to NCDs. It will enhance 'patient-centred care', in line with the World Health Organization's End TB strategy [45]. The strengths of our study were the enrolment of a large number of participants consecutively for 24 months to cover seasonality factors that might affect the incidence of tuberculosis cases. The study was integrated into routine TB activities to safeguard the representativeness of the participants included. Only 25 patients declined to participate in the study. The fact that patients from the whole region towards particular social strata were captured without bias, that way limiting the risk of selection bias. Furthermore, the screening of NCDs in our study was not limited to confirmed TB only but extended to all patients coming with TB symptoms to make sure that all patients were given an opportunity for earlier diagnosis of our target NCD conditions. To our knowledge, our study is the first to perform the screening for NCDs in TB-presumptive patients and assess the burden of NCDs and TB comorbidities in the central African region. All of the resources needed (laboratory reagents and machines; qualified medical staff) for the screening are available in all of the TB clinics referring patients to the CERMEL TB laboratory. There was no particular challenge regarding our staff collecting data on additional clinical information related to NCDs and risk factors during the screening of TB patients. Our study showed that the screening of diabetes and other co-morbidities is feasible in TB health care facilities. Moreover, a higher proportion of patients with

national medical insurance coverage in Gabon provides additional evidence of the feasibility of systematic screening without higher additional costs for the patients. This might not be the case in other sub-Saharan countries; however, systematic screening using at least diabetes point-of-care rapid capillary testing could be feasible. There are some limitations of our study. Due to self-reporting of some behaviour like alcohol drinking and smoking, social desirability bias may have affected the study findings. The physical or sportive activities of our study population as well as neoplasia co-morbidity, and kidney diseases were not reported. The same applies to chronic obstructive lung disease (COPD) as pulmonary function tests are still not available on-site. The lipid profile is known to be affected by acute infections [46] and antiretroviral treatment. The antiretroviral treatment data were not collected in our study. In the present study, HbAc1 measurement led to the diagnosis of three additional (3/29,10%) TB patients with diabetes. In patients without a medical history of diabetes, the concordance between fasting glucose test and HbA1C was 75% (9/12). Gupte et al. reported in their study [47] that the HbA1c levels declined during anti-tuberculosis treatment, suggesting that repeating HbA1c testing at treatment completion could reduce the risk of manifest diabetes. On the other hand, a scoping review on the use of HbA1c in the African setting suggested caution when interpreting results, since some co-morbidities such as anaemia and HIV infection could affect HbA1c levels [48]. Due to the cross-sectional design of the present study, we were not able to repeat the HbA1c measurements at the end of the treatment period. However, the fasting glucose tests were repeated at the beginning in patients without a medical history of diabetes (presenting with or without hyperglycaemia), to reduce the risk of diabetes misdiagnosis. However, the interpretation of our findings should be conducted with caution. We did not collect qualitative information about the acceptability of the study by a representative medical staff in charge of TB in the region, so the interpretation of the feasibility data should be done with caution. However, our study provided valuable epidemiological data on DM and NCDs in Gabon's Moyen-Ogooué region and suggest the feasibility of integrating systematic screening of DM and NCDs condition during TB consultation. Qualitative and quantitative studies investigating the feasibility, cost and effectiveness at the national level should be performed to adjust appropriate public health strategies.

Declaration of interests

None of the authors has a competing interest to declare.

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Author contributions

BRA, RE, and MPG conceptualised the study. BRA, RE, AAP, EM, MC, JCD, FJZ, and YJH participated in the acquisition of data, MPG, AAS, BRA, PGK and AAA provided and organised study resources. BRA, MPG, SM interpreted and analysed the data, BRA wrote the original draft with the input of KKG, MPG, and SM. RE, AAP, BRA have accessed and verified the data, and BRA and MPG were responsible for the decision to submit the manuscript. All authors contributed to the final version of the manuscript and approved the submission for publication.

Data sharing statement

Data for this study can be made available publicly. All interested persons can access the dataset from the corresponding author.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j. eclinm.2022.101316.

REFERENCES

1. Atun R, Davies JI, Gale EAM, et al. Diabetes in sub-Saharan Africa: from clinical care to health policy. Lancet Diabetes Endocrinol.2017;5:622–667.
2. Stubbs B, Siddiqi K, Elsey H, et al. Tuberculosis and non-communicable disease multimorbidity: an analysis of the world health survey in 48 low- and middle-income countries. Int J Environ Res Public Health. 2021;18:2439.
3. Ahmed M, Omer I, Osman SMA, Ahmed-Abakur EH. Association between pulmonary tuberculosis and type 2 diabetes in Sudanese patients. Int J Mycobacteriol. 2017;6:5.
4. Lonnroth K, Williams BG, Stadlin S, Jaramillo E, Dye C. Alcohol use as a risk factor for tuberculosis - a systematic review. BMC Public Health. 2008;8:289.
5. Forouzanfar MH, Afshin A, Alexander LT, et al. Global, regional,and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990-2015: a systematic analysis for the global burden of disease study 2015. Lancet. 2016;388:1659–1724.
6. Creswell J, Raviglione M, Ottmani S, et al. Tuberculosis and noncommunicable diseases: neglected links and missed opportunities.Eur Respir J. 2011;37:1269–1282.
7. Segafredo G, Kapur A, Robbiati C, et al. Integrating TB and noncommunicable diseases services: pilot experience of screening for diabetes and hypertension in patients with Tuberculosis in Luanda,Angola. PLoS ONE. 2019;14: e0218052.
8. Lin YH, Chen CP, Chen PY, et al. Screening for pulmonary tuberculosis in type 2 diabetes elderly: a cross-sectional study in a community hospital. BMC Public Health. 2015;15:3.
9. Dooley KE, Chaisson RE. Tuberculosis and diabetes mellitus: convergence of two epidemics. Lancet Infect Dis. 2009;9:737–746.
10. Marais BJ, Lonnroth K, Lawn SD, et al. Tuberculosis comorbidity with communicable and non-communicable diseases: integrating health services and control efforts. Lancet Infect Dis. 2013;13:436–448.
11. Belard S, Remppis J, Bootsma S, et al. Tuberculosis treatment outcome and drug resistance in Lambarene, Gabon: a prospective cohort study. Am J Trop Med Hyg. 2016;95:472–480.
12. Ateba-Ngoa U, Edoa JR, Adegbite BR, et al. Implementation of multidrug-resistant tuberculosis (MDR-TB) treatment in Gabon: lessons learnt from the field. Infection. 2019;47:811–816.
13. Word Health Organization (WHO). Tuberculosis Gabon country profile. Geneva: WHO, 2020 https://worldhealthorg.shinyapps.io/
14. World Health Organization. Noncommunicable Diseases Country Profiles. Geneva: WHO; 2018..https://www.who.int/nmh/countries/2018/gab_en.pdf?ua=1.
15. Atun R, Davies JI, Gale EAM, et al. Diabetes in sub-Saharan Africa: from clinical care to health policy. Lancet Diabetes Endocrinol.2017;5:622–667.
16. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol. 008;61:344–349.
17. Ramharter M, Agnandji ST, Adegnika AA, et al. Development of sustainable research excellence with a global perspective on infectious diseases: centre de Recherches Medicales de Lambarene (CERMEL), Gabon. Wien Klin Wochenschr. 2021;133:500–508.

18. Ramharter M, Adegnika AA, Agnandji ST, et al. History and perspectives of medical research at the Albert Schweitzer Hospital in Lambarene, Gabon. Wien Klin Wochenschr. 2007;119: 8–12.

19. Alabi AS, Traore AN, Loembe MM, et al. Enhanced laboratory capacity development: a boost for effective tuberculosis control in resource-limited settings. Int J Infect Dis. 2017;56:81–84.

20. Adegbite BR, Edoa JR, Achimi Agbo P, et al. Epidemiological,Mycobacteriological, and Clinical Characteristics of Smoking Pulmonary Tuberculosis Patients, in lambarene, Gabon: a Cross-Sectional Study. Am J Trop Med Hyg. 2020;103:2501–2505.

21. World Health Organization, International Diabetes Federation.Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia: report of a WHO/IDF consultation. 2006 http://www.who.int/diabetes/publications/diagnosis_diabetes2006/en/

22. Mancia G, De Backer G, Dominiczak A, et al. 2007 Guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J. 2007;28:1462–1536.

23. Parker E, Glasziou P. Use of evidence in hypertension guidelines: should we measure in both arms? Br J Gen Pract. 2009;59:e87–e92.

24. Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults(Adult Treatment Panel III). United States of America: national cholesterol education program national heart, lung, and blood institute national institutes of health, 2001.

25. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem. 1972;18:499–502.

26. World Health Organization. Obesity: Preventing and Managing the Global epidemic: Report of a WHO Consultation. Geneva: World Health Organization; 2000.

27. World Health Organization. Waist Circumference and Waist-Hipratio: Report of Expert Consultation. Geneva: World Health Organization; 2011.

28. Babor TF, Higgins-Biddle JC, Saunders JB, Monteiro MG. AUDIT :the Alcohol Use Disorders Identification test : Guidelines for use in Primary Health Care. 2nd ed. Geneva: World Health Organization;2000.

29. Dean AG, Arner TG, Sunki GG, et al. Epi InfoTM, a database and statistics program for public health professionals. CDC, Atlanta, GA, USA, 2011.

30. Ekeke N, Ukwaja KN, Chukwu JN, et al. Screening for diabetes mellitus among tuberculosis patients in Southern Nigeria: a multicentre implementation study under programme settings. Sci Rep.2017;7:44205.

31. Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria.: R Foundation for Statistical Computing,2020 https://www.R-project.org/.

32. Rembold CM. Number needed to screen: development of a statistic for disease screening. BMJ. 1998;317:307–312.

33. Ogbera AO, Kapur A, Abdur-Razzaq H, et al. Clinical profile of diabetes mellitus in tuberculosis. BMJ Open Diabetes Res Care. 2015;3.https://doi.org/10.1136/bmjdrc-2015-000112.

34. Workneh MH, Bjune GA, Yimer SA. Prevalence and associated factors of diabetes mellitus among tuberculosis patients in SouthEastern Amhara region, Ethiopia: a cross-sectional study. PLoSONE. 2016;11: e0147621.

35. Segafredo G, Kapur A, Robbiati C, et al. Integrating TB and noncommunicable diseases services: pilot experience of screening for diabetes and hypertension in patients with Tuberculosis in Luanda, Angola. PLoS ONE. 2019;14: e0218052.

36. Li XH, Yu F, Zhou YH, He J. Association between alcohol consumption and the risk of incident type 2 diabetes: a systematic review and dose-response meta-analysis. Am J Clin Nutr.2016; 103:818–829.

37. Pietraszek A, Gregersen S, Hermansen K. Alcohol and type 2 diabetes. A review. Nutr Metab Cardiovasc Dis. 2010;20:366–375.

38. Baliunas DO, Taylor BJ, Irving H, et al. Alcohol as a risk factor for type 2 diabetes. Diabetes Care. 2009;32:2123–2132.

39. Knott C, Bell S, Britton A. Alcohol consumption and the risk of type 2 diabetes: a systematic review and dose-response meta-analysis of more than 1.9 million individuals from 38 observational studies. Diabetes Care. 2015;38:1804–1812.

40. Husain K, Ansari RA, Ferder L. Alcohol-induced hypertension: mechanism and prevention. World J Cardiol. 2014;6:245–252.

41. Asturiningtyas IP, Mulyantoro DK, Kusrini I, Ashar H. Non-communicable disease comorbidity and multimorbidity among people with tuberculosis in Indonesia. ASRO. 2021;24. https://doi.org/10.36295/ASRO.2021.24191.

42. India Tuberculosis-Diabetes Study Group. Screening of patients with tuberculosis for diabetes mellitus in India. Trop Med Int Health. 2013;18:636–645.

43. White LV, Edwards T, Lee N, et al. Patterns and predictors of comorbidities in Tuberculosis: a cross-sectional study in the Philippines. Sci Rep. 2020;10:4100.

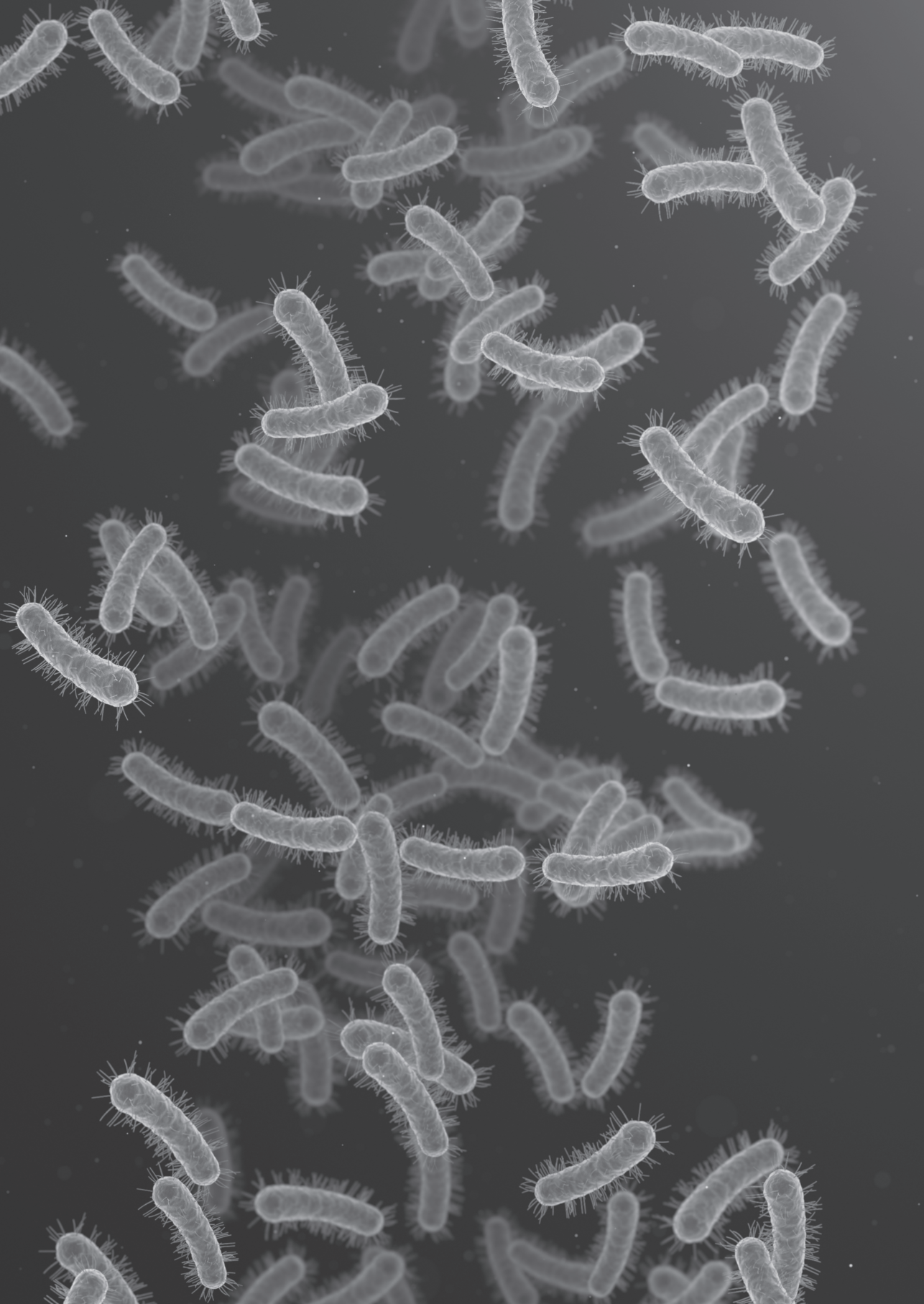
44. Njuguna B, Vorkoper S, Patel P, et al. Models of integration of HIV and noncommunicable disease care in sub-Saharan Africa: lessons learned and evidence gaps. AIDS. 2018;32:S33–S42.

45. Byrne AL, Marais BJ, Mitnick CD, et al. Feasibility and yield of screening for non-communicable diseases among treated tuberculosis patients in Peru. Int J Tuberc Lung Dis. 2018;22:86–92.

46. Visser BJ, Wieten RW, Nagel IM, Grobusch MP. Serum lipids and lipoproteins in malaria - a systematic review and meta-analysis.Malar J. 2013;12:442.

47. Gupte AN, Mave V, Meshram S, et al. Trends in HbA1c levels and implications for diabetes screening in tuberculosis cases undergoing treatment in India. Int J Tuberc Lung Dis.2018; 22:800–806.

48. George JA, Erasmus RT. Haemoglobin A1c or glycated albumin for diagnosis and monitoring diabetes: an african perspective. Indian JClin Biochem. 2018;33:255–261.



Chapter 3

Epidemiological, Mycobacteriological, and Clinical Characteristics of Smoking Pulmonary Tuberculosis Patients, in Lambaréné, Gabon: A Cross-Sectional Study

Adegbite B. R, Edoa J. R, Achimi Agbo P, Dejon-Agobé J. C, Essone P, Lotola-Mougeni F, Mbong Ngwese M, Mfoumbi A, Mevyann C, Epola M, Zinsou J. F, Honkpehedji Y. J, Agnandji S. T, Kremsner P. G, Alabi A. S, Adegnika A. A, and Grobusch M. P

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ABSTRACT

Gabon carries a high burden of both tuberculosis (TB) and smoking. This study examines the disease characteristics of smoking pulmonary TB patients in Lambaréné. We interviewed adult pulmonary TB patients in Lambaréné, between March 2016 and April 2019. Clinical and biological patient characteristics were collected. Bivariate and logistic regression analyses were performed to assess factors associated with smoking. The mean age of patients included was 31 years (±13). The proportion of smokers in our study was 30% (89/295). Smoking was significantly associated with patient-related diagnostic delay (adjusted odds ratio [AOR] = 8.18; 95% CI = 3.67–19.56), a higher number of pulmonary TB signs and symptoms (AOR = 2.74; 95% CI = 1.18–6.73), and a higher sputum mycobacterial load (AOR = 3.18; 95% CI = 1.33–8.11). The prevalence of smoking among TB patients is high and leads to aggravated disease as compared with controls. Our study findings suggest that smoking patients should be regularly screened for TB, to reduce diagnostic delay and TB transmission within the community. Smoking cessation activities should be included in the national TB control program in Gabon.

INTRODUCTION

Smoking and tuberculosis (TB) are two major public health problems worldwide. The WHO estimated in 2019 that 23% of the world population smokes [1]. Tobacco smoking is recognized as being associated with an increased risk of TB infection and disease [2,3] In addition, it is reported that active smoking is associated with poor TB treatment adherence, delayed smear conversion, TB treatment failure, relapse, and death during treatment [4,5]. It is also reported that TB patients who smoke exhibit more radiological findings, cavitary disease, and higher sputum smear grading than non-smokers during initial presentation [6]. Furthermore, some reports suggest that TB diagnostic delay is associated with smoking [7]. The current approach to TB control focuses on case detection and treatment. Recent studies suggest that to achieve TB control, it is necessary to reduce risk factors that contribute to the occurrence of TB infection and/or disease [8]. The prevalence of tobacco uses in Gabon reported by the WHO is 22.4% [9]. Smoking prevalence among TB patients could be higher than that in the general population. The prevalence of smoking among TB patients and the associated adverse effects are under-investigated in African countries that have a high incidence of TB, such as Gabon. To our knowledge, no previous studies have been performed to assess the prevalence and the burden of cigarette smoking among TB patients in Gabon. Gaining insights into the double burden of TB and tobacco use could help to establish the need for cessation services as a component of the TB program. This study aimed to determine the proportion of tobacco smokers among TB patients and to examine the disease characteristics of smoking pulmonary TB patients in Lambaréné and the surrounding villages in Moyen-Ogooué Province.

METHODS

Study design.

A cross-sectional study was conducted among TB patients enrolled between March 2016 and April 2019 at the Centre de Recherches Médicales de Lambaréné (CERMEL).

Study site and population.

Patients were recruited at five different sites in Lambaréné: 1) in- and outpatient departments of the Albert Schweitzer Hospital, 2) in- and outpatient departments of Georges Rawiri Regional Hospital, 3) the local outpatient HIV clinic (Centre de Traitement Ambulatoire), 4) the local outpatient TB clinic (Base d'épidémiologie), and 5) CERMEL, thus representing all "ports of entry" for TB patients into the local healthcare system. Centre de Recherches Médicales de Lambaréné is the TB national reference laboratory,

and all presumptive TB patients in Moyen-Ogooué Province and beyond are referred to the CERMEL. All patients older than 15 years visiting the CERMEL, with signs and symptoms compatible with TB, were invited to participate in the study. Those unable to answer our questionnaire and those with extrapulmonary disease were excluded.

Data collection, definitions, and procedures.

Demographic and clinical data were collected by study investigators. Sociodemographic data on education were also collected during the visit, and self-reported cigarette smoking status was collected using the questionnaire. For this study, the definition of a current smoker was expanded to include former smokers who had reported smoking cessation within the 2 months before TB diagnosis. This expansion was to minimize the misclassification of patients who temporarily quit smoking at the onset of symptoms. The duration of the illness was based on the patient's self-declaration of the onset of the first sign of TB to the date he/she presented for consultation. Patients who consumed alcohol were invited to provide information on the kind of alcoholic beverage and the approximate quantity consumed per week. The quantity of alcohol consumed per ml was converted to mg using standard drink conversion [10]. Men who consumed regularly more than 60 g/day of alcohol and women who consumed more than 40 g/day were considered high-risk alcohol users [10]. Samples for mycobacterial investigation were analyzed by auramine fluorochrome staining or GeneXpert assay according to the national guideline. Bacteriological confirmation of TB was based on the examination of two spot sputum samples.

Patients were considered to be smokers if they reported having smoked ≥ 1 cigarette(s)/day continuously. The burden of cigarette smoking was classified according to pack-years, calculated by multiplying the number of cigarettes smoked per day by the number of years the person has smoked divided by 20. Patient-related delay in diagnosis was defined as "yes" if the time of consultation was more than 21 days (>) and "no" if less (≤) than 21 days. Subsequent TB signs and symptoms were systematically assessed for each participant: cough, fever, dyspnea, chest pain, hemoptysis, night sweats, weight loss, and asthenia. A symptom score (0–8) was calculated based on the presence of symptoms or signs (1 point for each). The symptom score was categorized as "yes" if the patient presented or reported more than four (> 4) signs and/or symptoms or no if four or less. The WHO scale was used to categorize the severity of sputum mycobacterial load [11].

Data management and statistical analysis.

Study data were collected and managed using the research electronic data capturing tool [12,13]. To ensure the quality of data, double entry was performed by trained and independent data clerks. A clean database was extracted, and the analysis was conducted using R software version 3.6.1 (R Foundation for Statistical Computing, Vienna,

Austria). Proportions were used to describe qualitative variables and mean or median for quantitative variables. The characteristics of smokers versus those of non-smokers were compared first, using Pearson's χ^2 or Fisher's exact test. This analysis was followed by multivariate logistic regression. Factors known to be associated with smoking from the literature review and those identified during the univariate analysis were included in the multivariate model. We conducted manual backward stepwise elimination to choose the final model. Because gender was found to be associated with HIV infection, education level, and alcohol consumption, the interaction effect of gender variables was assessed in the model by adding the interaction term (gender: HIV infection, gender: high-risk alcohol consumption, and gender: education level). Variables with an adjusted ratio that had a *P*-value less than 0.05 at 95% CI were considered significant.

Ethics approval and consent to participate.

The study was approved by the Institutional Ethics Committee of the CERMEL. Written informed consent was obtained from all participants before study enrollment. The participants between the age of 16 and 18 years provided written assent in addition to written consent from their parent or legal guardian to participate in the study.

RESULTS

A total of 295 TB patients were included, with a mean age of 31 years (±13). Of those 295 patients, 60% (177/295) had obtained a secondary level of education, 30% (86/295) previously shared a household with a TB patient, and 80% (234/295) had never been treated for TB. High-risk alcohol consumption was reported in 45% (133/295) of individuals. The prevalence of HIV and TB coinfection was 31% (92/295).

Distribution of smoking status and associated factors.

The prevalence of smoking was 30% (89/295), and the median pack-years of smoking was 8 (IQR: 3–17). As presented in Table 1, bivariate analysis to detect factors associated with smoking indicated that smokers were predominantly male, and they consumed alcohol more often than non-smokers. HIV infection prevalence was higher among non-smokers than smokers. Smokers presented with more signs and or symptoms suggestive, or in line with, TB, and exhibited delays in time to diagnosis as compared with non-smokers.

Table 1 Characteristics of patients and factors related to smoking at the time of TB diagnosis at bivariate level

Variable	Non-cigarette smokers, *n* (row %) 206 (70)	Cigarette smokers, *n* (row%) 89 (30)	Total (*N* = 295)	*P*-value
Age-group (years)				0.204
16–24	76 (76)	24 (24)	100	
25–34	58 (72)	23 (28)	81	
35–44	36 (62)	22 (38)	58	
45–54	23 (66)	12 (34)	35	
≥ 55	13 (62)	8 (38)	21	
Gender				< 0.001
Female	126 (95)	7 (5)	133	
Male	80 (49)	82 (51)	162	
Education level				0.325
None	9 (75)	3 (25)	12	
Primary	49 (63)	29 (37)	78	
Secondary	133 (71)	54 (29)	187	
University	15 (83)	3 (17)	18	
Household contact of TB				0.931
No	139 (70)	60 (30)	201	
Yes	64 (67)	32 (33)	94	
History of TB treatment				0.783
No	174 (69)	77 (31)	251	
Yes	32 (73)	12 (27)	44	
High-risk alcohol consumption				< 0.001
No	143 (89)	18 (11)	161	
Yes	63 (47)	71 (53)	134	
More than four TB symptoms				0.391
No	70 (74)	25 (26)	95	
Yes	136 (68)	64 (32)	200	
Patient-related diagnostic delay				< 0.001
No	158 (84)	31 (16)	189	
Yes	48 (45)	58 (55)	106	
HIV coinfection				0.047
No	134 (66)	69 (34)	203	
Yes	72 (78)	20 (22)	92	
Sputum grading				0.020
3+	100 (64)	57 (36)	157	
2+	70 (82)	15 (18)	85	
1+	27 (68)	13 (32)	40	
Rare	9 (69)	4 (31)	13	

TB = tuberculosis.

From the multivariable analysis (Table 2), the following factors were independently associated with smoking: high-risk alcohol consumption (odds ratio [OR] = 6.26; 95% CI = 2.97–13.83), patient-related delayed diagnosis (adjusted OR [AOR] = 8.18; 95% CI = 3.67–19.56), higher (3+) sputum mycobacterial loads (AOR = 3.18; 95% CI = 1.33–8.11), and more than four TB signs and symptoms (AOR = 2.74; 95% CI = 1.18–6.73).

Table 2 Characteristics of smoking in TB patients

Variable		Bivariable		Multivariable	
		Odds ratio (95% CI)	*P*-value	Adjusted odds ratio (95% CI)	*P*-value
Education level	Secondary	Reference		Reference	
	None	0.82 (0.18–2.87)	0.774	0.92 (0.11–6.26)	0.932
	Primary	1.46 (0.83–2.54)	0.185	1.58 (0.69–3.64)	0.282
	University	0.49 (0.11–1.57)	0.278	0.46 (0.08–2.19)	0.350
High-risk alcohol consumption	No	Reference		Reference	
	Yes	8.95 (5.03–16.65)	< 0.001	6.26 (2.97–13.83)	< 0.001
Diagnostic delay	No	Reference		Reference	
	Yes	6.16 (3.61–10.71)	< 0.001	8.18 (3.67–19.56)	< 0.001
Sputum grading	2+	Reference		Reference	
	3+	2.66 (1.42–5.22)	0.003	3.18 (1.33–8.11)	0.012
	1+	2.25 (0.94–5.36)	0.067	3.19 (0.96–10.84)	0.060
	rare	2.07 (0.51–7.34)	0.273	3.56 (0.53–22.28)	0.178
HIV coinfection	No	Reference		Reference	
	Yes	0.54 (0.30–0.94)	0.035	1.19 (0.50–2.83)	0.699
More than four signs and symptoms	No	Reference		Reference	
	Yes	1.32 (0.77–2.30)	0.321	2.74 (1.18–6.73)	0.022

OR = odds ratio; TB = tuberculosis. Factors related to smoking at the time of TB diagnosis at multivariate logistic regression level. Adjusted for age, gender, and history of TB treatment.

DISCUSSION

The results show a high prevalence of smoking among TB patients diagnosed in Lambaréné between 2016 and 2019. Smoking was associated with alcohol consumption, more TB symptoms, higher sputum mycobacterial load, and consultation delay.

Similar to studies conducted in Senegal and Iran [14,15], we found a 30% prevalence of smokers among the included patients. This prevalence is higher than that reported in the general Gabonese population, especially in men [9]. However, the smoking prevalence observed in our cohort was lower than that in other countries, with approximately 40% (Malaysia) and 50% (South Africa) having been reported [16,17]. This difference could be

due to a background of tobacco-smoking habits in each country. The smoking prevalence in Malaysia's and South Africa's general population is higher than that in Gabon [18]. On the other hand, one explanation could be the choice of inclusion criteria in our study. As mentioned, we only included bacteriologically confirmed pulmonary TB patients, and daily smoking was used to categorize a smoker.

Effective TB control requires early diagnosis and prompt treatment. In our study, smoking was associated with consultation delay. Similar results were reported from Spain and Morocco [19,20]. Although the most common symptom of TB is cough, it may be difficult to perceive coughing as a hint of an underlying condition such as TB in smoking patients who are prone to coughing anyway. As in studies from Tunisia and Senegal [14,20], smokers in our study experienced more signs and symptoms. Smoking severely impedes the pulmonary immune system's function mainly via the inhibition of innate immune responses and pulmonary T-cell recruitment [22,23]. This could explain why smoking exposes one to more severe TB.

Our results showed higher mycobacterial loads among smoking TB patients at the time of diagnosis. These findings are similar to those reported by other studies [6,24]. Several studies in animal models and humans have shown that exposure to tobacco smoke causes immunological changes, acting on alveolar macrophages by decreasing the production of tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), and mucociliary clearance, thus promoting disease progression [22,23,25]. The increased severity of TB due to cigarette smoking is also seen on chest radiography, often exhibiting advanced lung lesions and cavitations in smokers, which could explain the capacity to produce more mycobacteria in the sputum by smoking patients [26,27].

Another finding in our study is the high prevalence of HIV coinfection and alcohol consumption. The HIV and TB coinfection rate was 31% in our study, and this is similar to a previous report on adults in Lambaréné [28]. This rate is higher than the 18% estimated by the WHO in the Gabon TB country profile in 2018 [29]; a difference that could be attributed to the number of TB patients tested for HIV in the WHO country report. Indeed, only 48% of TB cases were tested for HIV according to the data reported by the WHO. This underlines the importance to improve the screening of HIV in all TB patients in Gabon.

More than 40% of TB patients in our cohort were high-risk alcohol users, and alcohol consumption was associated with smoking. These two factors are classically associated with TB and have been reported in many studies [19,26,30]. However, the prevalence of high-risk alcohol consumption in our study is higher than that reported from Tanzania and Nigeria [30,31] Compared with other regions in Africa, Gabon had a higher general population alcohol consumption level and pattern [32]. These alcohol consumption levels are indeed relevant to many countries with high TB burdens[31]. To that end, in Gabon, interventions can be implemented to reduce the harm due to alcohol consumption. Such interventions include implementing regulations of the environment in which alcohol is

marketed, as well as individually directed interventions for those with at-risk levels of alcohol consumption.

We covered all TB diagnosis and treatment sites in the Moyen-Ogooué region. All pulmonary TB patients diagnosed during the study period were given the chance to be included. This is the first study in Gabon to investigate the burden of smoking among TB patients. Our study shows for the first time that in Gabon, the epidemiological profile of smoking TB pulmonary patients is characterized by the delay of consultation and the higher mycobacterial load. Therefore, TB smoking patients going undiagnosed could increase the community transmission of TB. A more structured study would be necessary to determine the impact of smoking on the community transmission of TB.

This study has some limitations such as a potential misclassification of exposure. This could be because the questionnaire used contained no information on other forms of tobacco intake. More so, we did not consider former smoking, and, most importantly, we had to confine our study to a single center. The restriction to a single center was due to limited resources and infrastructure not permitting us to conduct such research across the country at this stage. The logical next step is to perform such a study in Gabon and beyond across the Central African region in a multicentre prospective study, to understand the bigger epidemiological picture. Furthermore, the self-report approach was used to record tobacco consumption, and this can raise the issue of the credibility of participant answers. However, a study conducted by Brunet et al [17] in South Africa showed that self-reported tobacco consumption is an accurate measure of smoking status. Because of the cross-sectional design, the study showed an only an association between smoking and TB from the epidemiological point of view, and cannot show causality. That notwithstanding, we provide valuable information illustrating the prevalence of cigarette smoking among TB patients in Lambaréné and its association with TB manifestation.

CONCLUSION

In summary, our findings indicate a high prevalence of smoking among TB patients in Lambaréné. Tuberculosis patients who smoke demonstrate a greater delay in TB diagnosis, more TB-associated signs and symptoms, and a higher sputum mycobacterial load. National TB control programs in an endemic setting such as Gabon should include investigations of smoking behaviour and offer smoking cessation interventions. Community-based activities with the intention to screen TB among smokers should be envisaged, to facilitate early TB diagnosis among such populations and reduce TB transmission.

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REFERENCES

1. World Health Organization, 2019. Global Report on Trends in Prevalence of Tobacco Use 2000–2025, 3rd edition. Geneva, Switzerland: WHO. Available at: http://apps.who.int/iris/. Accessed February 29, 2020.
2. Bates MN, Khalakdina A, Pai M, Chang L, Lessa F, Smith KR, 2007.Risk of tuberculosis from exposure to tobacco smoke: a systematic review and meta-analysis. Arch Intern Med 167: 335–342.
3. Lugos MD, Hill PC, Hammond AS, Kendall L, Donkor S, Brookes RH, Owiafe PK, Ota MOC, Adetifa IMO, 2017. Mycobacterium tuberculosis infection in close childhood contacts of adults with pulmonary tuberculosis is increased by second-hand exposure to tobacco. Am J Trop Med Hyg 97: 429–432.
4. Tachfouti N, Nejjari C, Benjelloun MC, Berraho M, Elfakir S, El Rhazi K, Slama K, 2011. Association between smoking status, other factors and tuberculosis treatment failure in Morocco. Int J Tuberc Lung Dis 15: 838–843.
5. Maciel EL et al., 2013. Smoking and 2-month culture conversion during anti-tuberculosis treatment. Int J Tuberc Lung Dis 17:225–228.
6. Rathee D, Arora P, Meena M, Sarin R, Chakraborty P, Jaiswal A, Goyal M, 2016. Comparative study of clinico-bacterioradiological profile and treatment outcome of smokers and non-smokers suffering from pulmonary tuberculosis. Lung India 33: 507–511.
7. Das S, Basu M, Mandal A, Roy N, Chatterjee S, Dasgupta A, 2017. Prevalence and determinants of delay in diagnosis of pulmonary tuberculosis in Darjeeling district of West Bengal. J FamMed Prim Care 6: 627–635.
8. Rangaka MX, Cavalcante SC, Marais BJ, Thim S, Martinson NA,Swaminathan S, Chaisson RE, 2015. Controlling the seedbeds of tuberculosis: diagnosis and treatment of tuberculosis infection. Lancet Lond Engl 386: 2344–2353.
9. World Health Organization, 2019. Report on the Global Tobacco Epidemic, Gabon Country Profile. Geneva, Switzerland: WHO.Avaialble at: https://www.who.int/gho/countries/gab/country_profiles/en/. Accessed February 29, 2020.
10. World Health Organization, 2000. International Guide for Monitoring, Alcohol Consumption and Related Harm. Geneva, Switzerland: WHO. Available at: https://apps.who.int/iris/handle/10665/66529/. Accessed March 29, 2019.
11. World Health Organization, 2007. TB Diagnostics and Laboratory Strengthening. Definition of a New Sputum Smear-Positive TB Case. Geneva, Switzerland: WHO. Available at: https://www.who.int/tb/laboratory/policy_sputum_smearpositive_tb_case/en/. Accessed April 29, 2020.
12. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG, 2009. Research electronic data capture (REDCap)–a meta data driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 42:377–381.
13. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, McLeod L, Delacqua G, Delacqua F, 2019. The REDCap consortium: building an international community of software platform partners. J Biomed Inform 95: 103208.
14. Kombila UD, Mbaye FBR, Dia Kane Y, Ka W, Toure Badiane NO, 2018. Particularit´ es cliniques et radiologiques de la tuberculose pulmonaire chez le tabagique. Rev Mal Respir 35: 538–545.

15. Aryanpur M, Masjedi MR, Hosseini M, Mortaz E, Tabarsi P, Soori H, Emami H, Heydari G, Baikpour M, 2016. Cigarette smoking in patients newly diagnosed with pulmonary tuberculosis in Iran.Int J Tuberc Lung Dis 5: 679–684.

16. Awaisu A, Nik Mohamed MH, Abd Aziz N, Syed Sulaiman SA, Mohamad Noordin N, Muttalif AR, Ahmad Mahayiddin A, 2010. Tobacco use prevalence, knowledge, and attitudes among newly diagnosed tuberculosis patients in Penang state and Wilayah Persekutuan Kuala Lumpur, Malaysia. Tob Induc Dis 8: 3.

17. Brunet L et al., 2011. High prevalence of smoking among patients with suspected tuberculosis in South Africa. Eur Respir J 38: 139–146.

18. Global Health Observatory Data Repository, 2015. Prevalence Most Recent Adult Survey Data by Country. Available at: http://apps.who.int/gho/data/node.main.TOB1249?lang=en/. Accessed February 29, 2020.

19. Jim ´ enez-Fuentes MA et al.; TRWG, 2016. Factors associated with ´smoking among tuberculosis patients in Spain. BMC Infect Dis16: 486.

20. Janah H, Souhi H, Kouissmi H, Marc K, Zahraoui R, Benamor J,Soualhi M, Bourkadi JE, 2014. La tuberculose pulmonaire et le tabac : a propos de 100 cas [article in French]. Pan Afr Med J 19:202.

21. Fekih L, Boussoffara L, Abdelghaffar H, Hassene H, Fenniche S,Belhabib D, Zouari B, Megdiche ML, 2010. Effet du tabagisme sur la tuberculose pulmonaire. Rev Med Liege 65: 152–155.

22. Shaler CR, Horvath CN, McCormick S, Jeyanathan M, Khera A, Zganiacz A, Kasinska J, Stampfli MR, Xing Z, 2013. Continuous and discontinuous cigarette smoke exposure differentially affects protective Th1 immunity against pulmonary tuberculosis. PLoS One 8: e59185.

23. Aryanpur M, Mortaz E, Reza Masjedi M, Tabarsi P, 2016. Reduced the phagocytic capacity of blood monocyte/macrophages in tuberculosis patients is further reduced by smoking. Iran J Allergy Asthma Immunol 3: 174–182.

24. Prasad R, Suryakant, Garg R, Singhal S, Dawar R, Agarwal G, 2009. A case-control study of tobacco smoking and tuberculosis in India. Ann Thorac Med 4: 208–210.

25. Feng Y et al., 2011. Exposure to cigarette smoke inhibits the pulmonary T-cell response to influenza virus and Mycobacterium tuberculosis. Infect Immun 79: 229–237.

26. Altet-Gomez MN, Alcaide J, Godoy P, Romero MA, 2005. Clinical and epidemiological aspects of smoking and tuberculosis: a study of 13,038 cases. Int J Tuberc Lung Dis 9: 430–436.

27. Leung CC et al., 2015. Smoking adversely affects treatment response, outcome and relapse in tuberculosis. Eur Respir J 45:738–745.

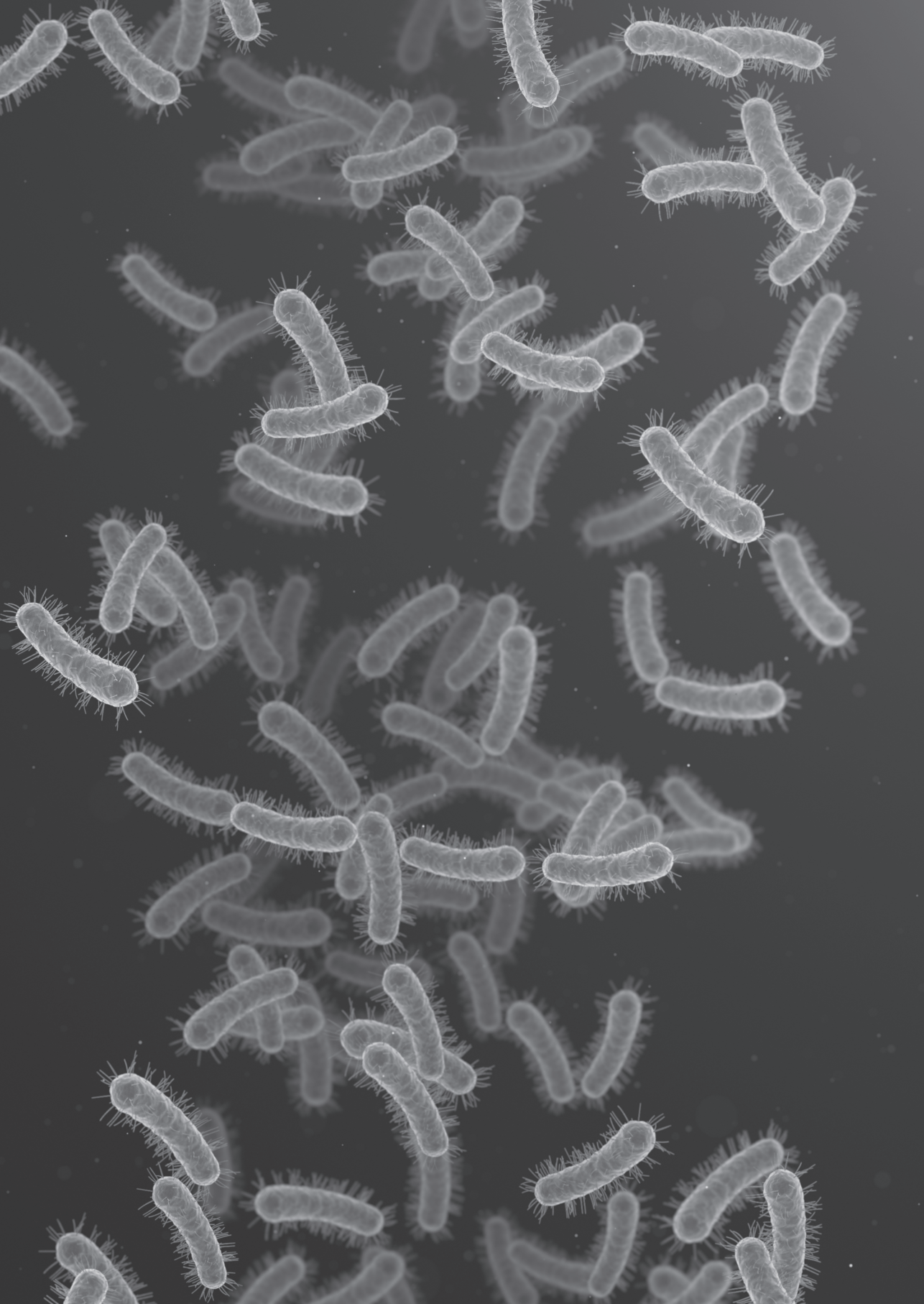
28. Niemann S et al., 2016. Tuberculosis treatment outcome and drug resistance in Lambaréné, Gabon: a prospective cohort study. Am J Trop Med Hyg 95: 472–480.

29. World Health Organization, 2018. Tuberculosis Country Profiles. Geneva, Switzerland: WHO. Available at: http://www.who.int/tb/country/data/profiles/en/. Accessed June 22, 2018.

30. Mwiru RS, Nagu TJ, Kaduri P, Fawzi W, Mugusi F, 2018. Prevalence and factors associated with alcohol drinking among HIV and tuberculosis co-infected patients in Dar es Salaam, Tanzania. AIDS Care 30: 173–177.

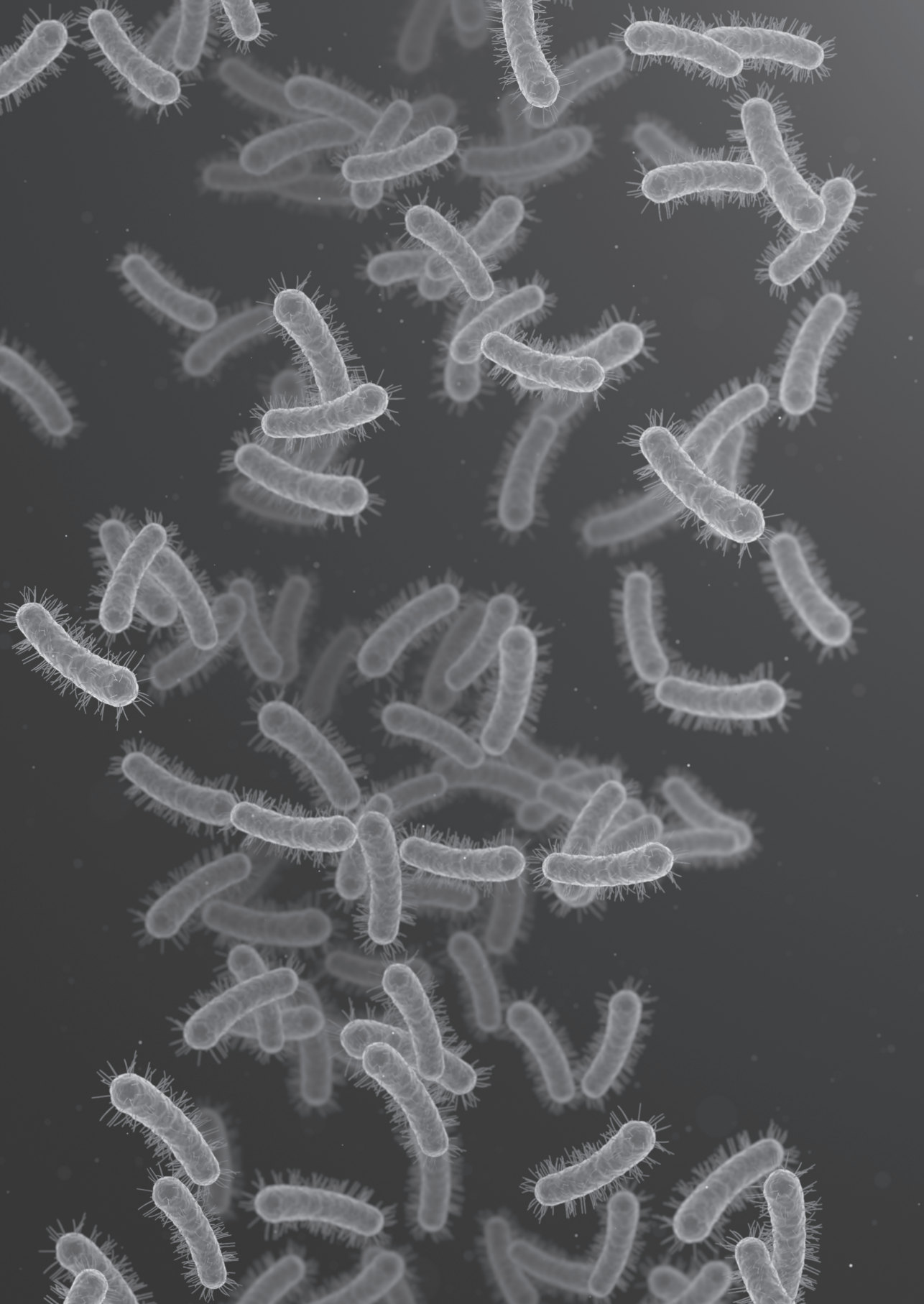
31. Imtiaz S, Shield KD, Roerecke M, Samokhvalov AV, Lonnroth K, Rehm J, 2017. Alcohol consumption as a risk factor for tuberculosis: meta-analyses and burden of disease. Eur Respir J 50:1700216.

32. World Health Organization, 2018. Alcohol Consumption: Levels and Patterns; Data by Country Gabon: Country Profiles. Geneva, Switzerland: WHO. Available at: https://www.who.int/gho/countries/gab/country_profiles/en/. Accessed May 4,2020.



Part 2

Drug-resistant tuberculosis in Gabon



Chapter 4

Resistance patterns among multidrug-resistant tuberculosis patients and trends-over-time analysis of national surveillance data in Gabon

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ABSTRACT

Objective: Routinely generated surveillance data are important for monitoring the effectiveness of MDR-TB control strategies. The incidence of rifampicin-resistant tuberculosis (RR-TB) is a key indicator for monitoring MDR-TB.

Methods: In a longitudinal nationwide retrospective study, eight years (2014-2021) of sputum samples from presumptively drug-resistant tuberculosis patients from all regions of Gabon were referred to the national tuberculosis reference laboratory. Samples were analysed using GeneXpert MTB/RIF and Genotype MTBDRsl version 2/Line Probe Assay.

Results: Of 3057 sputum samples from presumptive tuberculosis patients, both from local hospitals- as well as from referral patients; 334 were RR-TB. The median patient age was 33 years (interquartile range 26-43); one-third were newly-diagnosed drug-resistant tuberculosis patients; one-third were HIV-positive. The proportion of men with RR-TB was significantly higher than that of women (55% vs 45%; $p<0.0001$). Patients aged 25-35 years were most affected (32%; 108/334). The cumulative incidence of RR-TB was 17 (95% CI 15-19)/100,000 population over eight years. The highest incidences were observed in 2020 and 2021. A total of 281 samples were analysed for second-line drug resistance. The proportions of study participants with MDR-TB, pre-XDR-TB, and XDR-TB were 90.7% (255/281), 9% (25/281), and 0.3% (1/281), respectively. The most common mutation in fluoroquinolones resistance isolates was gyrA double mutation gyrA MUT3B and MUT3C (23%; 4/17). Most (64%; 6/8) second-line injectable drugs resistance isolates were characterised by missing both rrs WT2 and MUT2 banding.

Conclusion: The increasing incidence of MDR-TB infection in Gabon is alarming. It is highest in the 25-35 years age category. The incidence of MDR-TB infection in treatment-naïve patients calls for case-finding and contact-tracing strategy improvement.

INTRODUCTION

Multidrug-resistant tuberculosis (MDR-TB) is defined as tuberculosis caused by mycobacteria being resistant to at least rifampicin and isoniazid (the two essential first-line therapy backbone compounds) [1]. The global threat of MDR-TB highlights the need of identifying such resistance as soon as possible. About 470,000 people were diagnosed with MDR-TB and approximately 180,000 die every year, according to recent World Health Organization (WHO) estimates [1]. Rifampicin-resistant tuberculosis (RR-TB) infection is caused by a strain that is resistant to rifampicin with or without resistance to other first-line anti-TB drugs. Studies on drug resistance development show that isoniazid resistance develops first in most cases, followed by resistance to rifampicin or ethambutol, then resistance to pyrazinamide; and lastly, resistance to second-and third-line drugs [2–4]. Therefore, RR-TB without resistance to second-line drugs is generally considered as amounting to MDR-TB [4].

Gabon is one of the high-burden tuberculosis countries with an incidence of 527/ per 100.000 population [5,6], with a high prevalence of multidrug-resistant tuberculosis (MDR-TB) [7]. The alarming situation of the emergence of MDR-TB triggered a major effort to establish molecular surveillance and clinical care capacity in the country [7,8].

Few Sub-Saharan African countries report data on the burden of DR-TB based on periodic national data assessments [9,10]. We describe the national trends and the resistance pattern of rifampicin-resistant TB over eight years (2014-2021) in Gabon.

METHODS

Study design and participants

This is a retrospective longitudinal study using the national drug-resistant tuberculosis data. All records of patients with drug-resistant tuberculosis whose samples were submitted during the period between January 2014 and December 2021 were eligible. The STrengthening Reporting of Observational Studies in Epidemiology (STROBE) guideline has been followed to report this study [11].

Study setting and data collection

The national tuberculosis control program (PNLT) extended the national rifampicin resistance diagnostic capacity by providing each province with a GeneXpert machine in 2018. All of the provinces ship the rifampicin-resistant samples to the TB Reference Laboratory of the Centre de Recherches Médicales de Lambaréné (CERMEL), Gabon. As recommended by Gabon's national TB guidelines, the following patients are eligible for GeneXpert testing: children younger than fifteen years; people living with HIV; patients

with a history of TB treatment; case contacts of MDR-TB patients; and any patients considered to be at risk of having RR-TB by the attending physician. In case RR-TB is detected, second-line anti-TB drug resistance testing was performed. Since data was collected before the WHO 2021 updated definition of XDR and pre-XDR tuberculosis, the cases were defined and treated following the 2013 consolidated guidelines on drug-resistant tuberculosis [12]. Therefore, rifampicin resistance without resistance to the second-line drugs (levofloxacin, moxifloxacin, kanamycin, amikacin, and capreomycin) was considered to be MDR-TB and treated with second-line anti-TB drugs. Pre-extensively drug-resistant tuberculosis (pre-XDR-TB) was defined as resistance to at least rifampicin plus either a fluoroquinolone (levofloxacin, or moxifloxacin) or a second-line injectable anti-TB drug (kanamycin, amikacin, or capreomycin); extensively drug resistance tuberculosis (XDR-TB) as resistance to at least rifampicin to a fluoroquinolone and to a second-line injectable anti-TB drug.

Sputum sample collection and laboratory analysis

Two sputum samples from patients with presumptive pulmonary tuberculosis were collected. The sputa of patients with rifampicin resistance tuberculosis detected by GeneXpert MTB/RIF (Cepheid, Sunnyvale, CA, USA) were further analysed for second-line drug resistance using the Genotype MTBDRsl/ Line probe assay (Hain Life Science GmbH, Nehren, Germany). The GeneXpert MTB/RIF and Genotype MTBDRsl/ Line probe assay tests were carried out according to manufacturer instructions [13,14]. The line probe assay is a deoxyribonucleic acid (DNA) strip-based test determining *Mycobacterium tuberculosis* drug-resistant strains. It identifies resistance due to mutations in gyrA (from codon 85 to 96) and gyrB (from codon 536 to 541) [2] genes for fluoroquinolone (levofloxacin, or moxifloxacin), the rrs gene's (nucleic acid position 1401, 1402 and 1484) and the eis gene's promoter region (from -37 to -2 nucleotides upstream) for detection of resistance to the second-line injectable anti-TB drugs (kanamycin, amikacin, or capreomycin) used during the earlier years of the study period. Mutations are detected by either the binding of amplicons to probes targeting the most commonly occurring mutations (MUT probes); or by the lack of hybridisation (i.e. lack of binding) of the amplicons to the corresponding WT probes [13].

Data management and statistical analysis

The cumulative incidences with confidence intervals per (CI) 100,000 were calculated using RR-TB cases per the population estimate based on data from the National Population Census and Worldometer estimation [15]. Statistical analyses were performed using RStudio (R Foundation for Statistical Computing, Vienna, Austria). Quantum Geographic Information System software was used to identify the spatial trends of RR-TB and GeneXpert machine availability [16]. We investigated the variations in trends of RR-TB,

MDR-TB and pre-XDR-TB incidences and estimated the average annual per cent change (AAPC) with their 95% CI using a Joinpoint Trend Analysis software(Version 4.9.1.0, United States) [17].

Ethical consideration: Using of routine retrospective data was approved by the Institutional Ethics Committee of CERMEL(CEI/0152021). No additional data was collected from the patient.

RESULTS

Characteristics of patients with RR-TB

The samples analysed included all samples received during the study period. including samples from the local hospitals, as well as referral samples. Only rifampicin-resistant samples were referred to CERMEL. Rifampicin-sensitive samples from other sites were not included in this study; as this study focused on drug resistance surveillance data only, we were unable to provide data for drug-sensitive cases. Among a total of 3057 presumptive tuberculosis patients' sputum samples analysed during the study period, 334 rifampicin-resistant TB patients were identified (Fig 1). The median age of patients with RR-TB was 33 years (IQR 26-43). A total of 103/334 (31%) RR-TB patients were newly-diagnosed with tuberculosis, and the HIV-positive proportion was 35% (118/334) (Table 1). HIV infection was more prevalent in the 35 to 45 years and 46 to 55 years categories (Supplementary File S1).

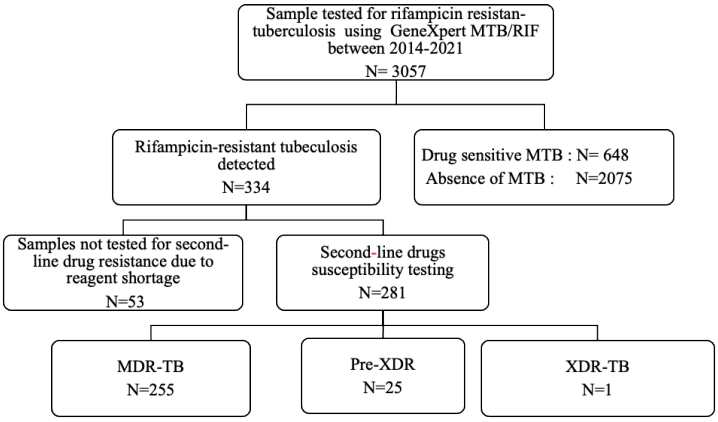

Figure1: Flowchart of patient recruitment and drug resistance pattern in Gabon from 2014-2021
Legend: MDR-TB(muti-drug resistant tuberculosis): resistance to rifampicin and resistance to isoniazid, without resistance to any second-line drugs; **pre-XDR-TB(pre-extensively drug-resistant tuberculosis):** resistance to at least rifampicin plus either a fluoroquinolone (levofloxacin, or moxifloxacin) or a second-line injectable anti-TB drug (kanamycin, amikacin, or capreomycin); **XDR-TB (Extensive drug-resistant tuberculosis):** resistance to any fluoroquinolone and to at least one of three second-line injectable drugs (capreomycin, kanamycin and amikacin), in addition to multidrug resistance.

Table1: Socio-demographic and baseline clinical characteristics of patients with rifampicin-resistant tuberculosis, Gabon, 2014–2021

Characteristic	All patients *N=334 (%)*	P-Value
Age group (Years)		**<0.0001**
15-24	55 (17)	
25-34	108 (32)	
35-44	67 (20)	
45-54	65 (19)	
55 and more	39 (12)	
Sex		**<0.0001**
Female	150 (45)	
Male	184 (55)	
HIV status		**<0.0001**
Negative	189 (57)	
Positive	118 (35)	
Unknown	27 (8)	
Patient category		**<0.0001**
New patient	103 (31)	
Previously treated for TB	174 (52)	
Unknown	57 (17)	

Incidence rate of rifampicin-resistant tuberculosis

Overall, the cumulative incidence of RR-TB was 17(95% CI 15-19)/100,000 inhabitants over eight years. More than half (54%;181/334) of the cases were from Estuaire province (the province around Libreville, the capital with an estimated 638,220 inhabitants in 2021); 26% (86/334) cases were from Moyen-Ogooué province (the province holding the reference tuberculosis laboratory), 7% (24/334) were from Ngounié, 6% (19/334) from Ogooué Maritime, 5% (16/334) from Woleu-Ntem, 2% (8/334) from Nyanga and Ogooué-Lolo provinces, respectively. The cumulative incidence of TB per province (region) showed that the Moyen-Ogooué had the highest incidence of RR-TB (Fig 2). Patients aged between 25 and 34 years old were most affected (32%,108/334); the proportion of men with RR-TB was significantly higher than that of women (55% vs 45%; p<0.0001; Table1).

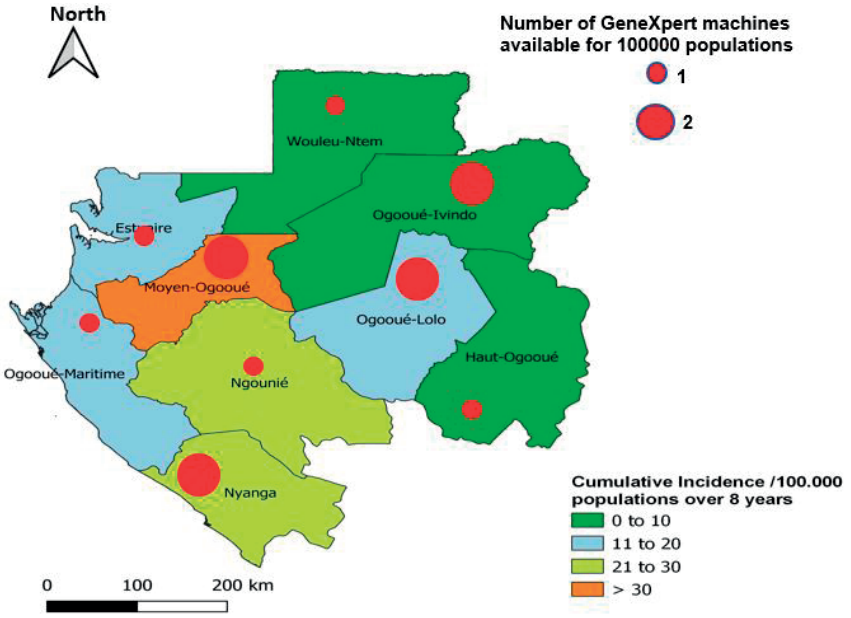

Figure 2: Rifampicin-resistant tuberculosis incidence per 100,000 population, Gabon, 2014–2021 superposed with GeneXpert machine availability

Drug resistance patterns

A total of 53 out of 334 samples were not passed on for second-line drug resistance analysis because of a temporary reagent shortage. The proportion of study participants having pre-XDR-TB and XDR-TB were 9% (25/281) and 0.3% (1/281), respectively (Fig 1). The proportion of patients with MDR-TB was 90.7% (255/281). A total of 17 fluoroquinolones

resistance isolates were identified. The most-common fluoroquinolone resistance banding pattern observed was the gyrA double mutation gyrA MUT3B and MUT3C (23%); 41% of isolates showed missing gyrA WT3 and MUT3A, MUT3B, MUT3C, MUT3D banding. For second-line resistance, eight defined mutations in the *rrs* gene were detected, and most (64% 6/8) of isolates were characterised by missing *rrs* WT2 and MUT2 banding. The XDR-TB case isolate was characterised by missing both *gyrA* WT3 and MUT3A, MUT3B, MUT3C, MUT3D banding and *rrs* WT2 and MUT2 banding (Table 2).

Table 2: Polymorphism patterns detected by Genotype MTBDRsl assay in drug-resistant ***Mycobacterium tuberculosis* strains**

Second-line drugs	Genes	MTBDRs Probe		Clinical implications
Fluoroquinolones resistance	*gyrA gene*	MUT 3A	2 (12)	Levofloxacin is not effective Moxifloxacin could be used at higher dose
		MUT3B	2 (12)	
		MUT 3C	1 (6)	Levofloxacin is not effective Moxifloxacin is not effective
		MUT3D	1 (6)	
		MUT3B and MUT3C	4(23)	
		gyrA WT3, MUT3A, MUT3B, MUT3C, MUT3D not developed	8 (41)	Levofloxacin is not effective Moxifloxacin could be used at higher dose
Total			N=17(100%)	
Second-line injectable drugs resistance	rrs gene	MUT 1	1 (12)	Amikacin, kanamycin and capreomycin are not effective
		rrs WT1 and MUT1 not developed	1 (12)	Kanamycin and capreomycin are likely not effective
		MUT 2	1 (12)	Amikacin, kanamycin and capreomycin are not effective
		rrs WT2 and MUT2 not developed	6 (64)	Kanamycin and capreomycin are likely not effective
Total			N=8(100%)	

Trends in incidence of rifampicin-resistant, pre-XDR and XDR-TB in Gabon 2014 –2021

Fig. 3 shows the trends in drug-resistant tuberculosis screening and its incidence from 2014 to 2021. The screening for drug-resistant tuberculosis increased significantly from 2016 to 2021, with the highest numbers observed between 2018 and 2020, before decreasing between 2020 and 2021. The incidence of RR-TB increased over time from one single case in 2014 to four cases per 100,000 inhabitants in 2021. The Joinpoint analysis showed that the incidence of RR-TB and MDR-TB have been increasing significantly by

18.7% per year (95%CI 2.9-37.1; p=0.027), and 18.8% (95%CI 0.8-39.8; p=0.042). The incidence of preXDR-TB did not change significantly (AAPC: 8.1; 95% CI -37.5-87.2; p=0.78).

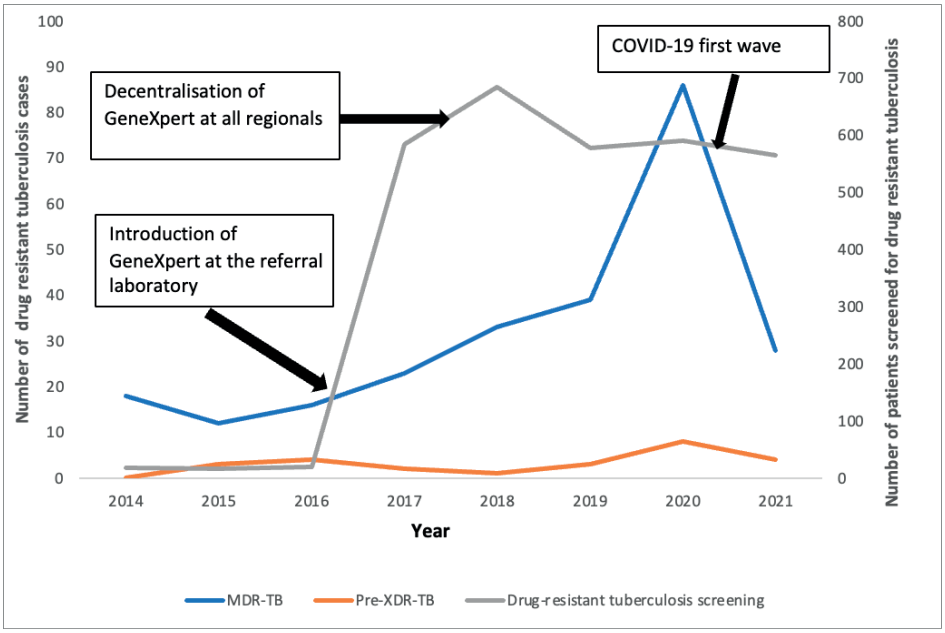

Figure 3. Trends over time of specimens sent in, and testing positive, for rifampicin-resistant tuberculosis in Gabon's referral tuberculosis laboratory between 2014-2021

DISCUSSION

We report patterns and trends over eight years of multidrug-resistant tuberculosis in Gabon. The overall incidence of MDR-TB is higher than what was reported in Uganda, the Republic of Congo [18], and Botswana [19], but lower than what was reported in South Africa in 2019 [20]. The higher burden of MDR-TB could be explained by the lack of resources to properly implement and supervise first-line drug treatment and might be owed in part to drug stock-outs. Indeed, TB treatment in Gabon is challenged by the intermittent unavailability of first-line drug treatment leading to involuntary discontinuation of TB treatment by the patients [21]. A contributor to the higher rate of loss-to-follow-up and discontinuation of treatment [7,22] is that most of the patients in the rural areas of the country live far from diagnostic and treatment facilities. This makes the directly observed TB treatment difficult to be applied. Our results further show that MDR-TB increased overtime, with the highest incidence observed between 2019 and 2020.

It could be explained by the fact that between 2017 and 2018 there was an unusually long period of first-line drug shortages and drugs were intermittently provided to patients. Moreover, in 2018, with the support of the Global Fund, the national tuberculosis control programme initiated the de-centralising of GeneXpert use in patients at risk of RR-TB. All of this contributed to the highest RR-TB case detection rates during the 2018 and 2020 periods. This case-finding strategy dynamics have been disrupted significantly by the COVID-19 pandemic which consequently reduced the number of RR-TB patients screened between 2020 and 2021 (Fig 3).

In our study, RR-TB was most frequently observed in 25- to 35-year-old, individuals. This is in line with the baseline characteristics of TB in Gabon reported earlier [8,22]. Our findings are comparable with what was reported by other studies conducted in Africa [9,23,24]. This population category is the most economically and socially active, with many contacts beyond the own household; being most exposed to and contributing most to the spread of tuberculosis. Furthermore, several tuberculosis-related co-morbidities including HIV infection, diabetes, smoking, illicit drug abuse, harmful alcohol consumption and mental health issues begin or worsen within this age category [25]. Finally, they encounter challenges in having access to adequate care due to many socio-economic factors. Therefore, tuberculosis control action should be intensified among adolescents and young adults in settings like those in Gabon. The high proportion of naïve TB treatment patients diagnosed with MDR-TB in the present national surveillance data-based study is an additional reason for adjusting and intensifying case finding and earlier initiation of MDR-TB treatment. Interestingly, the Moyen-Ogooué province yielded 26% of cases and the highest cumulative incidence per 100,000 inhabitants. This could be explained by the fact that the region holds the referral laboratory and the research centre where patients are actively screened for tuberculosis. The highest incidence is explained by the relatively small size of the population of this region as compared with the Estuaire province where more than half of the case was diagnosed.

Compared with other Central African countries (Congo and Cameroon), the proportion of pre-XDR TB in our study is higher [18,26], but lower as compared to what was reported in South Africa [20]. The studies in Congo and Cameroon were not conducted at the national level; however, the WHO country report confirms that the burden of MDR and pre-XDR TB in Gabon is the highest among those countries [27]. However, the small size of Gabon's general population should be considered for interpretation. The higher number of pre-XDR TB in Gabon could also be explained by the incorrect, and/or over-use of fluoroquinolones by some clinicians before the implementation of the national TB-MDR guidelines. The predominance of pre-XDR-TB has several important implications. Firstly, all patients with RR-TB (detected by GeneXpert) should mandatorily also have fluoroquinolones and other second-line anti-TB drugs tested for resistance before initiation of second-line TB treatment. Secondly, clinicians and decision-makers should

safeguard that the first-line drug-sensitive TB treatment guideline is followed properly to reduce the increase of MDR-TB.

The trend of pre-XDR incidence did not change significantly from 2014 to 2021. This is because since the first implementation in Gabon of the short MDR-TB treatment regimen and its recommendation by our team at the national level [8] up to 2020 (before the update of national MDR-TB treatment following the updated WHO recommendation replacing injectable second-line drugs), the MDR-TB patients were hospitalised during the whole treatment period and those receiving injectable drug ambulatorily, taking the oral drug under supervision. The patients are managed in selected healthcare centres in the country. This allows for rational use of the second-line drug and patient treatment compliance. However, the treatment is now increasingly becoming decentralised, including a range of regional hospitals to reduce patient transfer. The first case of XDR-TB was observed only recently (October 2021). The male patient was 38 years old, non-smoking, HIV-negative, and treated successfully (based on repeated smear negativity and 'clinical cure') in 2012 for drug-sensitive tuberculosis. This first case of XDR-TB alerted health authorities to the need for patients and health care training as well as an improved tuberculosis infection control strategy, in general, to avoid the spreading of XDR mycobacterium tuberculosis in the community.

As reported previously, our study confirms that most fluoroquinolone resistance is conveyed by gyrA mutations [28]. The detection of gyrase mutations helps to predict the presence and level of fluoroquinolone resistance. The high proportion of strains showing absences of both wild-type and polymorphisms in our study is an additional indication of the value of having the phenotypic drug sensitivity test (DST) and strain sequencing capacity in the referral tuberculosis laboratory to improve patient treatment, by adapting the drug regimen to the *Mycobacterium tuberculosis* strain causing the individual infection. To uncover transmission patterns at the population level, proper public health action based on tailored molecular-guided cluster analysis is ongoing by our research team. The sputum of patients is prospectively collected for the sequencing of the strain. The samples are sent to the collaborating centre in Borstel and training of local staff is done for capacity development.

Our study is subject to the usual limitations inherent to retrospective routinely-generated laboratory surveillance data. Moreover, there were some cases of RR-TB cases that did not undergo second-line DST, as no sample was sent to the national referral TB laboratory. We were not able to perform the phenotypic drug sensitivity test. The true national incidence of RR-TB might be slightly different from what is reported in our study. However, we received samples from patients living in all of the nine provinces of the country; therefore, our findings most likely provide a fair reflection of the general trends in RR-TB incidence in Gabon over the study period, assisting policymakers to adjust the MDR-TB control strategy. Given the rising prevalence of pre-XDR-TB surveillance

monitoring of TB treatment should be improved. We cannot exclusively associate the high incidence with an increase in cases. During the study period, there was an improvement in the case-finding strategy and diagnostic capacity of each regional laboratory. Consequently, an updated study will be necessary in future to confirm the hypothesis of a surge of cases of drug-resistant tuberculosis in Gabon.

CONCLUSION

During the past eight years, rifampicin-resistant TB incidence rates have consistently risen in Gabon, especially in the productive age group of the population. The extension of diagnostic capacity increases the total number diagnosed per year. Strengthening prevention and control programs, and actions should be imitated to reduce the burden of resistant tuberculosis. The national tuberculosis guideline should be revised for adding GeneXpert as a first-line diagnostic tool to improve earlier (and hence cost-effective) case detection. We also recommend national-level implementation and cost-effectiveness studies on decentralising drug-resistant tuberculosis treatment and home-based DOT. Moreover, further studies should be initiated to determine the transmission dynamics of multidrug-resistant strains using genotyping tools as well as studies aiming to investigate the risk factors for the development of MDR-TB in the population.

Author contributions: Conceptualisation BRA, JBA, MPG; methodology, BRA; data analysis, BRA and JBA; investigation, MED, RCM, CMB, JBA; JRE, TJD and JM; resources, AAA, MPG, AA, BL, PGK, SH; data curation, JBA; RCM, BRA; writing—original draft preparation BRA; writing review and editing, BRA, and MPG; supervision, MPG, AA and AAA. All authors have contributed to and agreed to the final version of the manuscript.

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Declaration

Potential conflict of interests: All authors declare that they have no competing interests to disclose.

REFERENCES

1. Word Health Organization (WHO) announces updated definitions of extensively drug-resistant tuberculosis. WHO Geneva [Internet]. 2021. Available from: https://www.who.int/news/item/27-01-2021-who-announces-updated-definitions-of-extensively-drug-resistant-tuberculosis
2. Manson AL, Cohen KA, Abeel T, Desjardins CA, Armstrong DT, Barry CE, et al. Genomic analysis of globally diverse Mycobacterium tuberculosis strains provides insights into the emergence and spread of multidrug resistance. Nat Genet. 2017;49:395–402.
3. Cohen KA, Abeel T, Manson McGuire A, Desjardins CA, Munsamy V, Shea TP, et al. Evolution of Extensively Drug-Resistant Tuberculosis over Four Decades: Whole Genome Sequencing and Dating Analysis of Mycobacterium tuberculosis Isolates from KwaZulu-Natal. PLoS Med. 2015;12:e1001880.
4. Meacci F, Orrù G, Iona E, Giannoni F, Piersimoni C, Pozzi G, et al. Drug Resistance Evolution of a Mycobacterium tuberculosis Strain from a Noncompliant Patient. J Clin Microbiol. 2005;43:3114–20.
5. Word Health Organization (WHO). Tuberculosis Gabon country profile [Internet]. Geneva: WHO; 2020. Available from: https://worldhealthorg.shinyapps.io/tb_profiles/?_inputs_&entity_type=%22country%22&lan=%22EN%22&iso2=%22GA%22
6. WHO global lists of high-burden countries for TB, multidrug/rifampicin-resistant TB (MDR/RR-TB) and TB/HIV, 2021–2025. Geneva: World Health Organization; 2021. [Internet]. Available from: https://cdn.who.int/media/docs/default-source/hq-tuberculosis/who_globalhbcliststb_2021-2025_backgrounddocument.pdf?sfvrsn=f6b854c2_9
7. Bélard S, Remppis J, Bootsma S, Janssen S, Kombila DU, Beyeme JO, et al. Tuberculosis Treatment Outcome and Drug Resistance in Lambaréné, Gabon: A Prospective Cohort Study. Am J Trop Med Hyg. 2016;95:472–80.
8. Ateba-Ngoa U, Edoa JR, Adegbite BR, Rossatanga EG, Madiou D, Mfoumbi A, et al. Implementation of multidrug-resistant tuberculosis (MDR-TB) treatment in Gabon: lessons learnt from the field. Infection. 2019;47:811–6.
9. Migliori GB, Dheda K, Centis R, Mwaba P, Bates M, O'Grady J, et al. Review of multidrug-resistant and extensively drug-resistant TB: global perspectives with a focus on sub-Saharan Africa: Drug-resistant TB. Trop Med Int Health. 2010;15:1052–66.
10. Dean AS, Zignol M, Cabibbe AM, Falzon D, Glaziou P, Cirillo DM, et al. Prevalence and genetic profiles of isoniazid resistance in tuberculosis patients: A multicountry analysis of cross-sectional data. PLoS Med. 2020;17:e1003008.
11. Elm E von, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. The Lancet. Elsevier; 2007;370:1453–7.
12. Word Health Organization. Definitions and reporting framework for tuberculosis – 2013 revision [Internet]. Geneva: WHO; 2014. Available from: https://apps.who.int/iris/bitstream/handle/10665/79199/9789241505345_eng.pdf?sequence=1
13. Cepheid international. Two-hour Detection of MTB and Resistance to Rifampicin.Xpert® MTB/RIF [Internet]. European Headquarters; Available from: https://p.widencdn.net/dmznvk/Cepheid-Xpert-MTB-RIF-Brochure-CE-IVD-0089-English

14. The Global Laboratory Initiative (GLI) Core, Group. Line probe assays for drug-resistant tuberculosis detection Interpretation and reporting guide for laboratory staff and clinicians [Internet]. GLI; Available from: https://stoptb.org/wg/gli/assets/documents/LPA_test_web_ready.pdf

15. Gabon population Data.net [Internet]. PopulationData.net. Available from: https://www.populationdata.net/pays/gabon/

16. QGIS Development Team (YEAR). QGIS Geographic Information System. Open Source Geospatial Foundation Project. http://qgis.osgeo.org.

17. Joinpoint Regression Program, Version 4.9.1.0 - April 2022; Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute.

18. Elion Assiana DO, Abdul JBPA, Linguissi LSG, Epola M, Vouvoungui JC, Mabiala A, et al. Epidemiological profile of multidrug-resistant and extensively drug-resistant Mycobacterium Tuberculosis among Congolese patients. Ann Clin Microbiol Antimicrob. 2021;20:84.

19. Mogashoa T, Melamu P, Derendinger B, Ley SD, Streicher EM, Iketleng T, et al. Detection of Second Line Drug Resistance among Drug Resistant Mycobacterium Tuberculosis Isolates in Botswana. Pathogens. 2019;8:208.

20. Ismail NA, Mvusi L, Nanoo A, Dreyer A, Omar SV, Babatunde S, et al. Prevalence of drug-resistant tuberculosis and imputed burden in South Africa: a national and sub-national cross-sectional survey. Lancet Infect Dis. 2018;18:779–87.

21. Bélard S, Janssen S, Osbak KK, Adegnika AA, Ondounda M, Grobusch MP. Limited access to drugs for resistant tuberculosis: a call to action. J Public Health Oxf Engl. 2015;37:691–3.

22. Adegbite BR, Edoa JR, Achimi Agbo P, Dejon-Agobé JC, N Essone P, Lotola-Mougeni F, et al. Epidemiological, Mycobacteriological, and Clinical Characteristics of Smoking Pulmonary Tuberculosis Patients, in Lambaréné, Gabon: A Cross-Sectional Study. Am J Trop Med Hyg. 2020;103:2501–5.

23. Shibabaw A, Gelaw B, Gebreyes W, Robinson R, Wang S-H, Tessema B. The burden of pre-extensively and extensively drug-resistant tuberculosis among MDR-TB patients in the Amhara region, Ethiopia. :13.

24. Ekaza N, Kacou-N'Douba A, Kouakou, Le Vacon, Altare, Potel,G, et al. Emergence in Western African countries of MDR-TB, focus on Côte d'Ivoire. BioMed Res Int [Internet]. Biomed Res Int; 2013 [cited 2022 Jan 20]; Available from: https://pubmed.ncbi.nlm.nih.gov/24093098/

25. Snow KJ, Sismanidis C, Denholm J, Sawyer SM, Graham SM. The incidence of tuberculosis among adolescents and young adults: a global estimate. Eur Respir J [Internet]. European Respiratory Society; 2018 [cited 2022 Apr 28];51. Available from: https://erj.ersjournals.com/content/51/2/1702352

26. Mbuh TP, Wandji A, Keugni L, Mboh S, Ane-Anyangwe I, Mbacham WF, et al. Predictors of Drug-Resistant Tuberculosis among High-Risk Population Diagnosed under National Program Conditions in the Littoral Region, Cameroon. De Molon RS, editor. BioMed Res Int. 2021;2021:1–9.

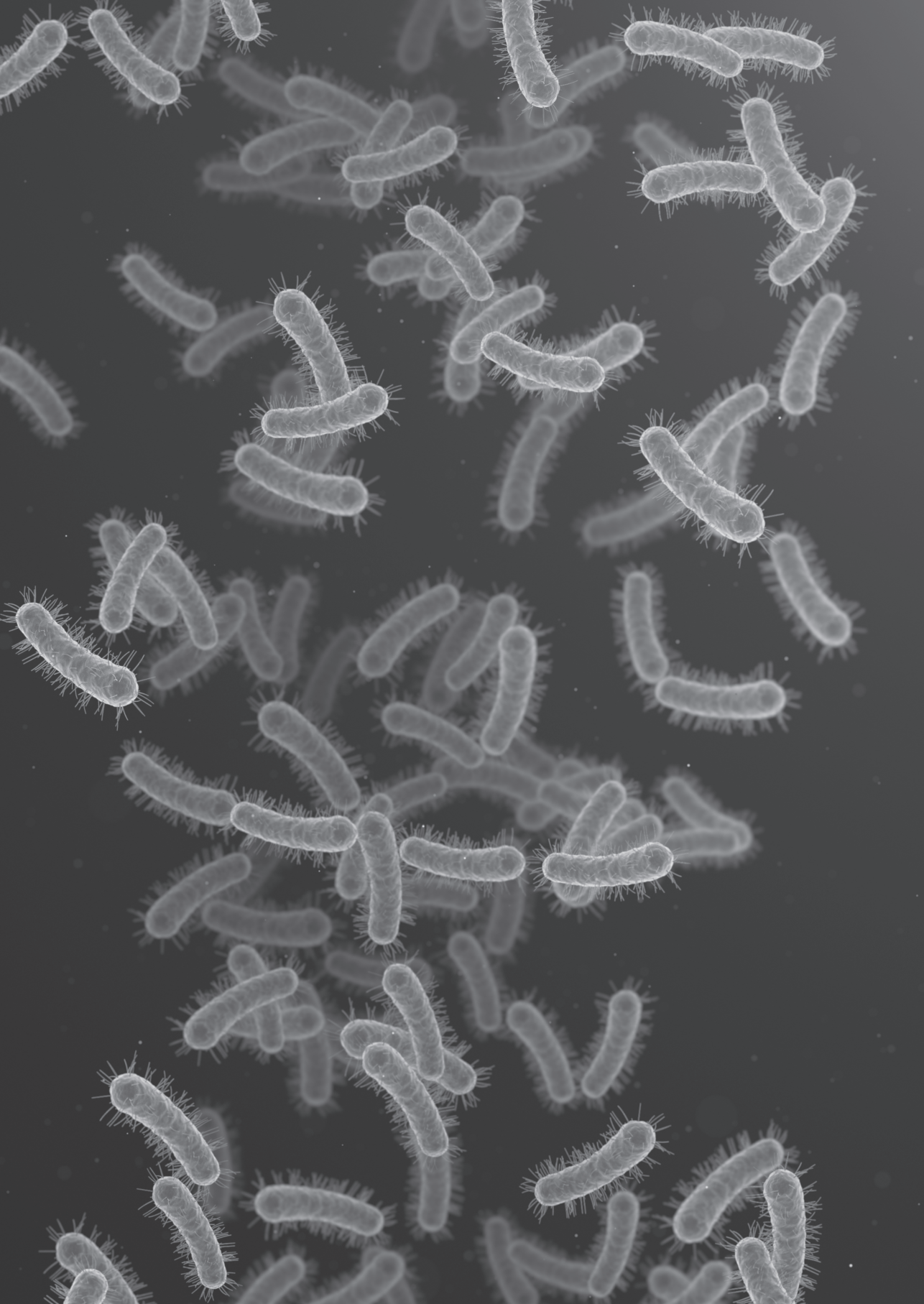
27. Global tuberculosis report 2021. Geneva: World Health Organization; 2021.

28. Kabir S, Tahir Z, Mukhtar N, Sohail M, Saqalein M, Rehman A. Fluoroquinolone resistance and mutational profile of gyrA in pulmonary MDR tuberculosis patients. BMC Pulm Med. 2020;20:138.

Supplementary File

Table S1. Participants according to age category

Characteristic	[15-25], N = 55	[25-35], N = 108	[35-45], N = 67	[45-55], N = 65	[55-97], N = 39
Patient category					
New patient	16 (29%)	35 (32%)	18 (27%)	24 (37%)	10 (26%)
Previously treated for TB	27 (49%)	57 (53%)	41 (61%)	27 (42%)	22 (56%)
Unknown	12 (22%)	16 (15%)	8 (12%)	14 (22%)	7 (18%)
SEX					
F	30 (55%)	56 (52%)	25 (37%)	25 (38%)	14 (36%)
M	25 (45%)	52 (48%)	42 (63%)	40 (62%)	25 (64%)
HIV status					
Negative	36 (65%)	65 (60%)	35 (52%)	25 (38%)	28 (72%)
Positive	17 (31%)	35 (32%)	27 (40%)	32 (49%)	7 (18%)
Unknown	2 (3.6%)	8 (7.4%)	5 (7.5%)	8 (12%)	4 (10%)



Chapter 5

Implementation of multidrug-resistant tuberculosis (MDR-TB) treatment in Gabon: lessons learnt from the field

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ABSTRACT

Purpose

Since May 2016, WHO recommended a 9–12 month short-treatment regimen for multidrug-resistant tuberculosis (MDR-TB) treatment known as the 'Bangladesh Regimen'. However, limited data exist on the appropriateness thereof, and its implementation in low- and middle-income countries (LMIC). We report here on the pilot phase of the evaluation of the Bangladesh regimen in Gabon, before its endorsement by the WHO.

Methods

Intensive training of hospital health workers as well as community information and education were conducted. GeneXpert-confirmed MDR-TB patients received the second-line anti-tuberculosis drugs (4KmMfxPtoHCfzEZ/5MfxCfzEZ). Sputum smears and cultures were done monthly. Adverse events were monitored daily.

Results

Eleven patients have been treated for MDR-TB piloting the short regimen. All were HIV-negative and presented in poor health with extensive pulmonary lesions. The overall sputum culture conversion rate was 64% after 4 months of treatment. Three patients developed marked hearing loss; one was a transient cutaneous rash. Of 11 patients in our continuous care, 7 (63.6%) significantly improved clinically and bacteriologically. One (9.1%) patient experienced a treatment failure, two (18.2%) died, and one (9.1%) was lost to follow-up.

Conclusions

Our pioneering data on systematic MDR-TB treatment in Gabon, with currently an almost total absence of resistance against the second-line drugs, demonstrate that a 9-month regimen has the capacity to facilitate early culture negativity and sustained clinical improvement. Close adverse events monitoring and continuous care are vital to success.

Keywords: **Multidrug resistance; Tuberculosis; Gabon; Short-course regimen**

INTRODUCTION

Multidrug-resistant tuberculosis (MDR-TB) and higher degrees of resistant tuberculosis are emerging health concerns including populations in sub-Saharan Africa, and a massive threat to TB programmes in many low- and middle-income countries [1]. However, in the majority of these countries, patients often only have very limited access to MDR-TB treatment and data are still scarce on incidence, prevalence, molecular characteristics, treatment, and outcome [1]. In Gabon, despite case reports of treatment failure to the first-line TB therapy [2], it was only in 2013 that a more comprehensive assessment of the epidemiology of MDR-TB was conducted for the first time [3]. This study, carried out in Lambaréné, a semi-urban town of around 30.000 inhabitants, indicated an MDR rate of 4/91 (4%) and 4/13 (31%) in new and retreatment TB cases, respectively [3]. This rate is quite high and is comparable to the prevalence reported from highly MDR-TB endemic countries [4, 5]. At the time of the official report on the first MDR-TB cases in Lambaréné and their growing number, the Gabonese TB programme lacked access to second-line anti-tuberculosis drugs as well as specialized and dedicated treatment facilities [6]. In response to this epidemic, MDR-TB was recognized as a public health emergency in Gabon; and in September 2015, the first MDR-TB treatment center was opened in Lambaréné, at the Georges Rawiri Hospital (GRH), with technical support provided by CERMEL's clinical and mycobacteriology laboratory teams. In parallel, the Centre de Recherches Médicales de Lambaréné (CERMEL) obtained funding from the German Ministry of Health for the acquisition of the second-line anti-tuberculosis drugs for the evaluation of a 9–12 month short-course treatment regimen of MDR-TB. This short-course treatment was already evaluated by the International Union Against Tuberculosis and Lung Disease (IUALTD, 'The Union') in several countries in Africa and Bangladesh before its endorsement by the WHO in May 2016 [7]. As a result of the collaboration between CERMEL and the Ministry of Health in Gabon, the first MDR-TB patients were initiated on a short-course treatment regimen in September 2015; in a study aimed at evaluating the implementation of the 9–12-month short regimen for the treatment of MDR-TB. We report here the experience gained during the treatment of those first MDR-TB patients in Gabon' and comment on the appropriateness of the standard 9-month regimen in our setting.

METHODS

Study design

Data presented in this small pilot case series were collected from the first participants—with bacteriologically confirmed multidrug-resistant tuberculosis (MDR-TB). The study protocol was largely inspired by The Union research protocol implemented in nine

countries in Africa, aimed at testing the efficacy and effectiveness of a 9-month short-course regimen for the treatment of MDR-TB [8].

Study site and study population

This ongoing study is conducted by CERMEL. The patients, all originating from the Moyen Ogooue province of Gabon, were followed up at the GRH in Lambaréné and at the Bongolo Evangelical Hospital (BH) in Lebamba. The study population consists of consecutive patients with bacteriologically confirmed MDR-TB, and no randomisation procedure was performed. Patients were included in the study if they are 15 years of age or older; have never been treated with the second-line anti-TB drugs for more than 1 month; and provided written informed consent to participate and intend to adhere to treatment, including hospitalisation for possibly months according to need, and willingness to accept treatment directly observed by a health worker. Patients were excluded from the study in case of pregnancy; a very poor clinical condition as judged by the specialist clinician in charge; a history of hypersensitivity to any of the drugs or a QTc interval of longer than 500 ms in the baseline ECG.

MDR-TB diagnosis samples for mycobacterial investigation were first analysed by microscopy as per the national guidelines. Both the conventional Ziehl–Neelsen (ZN) and auramine fluorochrome (FM) staining were used, with interpretation (positivity) based on the results of the latter. Samples were concomitantly processed with the Gene Xpert MTB/RIF assay according to the manufacturer's instructions. The mycobacteria growth indicator tube, MGIT (BACTEC MGIT 960 TB System, BD Diagnostics), was used for mycobacterial culture and drug susceptibility testing (DST). *Mycobacterium tuberculosis* Complex (MTBC) was confirmed in positive cultures by the GenoType MTBC assay (Hain Life Sciences, Nehren, Germany). DST of confirmed MTBC isolates to the first-line drugs RIF, INH, EMB, PZA, and STR was performed using the MGIT 960 system following the manufacturer's instructions (BBLTM MGIT™ SIRE and PZA test kits, Becton–Dickinson, Franklin Lakes, NJ, USA). In case of any resistance to the first-line drugs, DST was also performed for the following second-line drugs: ethionamide (ETO), ofloxacin (OFX), cycloserine (CS), amikacin (AM), 4-aminosalicylic acid (PAS), and capreomycin (CM). For quality control purposes and genotyping, part of the samples were referred to a collaborating supranational laboratory, the German National Reference Center (NRC) for Mycobacteria in Borstel, Germany.

Treatment regimen

The treatment regimen comprises an intensive phase of 4 months with Kanamycin (Km), Moxifloxacin (Mfx), Prothionamide (Pto), Clofazimine (Cfx), Isoniazid (H), Ethambutol (E), and Pyrazinamide (Z) (4KmMfxPtoHCfzEZ) followed by a continuation phase of 5 months comprising MfxCfzEZ. All drugs are given daily under direct observation (DOT); the dosage of each medication is according to weight.

Follow-up during treatment

All patients were hospitalised during the intensive phase to increase treatment adherence and for optimal recording of drug-related adverse events. During this phase, direct sputum smear microscopy and culture were performed monthly to monitor sputum conversion. If direct sputum smear microscopy and sputum culture remained positive at the end of month 4, the intensive phase was extended for a maximum of 2 months [8]. Treatment of patients failing to respond bacteriologically (lack of conversion) at the end of month 6 would be discontinued and switched to individualised treatment, subject to the availability of appropriate replacement drugs. Patients who had sputum conversion at the end of the intensive phase were discharged from the hospital at the start of the continuation phase. Subsequently, treatment was provided daily at home under direct observation by a trained nurse, who also records any possible drug-related adverse events. All patients undergo periodic clinical and laboratory check-ups. To document any relapse, patients were followed up actively for 6 months, and were allowed to re-visit the research centre or the GRH unrestrictedly and for an unlimited period after the treatment period.

Monitoring and management of adverse drugs events

Adverse events, or absence thereof, were recorded daily by an attending nurse or physician during the medical round. Monitoring for adverse drug events also includes clinical evaluations and laboratory investigations performed periodically.

Data management and statistical analysis

Data on medical files were captured using RedCap. Treatment outcome was determined according to WHO definitions and its last reporting framework for tuberculosis [9]. Per-protocol and intention-to-treat analyses were applied to characterize treatment outcomes.

Ethical considerations

The study protocol was explained to each patient. Written informed consent was obtained from each participant or their legal representative before inclusion. The study was approved by the Gabon National Ethics Committee "Comité National d'Éthique pour la Recherche" (CNER) and received authorisation from the Ministry of Public Health of Gabon.

RESULTS

Patient description

The study started on 15th September 2016. We present data collected from the first 11 MDR-TB patients who have been treated with the 9-month short regimen. Patient characteristics on admission are presented in Table 1. In summary, ages ranged from 19

to 62 years with a median of 27 years. The sex ratio (M: F) was 1.75. All patients were HIV-negative; one was diabetic (diagnosed and under treatment before MDR-TB treatment initiation). Eight patients were previously treated for DS-TB, with most of them having received at least two treatment courses. The median number of previous DS-TB treatment episodes per patient was 3.

Table 1 Patient characteristics on admission

Patient no.	#1	#2	#3	#4	#5	#6	#7	#8	#9	#10	#11
Age in years	27	20	19	26	50	27	35	62	20	31	26
Sex	F	M	M	F	F	M	M	M	M	F	M
Number of previous Tx courses for DS-TB	3	2	3	5	0	3	4	3	UK	3	0
Last previous Tx for DS-TB	2013	2012	2012	2010	NA	2014	2014	2015	UK	2013	NA
Site of infection	P	P	P/EP	P/EP	P	P	P	P	P	P	P
Antibiotic resistance	INH, RMP, EMB, PZA, SM	INH, RMP, EMB, PZA, SM	INH, RMP, EMB, PZA	INH, RMP, EMB, PZA, SM	INH, RMP	INH, RMP, EMB, PZA	INH, RMP, EMB, PZA	INH, RMP, EMB, PZA	INH, RMP	INH, RMP	INH, RMP

The timing of routine examinations and laboratory investigations are summarized in Supplementary Table 1. Sputum examination at baseline showed the presence of AFB in all patients. Resistance to rifampicin was established by Gene Xpert MTB/RIF testing and further confirmed phenotypically by culture and DST. All patients' isolates were resistant to rifampicin, isoniazid, and pyrazinamide.

Treatment outcomes

Seven patients (63.6%) were cured, one (9.1%) failed treatment, two (18.2%) died, and one (9.1%) was lost to follow-up and could not be evaluated [9]. The overall sputum culture conversion rate was 64% after 4 months of treatment. All cured patients were actively followed up for additional 6 months after treatment, and none experienced a relapse.

Adverse events

In general, all patients developed at least one AE. Gastrointestinal symptoms were the most frequent but usually diminished by the end of the intensive phase. Five patients presented signs of a decreased hearing capacity that could not be objectified/quantified due to a lack of audiometric testing equipment. At month 2, one patient presented with a serious cutaneous hypersensitivity reaction. This condition resolved at month 4 after

adequate treatment. One patient presented with massive haemoptysis and one other patient was transferred back at her request to another hospital beyond reach for our team and developed terminal hepatic failure about 4 months after treatment initiation. Supplementary Table 2 provides the details of the nature and occurrence of adverse events (AEs) during the treatment phase and their duration.

Cost of treatment

The total cost of the treatment of all patients reported here amounted to 61,432 USD. The mean cost of the MDR-TB treatment per patient was 5585 USD. This overall cost included hospitalisation, laboratory tests, nutritional support, and drug costs; with the majority of drugs having been sourced through donations, the hospitalisation costs amounted to 80.6% of the total cost of treatment.

DISCUSSION

MDR-TB represents an emerging public health concern in Gabon. Despite the increasing number of cases, few, if any, treatment options were available in the country until recently [2, 3, 10]. Here, we report on the outcome of a pilot treatment phase that aimed to introduce and implement the 9–12 month short-regimen scheme before its endorsement by the WHO in May 2016 [7].

The appropriateness of the abridged WHO MDR-TB regime has been disputed [11]. Lange et al. [11] point out that given the respective prevailing drug resistance patterns e.g., in the Western European region and the Eastern European region, only 7.8% [12] and 4.2% [13] of patients with DR-TB would be eligible for the short-course regimen. In Singapore, Indonesia and other South East Asian countries, the figure would be 30% [14]; of the other regions examined, only Brazil would yield 50–55% eligible patients [15]. However, with until recently an almost complete absence of second- and third-line TB drugs [3], our setting renders patient cohorts such as the one presented here as an ideal candidate for the abridged WHO regimen, which is in situations where due to previous lack of access to second-line treatments, resistance to second-line drugs is by-and-large absent.

The medical history of the patients included in this case series indicates a delay in the diagnosis of MDR-TB that led to unnecessary and ineffective treatment with first-line drugs. Consequently, this led to profound health deterioration, extensive lung lesions, and irreversible sequelae such as chronic respiratory failure. Moreover, DST indicated that mycobacteria isolated from all patients were resistant to at least three of the first-line anti-tuberculosis drugs, which could be a consequence of repeated treatment [16] emphasising the importance of early diagnosis and treatment of MDR-TB.

Under the standardized treatment regimen, sputum culture conversion was obtained already after 3 months of treatment in nine patients, whereas sputum conversion by microscopy, possibly due to the presence of dead bacteria, was observed after 4 months of treatment in seven patients. This confirms the necessity of culture for the monitoring of treatment outcomes. A similar delay in smear conversion over culture conversion has been reported elsewhere [17] and is probably linked to the presence of dead bacilli hidden in cavities and later on released into the airways. Given that infectiousness is associated with positive sputum culture results and is highest when the smear results are also positive [18], data from our small patient cohort indicate that MDR-TB patients' infectiousness was already reduced by month 2 and reached null by month 3 of treatment (data not shown).

All patients experienced at least one AE during the treatment phase that was managed accordingly. As expected, the most common AEs were gastrointestinal and consisted mainly of nausea and vomiting. One patient experienced a cutaneous hypersensitivity reaction that was not clearly attributable to an individual drug. This reaction resolved after 2.5 months of symptomatic management without discontinuation of therapy. Towards the end of the continuation phase, two patients complained about significant hearing loss. Although this is surely caused by the prolonged administration of kanamycin, it is possible that these patients who already received streptomycin several times before already had established sub-clinical cochlear lesions. Unfortunately, due to logistical constraints, we were not able to quantify the hearing loss. Management of MDR-TB patients is multidisciplinary and usually requires expertise and medical equipment not available in remote hospitals. This could affect the outcome of their treatment, particularly with regard to the monitoring, prevention, and treatment of drug adverse effects. This limitation should be addressed in the future by encouraging the policymaker to provide an appropriate logistic tool for efficient monitoring.

One patient died in the first month of treatment. Clinical and radiological features on admission depicted extensive lung damage that could be linked to delay in receiving adequate MDR-TB treatment. The liver failure occurred in one patient towards the end of the intensive phase. This patient who worked in Libreville was referred to our team in Lambaréné for the initiation of her MDR-TB treatment. Hospitalisation in Lambaréné was originally planned to last for the whole duration of the intensive phase. However, due to family and professional issues, the patient was discharged from our MDR-TB treatment unit and referred to a treating physician in Libreville. Liver enzymes before discharge in Lambaréné were within normal ranges.

The cost of treatment in our patient cohort is lower compared to a study in South Africa which reported 17,164 USD per patient [19], but our findings equate to those reported from, e.g., the Philippines, Peru, and Nigeria (3613; 2423, 2095 USD, respectively) [20, 21]. The treatment cost is strongly correlated with the country's socio-economic

profile and the level of hospital care, as well as the sourcing/financing of the drugs. However, all of these studies agree that the largest cost of care is attributable to prolonged hospitalisation. Despite evidence that hospitalisation is desirable during the infective period and to achieve the highest rate of treatment adherence, ambulatory care approaches should be encouraged where possible and as early as possible to reduce the cost of treatment.

In summary, the implementation of the MDR-TB short-treatment regimen led to clinical improvement and sputum conversion in most of the patients. Early treatment could prevent extensive lung damage and death. All patients experienced at least one adverse event that included adverse cutaneous drug reaction and impaired hearing function but did not lead to an interruption of the treatment. One patient experienced a severe and fatal adverse event. The problems of managing this patient highlight the importance of expanding the MDR-TB treatment capacity to other provinces to facilitate country-wide appropriate patient care. At the time of this study, Lambaréné was the only site of MDR-TB treatment. Patients could not be transferred safely to other provinces near their residences to continue the treatment.

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REFERENCES

1. Nourzad S, Jenkins HE, Milstein M, Mitnick CD. counting the missing cases: estimating the global burden of multidrug-resistant tuberculosis among prevalent cases of tb. Int J Tuberc Lung Dis Off J Int Union Tuberc Lung Dis. 2017;21:6–11.
2. Mounguengui D, Ondounda M, Lawson JMM, Fabre M, Gaudong L, Mangouka L, et al. Tuberculose multirésistante à l'hôpital d'instruction des armées de Libreville (Gabon) à propos de 16 cas. Bull Société Pathol Exot. 2012;105:1–4.
3. Bélard S, Remppis J, Bootsma S, Janssen S, Kombila DU, Beyeme JO, et al. Tuberculosis treatment outcome and drug resistance in lambaréné, Gabon: a prospective cohort study. Am J Trop Med Hyg. 2016;95:472–80.
4. Zignol M, Dean AS, Falzon D, van Gemert W, Wright A, van Deun A, et al. Twenty years of global surveillance of antituberculosis-drug resistance. N Engl J Med. 2016;375:1081–9.
5. Pablos-Méndez A, Raviglione MC, Laszlo A, Binkin N, Rieder HL, Bustreo F, et al. Global surveillance for antituberculosis-drug resistance, 1994–1997. World Health Organization-International Union against Tuberculosis and Lung Disease Working Group on Anti-Tuberculosis Drug Resistance Surveillance. N Engl J Med. 1998;338:1641–9.
6. Bélard S, Janssen S, Osbak KK, Adegnika AA, Ondounda M, Grobusch MP. Limited access to drugs for resistant tuberculosis: a call to action. J Public Health Oxf Engl. 2015;37:691–3.
7. WHO Treatment Guidelines for Drug-Resistant Tuberculosis, 2016 Update. Geneva: World Health Organization; 2016. http://www.ncbi.nlm.nih.gov/books/NBK390455/. Accessed 17 Jun 2017.
8. Trébucq A, Schwoebel V, Kashongwe Z, Bakayoko A, Kuaban C, Noeske J, et al. Treatment outcome with a short multidrug-resistant tuberculosis regimen in nine African countries. Int J Tuberc Lung Dis. 2018;22:1725. http://www.ingentaconnect.com/content/10.5588/ijtld.17.0498. Accessed 18 Feb 2019.
9. WHO| Definitions and reporting framework for tuberculosis. WHO. http://www.who.int/tb/publications/definitions/en/. Accessed 28 Jul 2018.
10. Alabi AS, Traoré AN, Loembe MM, Ateba-Ngoa U, Frank M, Adegnika AA, et al. Enhanced laboratory capacity development: a boost for effective tuberculosis control in resource-limited settings. Int J Infect Dis IJID Off Publ Int Soc Infect Dis. 2017;56:81–4.
11. Lange C, Chesov D, Heyckendorf J, Leung CC, Udwadia Z, Dheda K. Drug-resistant tuberculosis: an update on disease burden, diagnosis and treatment. Respirol Carlton Vic. 2018;23:656–73.
12. Lange C, Duarte R, Fréchet-Jachym M, Guenther G, Guglielmetti L, Olaru ID, et al. Limited benefit of the new shorter multidrug-resistant tuberculosis regimen in Europe. Am J Respir Crit Care Med. 2016;194:1029–31.
13. Balabanova Y, Fiebig L, Ignatyeva O, Riekstina V, Danilovits M, Jaama K, et al. Multidrug-resistant TB in Eastern region of the EU: is the shorter regimen an exception or a rule? Thorax. 2017;72:850–2.
14. Chee CBE, KhinMar KW, Sng LH, Jureen R, Cutter J, Lee VJM, et al. The shorter multidrug-resistant tuberculosis treatment regimen in Singapore: are patients from South–East Asia eligible? Eur Respir J. 2017. https://doi.org/10.1183/13993003.00753-2017.

15. Dalcolmo M, Gayoso R, Sotgiu G, D'Ambrosio L, Rocha JL, Borga L, et al. Effectiveness and safety of clofazimine in multidrug-resistant tuberculosis: a nationwide report from Brazil. Eur Respir J. 2017. https://doi.org/10.1183/13993003.02445-2016.

16. Berhan A, Berhan Y, Yizengaw D. A meta-analysis of drug-resistant tuberculosis in sub-saharan africa: how strongly associated with previous treatment and HIV co-infection? Ethiop J Health Sci. 2013;23:271–82.

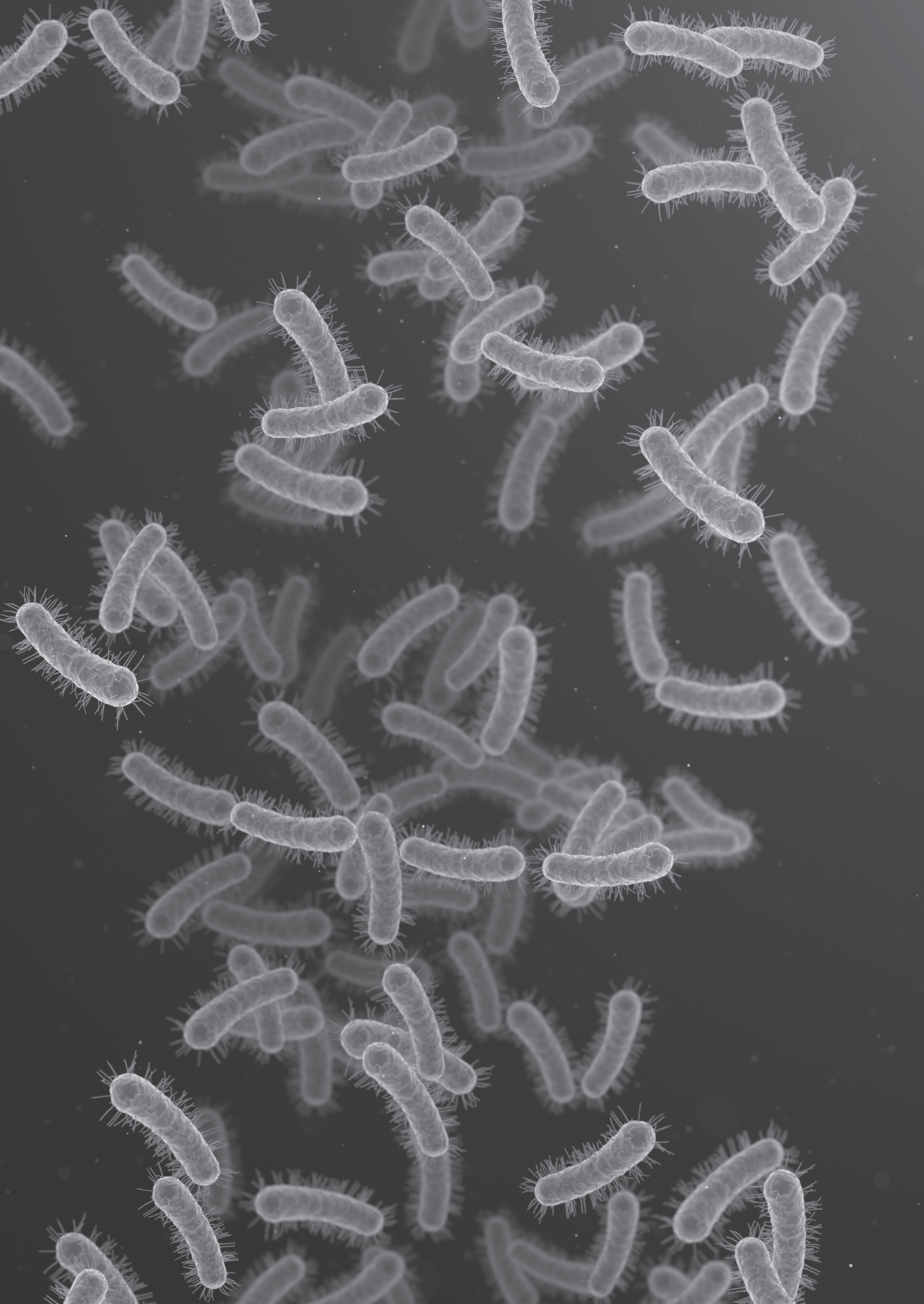
17. Ko Y, Shin JH, Lee H-K, Lee YS, Lee S-Y, Park SY, et al. Duration of pulmonary tuberculosis infectiousness under adequate therapy, as assessed using induced sputum samples. Tuberc Respir Dis. 2017;80:27–34.

18. Guidelines for the Investigation of contacts of persons with infectious tuberculosis recommendations from the National Tuberculosis Controllers Association and CDC. https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5415a1.htm. Accessed 17 Jun 2017.

19. Schnippel K, Rosen S, Shearer K, Martinson N, Long L, Sanne I, et al. Costs of inpatient treatment for multi-drug-resistant tuberculosis in South Africa. Trop Med Int Health TM IH. 2013;18:109–16.

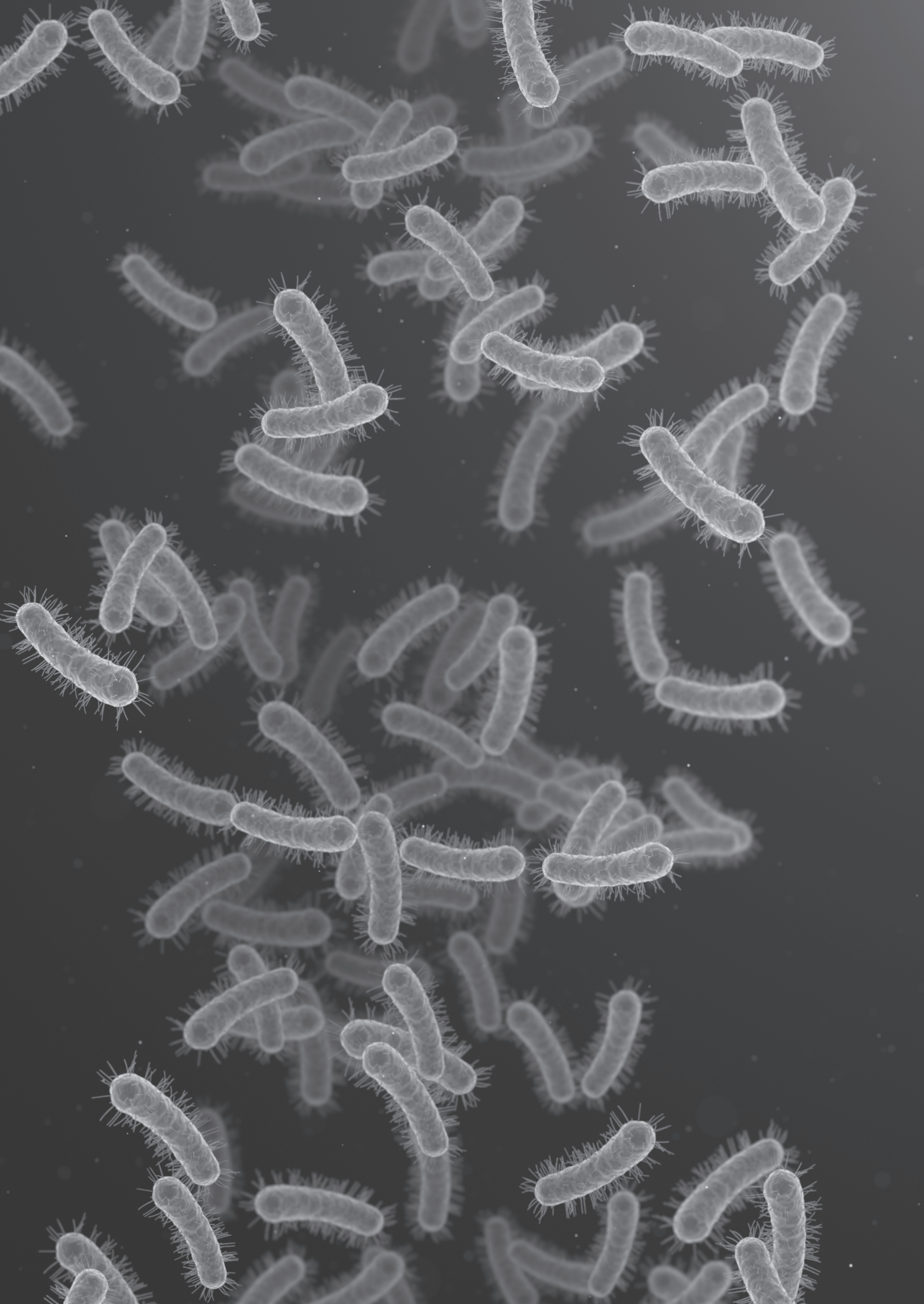
20. Musa BM, John D, Habib AG, Kuznik A. Cost-optimization in the treatment of multidrug resistant tuberculosis in Nigeria. Trop Med Int Health. 21:176–82. https://onlinelibrary.wiley.com/doi/abs/10.1111/tmi.12648. Accessed 28 Jul 2018.

21. Fitzpatrick C, Floyd K. A systematic review of the cost and cost effectiveness of treatment for multidrug-resistant tuberculosis. PharmacoEconomics. 2012;30:63–80.



Part 3

Improving sepsis diagnosis and awareness



Chapter 6

Clinical features, treatment outcomes and mortality risk of tuberculosis sepsis in HIV-negative patients: a systematic review and meta-analysis of case reports

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ABSTRACT

Purpose: Tuberculosis sepsis (TBS) is sepsis due to the *Mycobacterium* species causing tuberculosis (TB). It seems to be rare in HIV-negative patients and mainly individual case reports have been reported. This systematic review summarises the epidemiology, clinical features, and treatment outcomes of TBS in HIV-negative patients.

Methods: An electronic search of PubMed, Embase, Web of Science, and Google Scholar was performed to identify published case reports of TBS between January 1991 and September 2022.

Results: Twenty-five articles reported 28 cases of TBS in HIV- negative patients, among which 54% (15/28) were women; with 50% (14/28) of patients not having reported predisposing factors. A total of 64% (18/28) of patients died, and the diagnosis was obtained for many of them only post-mortem. Two of the reports mentioned the BCG vaccination status. A higher proportion of deaths occurred in patients with delayed diagnosis of sepsis. The probability of survival of patients diagnosed with tuberculosis sepsis was 68% on day 10; 41% on day 20; and 33% on day 30 after admission.

Conclusions: Our review showed TBS occurred in HIV-negative patients and some of them have no known immunocompromised underlying co-morbidity. TBS might not be rare as clinicians thought but might be prone to be missed. In endemic settings, *Mycobacterium tuberculosis* aetiology of sepsis should be accounted for early, irrespective of HIV infection status.

Keywords: Sepsis; tuberculosis septic shock; tuberculosis in intensive care unit; case fatality for tuberculosis septic shock; tuberculosis sepsis

INTRODUCTION

Sepsis and tuberculosis kill around 11 million [1] and 1.5 million people per year [2], respectively. Tuberculosis sepsis (TBS), also known as sepsis tuberculosis gravissima, was first described by Landouzy in 1908 [3]. TBS has been mostly reported in HIV-infected patients [4–7]; however, it can also occur in immunocompetent patients [8,9].

It has been estimated that half of TBS remains undiagnosed at the time of death [10]. An analysis of the United States' databases of patients with sepsis showed that fifteen per cent of patients did not have clinical signs and symptoms leading to suspect sepsis on admission [11]. The mortality rate was worst in this group of patients as compared to the group of patients with sepsis at presentation [11]. Prompt diagnosis and early treatment are key to the management of sepsis. Delay in antibiotics administration is associated with the worsening of sepsis severity both in sepsis in general and in TB sepsis in particular [12,13].

TBS carries a fatal prognosis because it is overlooked by clinicians; mainly in the case of patients without HIV infection [10]. A case series reported by Kethireddy et al. suggests that most TBS patients died [13], likely because TBS is not coming into the mind of the clinician as an alternative diagnostic or aetiology of organ failure. These findings highlight the critical need to improve clinicians' awareness of TBS. This systematic review and meta-analysis aim to better understand the epidemiology, clinical features, and factors associated with the treatment outcome of TBS in HIV-negative patients.

METHODS

The Search Strategy and Inclusion Criteria

The review was undertaken and reported by following the preferred reporting items for systematic review and meta-analysis (PRISMA 2020 and PRISMA-S guidelines [14,15]. The protocol of the review was registered with PROSPERO (CRD42022296768).

An electronic search of the published literature was conducted on December 1, 2021, and updated on September 25, 2022, in PubMed, Embase, Web of Science (core collection) and Google Scholar to identify case reports or case series of tuberculosis sepsis. As suggested by PRISMA-S [15] and Bramer and collaborators [16], the first 200 results on Google Scholar were selected. We also searched the reference lists of the included case reports. The following search terms were used in PubMed:

("tuberculosis"[All Fields] OR "tuberculosis"[MeSH Terms] OR "tuberculosis"[All Fields] OR "tuberculoses"[All Fields] OR "tuberculosis s"[All Fields]) AND ("sepsis"[MeSH Terms] OR "sepsis"[All Fields]) AND ((("ieee int conf automation sci eng case"[Journal] OR "case phila"[Journal] OR "case"[All Fields]) AND "report*"[All Fields]) OR (("ieee int conf

automation sci eng case"[Journal] OR "case phila"[Journal] OR "case"[All Fields]) AND "serie*"[All Fields])) . The full description of the search strategy of the others databases used is reported in Supplementary File S1. Additionally, we conducted a cross-reference analysis to retrieve manuscripts that were not identified during our initial search. With the purpose of uniformly applying consensus criteria for the definition of sepsis, we restricted the case reports or series to be included to those published after the first consensus definition of sepsis by the American College of Chest Physicians and the Society of Critical Care Medicine (1991) [17,18]. We excluded case reports (a) with unclear clinic-pathological data of the diagnosis of sepsis or lack of information on the diagnostic method and treatment outcome; (b) duplicate cases using Rayyan platform [19]; (c) TBS cases in HIV-infected patients; (d); case reports in languages other than English or French; (e) tuberculosis bloodstream infections not fulfilling sepsis criteria; (f) sepsis cases due to *Mycobacterium* species other than *Mycobacterium tuberculosis*, *M. bovis* and *M. africanum*; and (g) new-borns or infants with congenital tuberculosis not reported as tuberculosis sepsis. The titles and abstracts were initially screened independently by two reviewers (EJR and NOE). The full texts of the relevant articles were assessed for inclusion by two independent reviewers (BRA and NOE) using the Rayyan platform [19]. The agreement of both reviewers was required for inclusion and exclusion. Any disagreement was resolved by consensus. If BRA and NOE did not agree after discussion, a third investigator (YJH) was consulted. The full list of excluded cases is reported in Supplementary File S2.

Data extraction and quality assessment

The following data were extracted from the original studies: first author; year of publication; country of origin; study population and participant demographics and baseline characteristics; clinical features, outcomes, and times of measurement. BRA and NOE independently extracted data using the items pre-defined on the excel sheet. The quality of included studies was assessed with the Joanna Briggs Institute Critical Appraisal Checklist for Case Reports [20], which consists of eight yes/no/unclear questions which led to the overall appraisal: 'Include', 'Exclude' or 'Seek further info'.

Summary measures and statistical analysis

Descriptive statistics of publication characteristics and patient demographic variables were performed. Case report data were grouped by type of patients (adult or infant). The patients' sociodemographic data were presented separately for adults and infants. The means of age, time to diagnosis of tuberculosis sepsis, time to initiation of an empiric anti-tuberculosis treatment and corresponding standard deviation (SD) were described for each category of patients. To better describe factors associated with death; the clinical features, the predisposing co-morbidities, and initial diagnosis were ranged into three categories maximum. Fisher's exact test was used to identify factors significantly

associated with death. Cox's regression logistic was not performed as planned in the protocol due to the small number of cases.

RESULTS

The initial database search identified 2337 articles, of which 1416 were screened using the abstract and title. A total of 137 full articles were assessed for eligibility and 25 articles (28 individual case reports) were included in the final analysis (Fig. 1). All case reports included in this review met the 'Include' overall appraisal using the Joanna Briggs Institute tool and were classified as Low risk of bias (see Supplementary File S3).

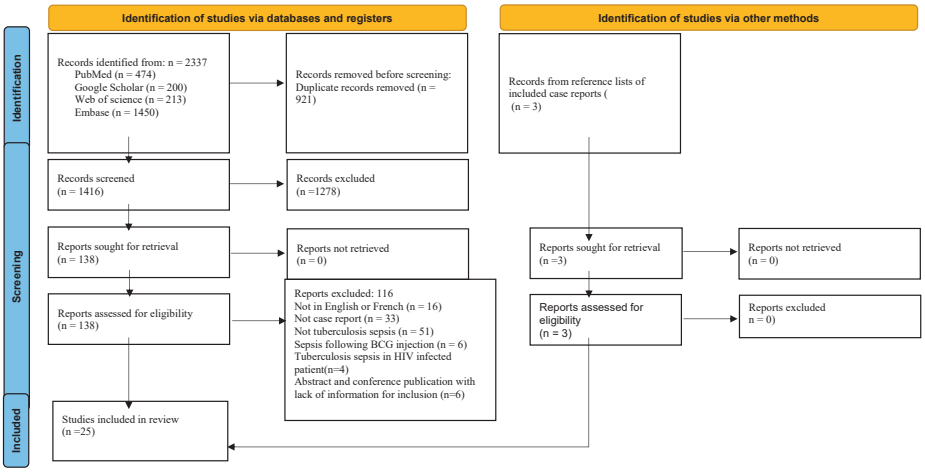

Figure 1. Flowchart of the study selection process

Patient demographics, co-morbidities, predisposing factors, and clinical manifestation

Among the total of 28 individual cases [21–45], four of them were infants (Table1). The mean age of the infants was 23 days (SD=9). The mean age of adults was 44 years (SD=18). A total of 15/28 (54%) cases were women. For 50% (14/28) of the patients, no pre-disposing factors were reported. BCG vaccination status was only reported in two cases. The main chief complaints were 'weakness' and 'dyspnoea', Table 2. A total of 61% (17/28) of patients reported cough, and all of the patients had a fever, respiratory distress, and hypotension. Leukopenia was the most common laboratory abnormality reported.

Tuberculosis sepsis diagnosis and patient management and treatment outcomes

For 75% (3/4) of infants, the initial diagnosis at admission was sepsis, and patients were managed in the intensive care unit; while only 46% (11/24) of adults were diagnosed with sepsis on admission. The empiric anti-tuberculosis was initiated in 53% (15/28) of the patients, and the mean time lapse from presentation to treatment initiation was six days (SD=9; Table 3). Most (18/28; 64%) patients died within 30 days of the presentation, and in 39% (7/18), the TBS diagnosis was confirmed post-mortem. The diagnosis of tuberculosis was confirmed by either blood culture, extrapulmonary liquid culture, or sputum microscopic, TB molecular diagnosis /culture or pathology of infected organ biopsy (Table 1). The probability of survival of patients diagnosed with tuberculosis sepsis was 68% on day 10; 41% on day 20; and 33% on day 30 after admission, Fig. 2. A higher proportion of death occurred in patients with other diagnoses than sepsis at admission. The mean time (day) of starting empiric antituberculosis treatment since the presentation was 10 (SD=4) in patients who died, while the treatment was imitated earlier in the patients who survived (mean time =5, SD=3).

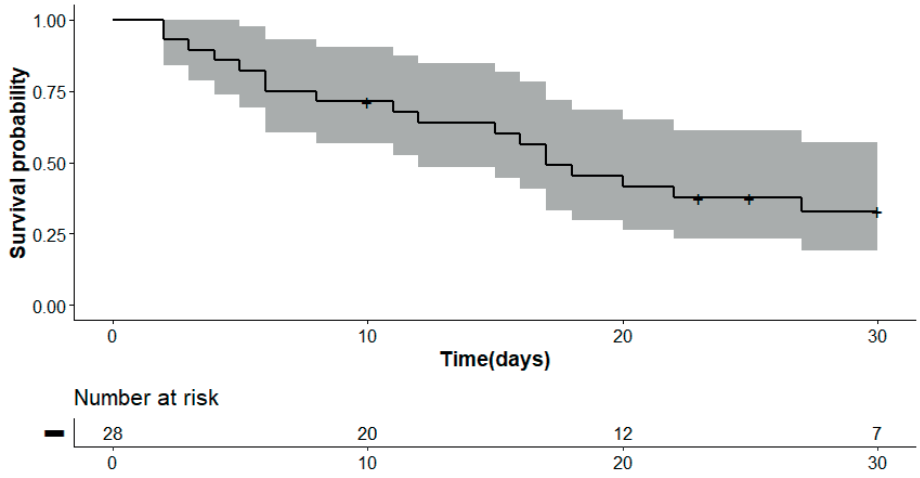

Figure 2. Survival probability patients diagnosed with tuberculosis sepsis

DISCUSSION

We performed a systematic review and meta-analysis of published cases of tuberculosis sepsis in HIV-negative patients from 1991, up to September 25, 2022. The major findings were that the half of patients did not report known underline immunocompromised comorbidity, 61% (17/28) reported cough at admission, 64% (18/28) died within 30 days

since presentation and the TBS diagnosis was confirmed only at post-mortem for 39% (7/18) of the patients who died. A higher proportion of death occurred in adult patients with delayed initiation of anti-tuberculosis treatment.

The major challenge of tuberculosis sepsis is the delay of diagnosis or difficulty of its recognition by clinicians. Our study confirms that there are no specific signs or symptoms of TBS and that patients present with the common sign of sepsis. Recent research and advocacy improve the awareness of clinicians on tuberculosis bacteraemia and/or sepsis in HIV patients [46–49]. However, our review shows that tuberculosis sepsis can occur in patients without HIV infection or known co-morbidities. Therefore, TBS should be investigated in any tuberculosis patient presenting sepsis signs irrespective of HIV status. In highly TB- endemic settings, we recommend broadening the investigation of the aetiology of sepsis to *Mycobacterium tuberculosis.* The culture of samples is currently the gold standard for tuberculosis diagnosis. However, culture takes two to six weeks to be reported. Therefore, rapid molecular diagnostic such as GeneXpert is suggested in the purpose to allow as soon as possible anti-tuberculosis treatment. However, the pulmonary manifestations were not common in all cases of TBS and *the Mycobacterium tuberculosis* is not identifiable all-time in the sputum. The sensibility of GeneXpert in extrapulmonary samples ranged from 55.2% to 69.9% [50–52]. Barr et al. suggested that a combination of sputum GeneXpert, blood culture and urine lipoarabinomannan, could improve the diagnostic yield of TB in critically ill adult patients [14]. There is a need to improve the diagnostic tools for disseminated tuberculosis which increase the risk to develop TBS. A risk score derived from a model containing independent predictors has been suggested; however, it was derived from patients with HIV infection only and needs to be validated in other settings [7]. The clinical feature of TBS does not seem to be different according to the HIV infection status of the patients. Therefore, the clinician should keep in mind the alternative diagnosis of TBS in HIV-negative patients with tuberculosis signs associated with organ failure manifestations. With BCG vaccination protecting from TB meningitis and sepsis at least at a younger age, it would be important if future reports would include this information routinely.

Strengths and weaknesses

Using a systematic search strategy in four widely used databases, we increased the chance to identify all case reports of tuberculosis sepsis. Despite having applied refined selection inclusion criteria, there is the possibility of missing some important case reports. Publication bias is another weakness of case report review since only rare and untypical observations are more likely to be published. The publication of case reports also depends on the research experience and ability of the clinician in charge of the case seeming to be unusual. The BCG vaccination status was reported only in one case report. The proportion of TBS cases without known co-morbidity is impressive. Since this is a summary of case

reports published, we cannot ensure that an in-depth investigation (including further laboratory assessments) will confirm or refute the absence of co-morbidities in these patients. Therefore, the interpretation of our findings should be done with caution. The role of radiology imaging in the diagnosis of not bacteriological confirmed is well known. We did not extract such information from the articles included. Despite these limitations, our review is of clinical practice and research implications interest because findings from this review contribute to improving the awareness of clinicians on the clinical feature of tuberculosis sepsis and showed that it could occur in infant and adult patients irrespective of HIV infection status.

CONCLUSIONS

TBS is reported as a case report because of its rare incidence in many settings. It is not usually suspected in the first place, inducing a risk of delayed diagnosis. Most case reports had death as an outcome and the mortality rate is more frequent in groups of patients where the diagnosis of TBS was not suspected at admission. In an endemic setting, TBS should be envisaged in patients with tuberculosis likely symptoms presenting sepsis signs as well. Empiric anti-tuberculosis treatment should be initiated as soon as possible.
Supplementary Materials: Supplementary File S1- Search strategy; Supplementary File S2-Overview of excluded studies; Supplementary File S3-Risk of bias assessment.
Author Contributions: Conceptualisation: BRA, NOE; Validation: MPG; Investigation and article search: JRE, NOE, BRA, JYH. BRA, JYH and NOE, independently screened and extracted data from the studies; Original draft preparation: BRA and MPG; Writing—review and editing: NOE, AAA, JYH, JRE, JCD, JFZ, MPG. All authors have read and endorsed the final version of the manuscript.
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Declarations

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REFERENCES

1. World Health Organization. Global report on the epidemiology and burden of sepsis: current evidence, identifying gaps and future directions. Geneva: WHO; 2020.
2. World Health Organization. Global tuberculosis report 2020. [Internet]. Geneva: WHO; 2020. Available from: http://apps.who.int/bookorders
3. Rubin ZA, Leonard MK, Martin GS. Brief Report: Tuberculosis Sepsis and Activated Protein C. Am J Med Sci. 2006;332:48–50.
4. Lewis JM, Feasey NA, Rylance J. Aetiology and outcomes of sepsis in adults in sub-Saharan Africa: a systematic review and meta-analysis. Crit Care Lond Engl. 2019;23:212.
5. Byashalira K, Mbelele P, Semvua H, Chilongola J, Semvua S, Liyoyo A, et al. Clinical outcomes of new algorithm for diagnosis and treatment of Tuberculosis sepsis in HIV patients. Int J Mycobacteriology. 2019;8:313.
6. Kerkhoff AD, Barr DA, Schutz C, Burton R, Nicol MP, Lawn SD, et al. Disseminated tuberculosis among hospitalised HIV patients in South Africa: a common condition that can be rapidly diagnosed using urine-based assays. Sci Rep. 2017;7:10931.
7. Jacob ST, Pavlinac PB, Nakiyingi L, Banura P, Baeten JM, Morgan K, et al. Mycobacterium tuberculosis bacteremia in a cohort of HIV-infected patients hospitalized with severe sepsis in Uganda–high frequency, low clinical and derivation of a clinical prediction score. PloS One. Public Library of Science San Francisco, USA; 2013;8:e70305.
8. Eshiwe C, Shahi F, Gordon N, Lillie P. Rare and unusual case of hepatic and disseminated tuberculosis in an immunocompetent patient. BMJ Case Rep. 2019;12:e229384.
9. Sydow M, Schauer A, Crozier TA, Burchardi H. Multiple organ failure in generalized disseminated tuberculosis. Respir Med. 1992;86:517–9.
10. Gupta RK, Lucas SB, Fielding KL, Lawn SD. Prevalence of tuberculosis in post-mortem studies of HIV-infected adults and children in resource-limited settings: a systematic review and meta-analysis. AIDS Lond Engl. 2015;29:1987–2002.
11. Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. N Engl J Med. 2003;348:1546–54.
12. Whiles BB, Deis AS, Simpson SQ. Increased Time to Initial Antimicrobial Administration Is Associated With Progression to Septic Shock in Severe Sepsis Patients. Crit Care Med. 2017;45:623–9.
13. Kethireddy S, Light RB, Mirzanejad Y, Maki D, Arabi Y, Lapinsky S, et al. Mycobacterium tuberculosis Septic Shock. Chest. 2013;144:474–82.
14. 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;n71.
15. PRISMA-S Group, Rethlefsen ML, Kirtley S, Waffenschmidt S, Ayala AP, Moher D, et al. PRISMA-S: an extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews. Syst Rev. 2021;10:39.
16. Bramer WM, Rethlefsen ML, Kleijnen J, Franco OH. Optimal database combinations for literature searches in systematic reviews: a prospective exploratory study. Syst Rev. 2017;6:245.

17. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest. 1992;101:1644–55.

18. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315:801–10.

19. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan—a web and mobile app for systematic reviews.https://link.springer.com/epdf/10.1186/s13643-016-0384-4. 2016.

20. Moola S, Munn Z, Tufanaru C, Aromataris. Chapter 7: Systematic reviews of aetiology and risk. In: Aromataris E, Munn Z (Editors),Critical Appraisal Checklist for Case Reports.Joanna Briggs Institute Reviewer's Manual. The Joanna Briggs Institute; 2017.

21. Siemann M, Rabenhorst G, Bramann A, Renk C. A case of cryptic miliary tuberculosis mimicking cholecystitis with sepsis. Infection. 1999;27:44–5.

22. Colunche C, Angeles B, Maguiña M, Yachachin J, Chavez W, Diaz J, et al. Acute Respiratory Failure and Sepsis Due to Multidrug-Resistant Tuberculosis (MDR-TB) in a Pregnant Midwife. D47 Tuberc CASE Rep [Internet]. American Thoracic Society; 2018 [cited 2022 Mar 21]. p. A6962–A6962. Available from: https://www.atsjournals.org/doi/abs/10.1164/ajrccm-conference.2018.197.1_MeetingAbstracts.A6962

23. Nakbanpot S, Rattanawong P. Congenital Tuberculosis because of Misdiagnosed Maternal Pulmonary Tuberculosis during Pregnancy. Jpn J Infect Dis. 2013;66:327–30.

24. Mazade MA, Evans EM, Starke JR, Correa AG. Congenital tuberculosis presenting as sepsis syndrome: case report and review of the literature: Pediatr Infect Dis J. 2001;20:439–42.

25. Sun L, Yang Z, Yang F, Wang Z, Li H, Wang H, et al. Diagnosis of Mycobacterium tuberculosis Septic Shock in Patients With Anti-synthetase Syndrome Based on Next-Generation Sequencing: A Case Report and Literature Review. Front Med. 2021;8:675041.

26. Barbosa OA, Teles FM, Maia ACC, Pessoa GMF, de Alencar IM, de Sousa ET, et al. Disseminated hematogenous tuberculosis in puerperium—case report. Oxf Med Case Rep. 2019;2019:479–81.

27. Lee C-Y, Tsai H-C, Lee SS-J, Sy C, Chen Y-S. Disseminated tuberculosis presenting as tuberculous peritonitis and sepsis tuberculosa gravissima in a patient with cirrhosis of the liver: A diagnosis of challenge. J Microbiol Immunol Infect. 2016;49:608–12.

28. Kindler T, Schindel C, Brass U, Fischer T. Fatal sepsis due to Mycobacterium tuberculosis after allogeneic bone marrow transplantation. Bone Marrow Transplant. 2001;27:217–8.

29. Mitchon GJ, Barlow JL. Fatal Sepsis From Mycobacterium Tuberculosis In An Hiv-Negative Alcoholic Female. :1.

30. Sydow M, Schauer A, Crozier TA, Burchardi H. Multiple organ failure in generalized disseminated tuberculosis. Respir Med. 1992;86:517–9.

31. Okascharoen C, Nuntnarumit P, Sirinavin S. Neonatal Tuberculosis Associated With Shock, Disseminated Intravascular Coagulation, Hemophagocytic Syndrome, and Hypercalcemia: A Case Report. J Perinatol. 2003;23:79–81.

32. Eshiwe C, Shahi F, Gordon N, Lillie P. Rare and unusual case of hepatic and disseminated tuberculosis in an immunocompetent patient. BMJ Case Rep. 2019;12:e229384.

33. Dabaja M, Herc E. RIPE Treatment Failure in a Patient with Mycobacterium tuberculosis sepsis. Am J Respir Crit Care Med. 2017;195:A6008.

34. Schröder J, Vogel I, Thybusch A, Kremer B, Siemann M. Sepsis syndrome induced by tuberculous perforation of the oesophagus. Infection. 1996;24:162–3.

35. Pène F, Papo T, Brudy-Gulphe L, Cariou A, Piette JC, Vinsonneau C. Septic Shock and Thrombotic Microangiopathy Due to Mycobacterium tuberculosis in a Nonimmunocompromised Patient. Arch Intern Med. 2001;161:1347.

36. Angoulvant D, Mohammedi I, Duperret S, Bouletreau P. Septic shock caused by Mycobacterium tuberculosis in a non-HIV patient. Intensive Care Med. 1999;25:238–238.

37. Sheldon D, Han J. Septic shock from disseminated mycobacterium tuberculosis. Chest. 2018;154:290A.

38. Michel P, Barbier C, Loubière Y, Hayon J-H, Ricôme J-L. Three cases of septic shock due to tuberculosis without HIV pathology. Intensive Care Med. 2002;28:1827–8.

39. Reisinger AC, Hermann J, Vagena FR, Hackl G, Eller P. Tuberculosis sepsis after tocilizumab treatment. Clin Microbiol Infect. 2020;26:1493–4.

40. Mishra R, Patel HK, Singasani R, Vakde T. Tuberculosis septic shock, an elusive pathophysiology and hurdles in management: A case report and review of the literature. World J Crit Care Med. 2019;8:72–81.

41. Al Argan R, Al Elq A. Tuberculosis-associated immune thrombocytopenia: A case report. Saudi J Med Med Sci. 2018;6:160.

42. Maini B, Gupta VK, Narang S. Septic Shock Due to Tuberculosis in Down Syndrome. Indian Pediatr. 2012;49:481–2.

43. Trebuss KA, Buttemer S, Wilkinson JS, Xu J, Rossiter JP, Moore KM. Death of a 29-Year-Old Male from Undifferentiated Sepsis. Can J Infect Dis Med Microbiol. 2016;2016:1–6.

44. Rowe CM, Desai N, Coathup R, Cepkova M. An unusual case of sepsis? A rare presentation of a common disease. BMJ Case Rep. 2015;bcr2014207698.

45. Klimko A, Brandt A, Brustan M. A Case of Miliary Perinatal Tuberculosis in a Preterm Newborn Infant Presenting as Peritonitis. CUREUS. 2020;12.

46. Frigati L, Maskew M, Workman L, Munro J, Andronikou S, Nicol MP, et al. Clinical Predictors of Culture-confirmed Pulmonary Tuberculosis in Children in a High Tuberculosis and HIV Prevalence Area. Pediatr Infect Dis J. 2015;34:e206-210.

47. Sanguanwongse N, Cain KP, Suriya P, Nateniyom S, Yamada N, Wattanaamornkiat W, et al. Antiretroviral therapy for HIV-infected tuberculosis patients saves lives but needs to be used more frequently in Thailand. J Acquir Immune Defic Syndr 1999. 2008;48:181–9.

48. Schutz C, Barr D, Andrade BB, Shey M, Ward A, Janssen S, et al. Clinical, microbiologic, and immunologic determinants of mortality in hospitalized patients with HIV-associated tuberculosis: A prospective cohort study. PLoS Med. 2019;16:e1002840.

49. Barr DA, Lewis JM, Feasey N, Schutz C, Kerkhoff AD, Jacob ST, et al. Mycobacterium tuberculosis bloodstream infection prevalence, diagnosis, and mortality risk in seriously ill adults with HIV: a systematic review and meta-analysis of individual patient data. Lancet Infect Dis. 2020;20:742–52.

50. Aricha SA, Kingwara L, Mwirigi NW, Chaba L, Kiptai T, Wahogo J, et al. Comparison of GeneXpert and line probe assay for detection of Mycobacterium tuberculosis and rifampicin-mono resistance at the National Tuberculosis Reference Laboratory, Kenya. BMC Infect Dis. 2019;19:852.

51. Pandey P, Pant ND, Rijal KR, Shrestha B, Kattel S, Banjara MR, et al. Diagnostic Accuracy of GeneXpert MTB/RIF Assay in Comparison to Conventional Drug Susceptibility Testing Method for the Diagnosis of Multidrug-Resistant Tuberculosis. PLOS ONE. Public Library of Science; 2017;12:e0169798.

52. Al-Darraji HAA, Razak HA, Ng KP, Altice FL, Kamarulzaman A. The Diagnostic Performance of a Single GeneXpert MTB/RIF Assay in an Intensified Tuberculosis Case Finding Survey among HIV-Infected Prisoners in Malaysia. PLOS ONE. Public Library of Science; 2013;8:e73717.

Table1. Overview of included studies and descriptive data

Authors	Years	Title	Sex	Category	BCG Vaccination	Age (Days for Infant/ Year for adult)	First diagnosis	Comorbidity	Treatment outcome	Site of tuberculosis infection	Bacteriological investigation
Artsiom et al	2020	A Case of Miliary Perinatal Tuberculosis in a Preterm Newborn Infant Presenting as Peritonitis	M	Infant	Yes	25	Peritonitis	No	Discharged	Pulmonary Tuberculosis	Gastric aspirate culture: Positive
Nakbanpot et al	2013	Congenital Tuberculosis because of Misdiagnosed Maternal Pulmonary Tuberculosis during Pregnancy	F	Infant	Not reported	19	Sepsis	Prematurity	Death	Pulmonary Tuberculosis	Sputum culture: Positive
Barbosa et al	2013	Disseminated hematogenous tuberculosis in puerperium—case report	F	Adult	Not reported	22	Chorioamnionitis	Pregnancy	Death	Pulmonary and extrapulmonary Tuberculosis	Post-mortem pathology of lung, liver, and uterus: giant cells, caseous necrosis and acid-fast bacilli
Chun-Yuan et al	2016	Disseminated tuberculosis presenting as tuberculous peritonitis and sepsis tuberculosa gravissima in a patient with cirrhosis of the liver: A diagnosis of challenge	M	Adult	Not reported	81	Peritonitis	Cirrhosis	Death	Pulmonary and extrapulmonary Tuberculosis	Blood, ascites, and sputum culture: Positive
Kindler et al	2001	Fatal sepsis due to Mycobacterium tuberculosis after allogeneic bone marrow transplantation	M	Adult	Not reported	34	CMV reactivation	Bone marrow transplantation	Death	Pulmonary Tuberculosis and extrapulmonary Tuberculosis	Tracheal aspirates culture: Positive

Table1. Overview of included studies and descriptive data (continued)

Authors	Years	Title	Sex	Category	BCG Vaccination	Age (Days for Infant/ Year for adult)	First diagnosis	Comorbidity	Treatment outcome	Site of tuberculosis infection	Bacteriological investigation
Mitchon et al	2017	Fatal Sepsis from Mycobacterium Tuberculosis In An HIV-Negative Alcoholic Female	F	Adult	Not reported	28	Sepsis	No	Death	Pulmonary and extrapulmonary Tuberculosis	Excisional biopsy of a chest wall lymph node: necrotising granulomas Ascites punction culture: Positive
Sydow et al	1992	Multiple organ failure in generalized disseminated tuberculosis	M	Adult	Not reported	72	Sepsis	No	Death	Pulmonary and extrapulmonary Tuberculosis	Post-mortem cultures of multiorgan (lungs, liver, adrenal cortex, both kidneys, spleen): Positive
Okascharoenet al	2003	Neonatal Tuberculosis Associated With Shock, Disseminated Intravascular Coagulation, Hemophagocytic Syndrome, and Hypercalcemia: A Case Report	F	Infant	Not reported	14	Sepsis	No	Discharged	Pulmonary and extrapulmonary Tuberculosis	Microscopic examination of tracheal and gastric aspirates: Positive
Eshiwe et al	1999	Rare and unusual case of hepatic and disseminated tuberculosis in an immunocompetent patient	F	Adult	Not reported	17	Sepsis	History of tuberculosis	Discharged	Pulmonary and extrapulmonary Tuberculosis	Aspirate of the liver cyst on auramine stains; and PCR and culture: positive for TB

Table1. Overview of included studies and descriptive data (continued)

Authors	Years	Title	Sex	Category	BCG Vaccination	Age (Days for Infant/ Year for adult)	First diagnosis	Comorbidity	Treatment outcome	Site of tuberculosis infection	Bacteriological investigation
Mohamad et al	1996	RIPE Treatment Failure in a Patient with Mycobacterium tuberculosis sepsis	M	Adult	Not reported	48	Sepsis	No	Discharged	Extrapulmonary tuberculosis	Sputum PCR and culture: Positive
Schroder et al	2018	Sepsis Syndrome Induced by Tuberculous Perforation of the Esophagus	M	Adult	Not reported	39	Immune thrombocytopenic purpura	No	Death	Pulmonary and extrapulmonary Tuberculosis	Sputum and specimens of pleural empyema microscopy and culture: Positive
Al Argan et al	2020	Tuberculosis-associated Immune Thrombocytopenia: A Case report	F	Adult	Not reported	46	Aggressive lymphoma	Corticoid or immunomodulation therapies	Discharged	Pulmonary Tuberculosis	Sputum and lymph nodes microscopy and culture: Positive
Reisinger et al	2020	Tuberculosis sepsis after tocilizumab treatment	M	Adult	Not reported	36	Sepsis	No	Discharged	Extrapulmonary tuberculosis	Ziehle Neelsen staining showed acid-fast rods , and mycobacterial PCR detected high concentrations of Mycobacterium tuberculosis DNA complexes in the explanted inguinal lymph node

Table1. Overview of included studies and descriptive data (continued)

Authors	Years	Title	Sex	Category	BCG Vaccination	Age (Days for Infant/ Year for adult)	First diagnosis	Comorbidity	Treatment outcome	Site of tuberculosis infection	Bacteriological investigation
Sieamann et al	1998	A Case of Cryptic Miliary Tuberculosis Mimicking Cholecystitis with Sepsis	F	Adult	Not reported	69	Cholecystis	No	Death	Pulmonary and extra pulmonary Tuberculosis	Liver biopsy (post mortem): identified acid-fast bacilli Blood culture: Positive
Limin et al	2021	Diagnosis of Mycobacterium tuberculosis Septic Shock in Patients with Anti-synthetase Syndrome Based on Next-Generation Sequencing: A Case Report and Literature Review	F	Adult	Not reported	51	Acute suppurative arthritis	Corticoid or immunomodulation therapies	Death	Extrapulmonary tuberculosis	Blood culture: Negative Pleural effusion culture: Negative articular cavity effusion: Negative Blood and articular cavity effusion next-generation sequencing: Positive

Table1. Overview of included studies and descriptive data (continued)

Authors	Years	Title	Sex	Category	BCG Vaccination	Age (Days for Infant/ Year for adult)	First diagnosis	Comorbidity	Treatment outcome	Site of tuberculosis infection	Bacteriological investigation
Mazade et al	2001	Congenital tuberculosis presenting as sepsis syndrome: case report and review of the literature	F	Infant	Not reported	34	Sepsis	History of tuberculosis	Discharged	Pulmonary tuberculosis	Blood culture: Negative -Tracheal aspirates culture: Positive - Tracheal aspirates acid-fast bacteria: Positive
Mishra et al	2019	Tuberculosis septic shock, elusive pathophysiology and hurdles in management: A case report and review of literature	F	Adult	Not reported	67	Tuberculosis	Hypertension	Death	Pulmonary and extrapulmonary Tuberculosis	Broncho alveolar lavage culture: Positive
Mishra et al	2019	Tuberculosis septic shock, an elusive pathophysiology and hurdles in management: A case report and review of literature	F	Adult	Not reported	49	Tuberculosis	Hypertension	Death	Pulmonary Tuberculosis	Sputum microscopy, PCR and culture: Positive
Pene et al	2001	sepsis shocks du to mycobacterium tuberculosis in non-immunocompromised patient	F	Adult	Not reported	69	Sepsis	No	Death	Pulmonary Tuberculosis	Sputum and Ascites culture: Positive
Angoulvant et al	1998	Septic shock caused by Mycobacterium tuberculosis in a non-HIV patient	M	Adult	Not reported	44	Sepsis	No	Death	Extrapulmonary tuberculosis	Bronchoalveolar lavage culture: Positive

Table1. Overview of included studies and descriptive data (continued)

Authors	Years	Title	Sex	Category	BCG Vaccination	Age (Days for Infant/ Year for adult)	First diagnosis	Comorbidity	Treatment outcome	Site of tuberculosis infection	Bacteriological investigation
Michel et al	2001	Three cases of septic shock due to tuberculosis without HIV pathology	M	Adult	Not reported	47	Tuberculosis	No	Death	Extrapulmonary tuberculosis	Bronchial aspiration culture: Positive
Michel et al	2001	Three cases of septic shock due to tuberculosis without HIV pathology	M	Adult	Not reported	41	Pneumothorax	No	Death	Extrapulmonary tuberculosis	Bronchial aspiration culture: Positive
Michel et al	2001	Three cases of septic shock due to tuberculosis without HIV pathology	F	Adult	Not reported	60	Severe community-acquired pneumonia	Chronic kidney failure	Death	Extrapulmonary tuberculosis	Bronchial aspiration culture: Positive
Colunche et al	2018	Acute respiratory failure and sepsis due to multidrug-resistant tuberculosis in pregnant midwife	F	Adult	Not reported	20	Sepsis	Pregnancy	Discharged	Pulmonary tuberculosis	Sputum PCR and culture: Positive
Sheldon et al	2018	Septic shock from disseminated *M. tuberculosis*	M	Adult	Not reported	47	Sepsis	Crohn's Disease	Discharged	Pulmonary and extrapulmonary Tuberculosis	Sputum culture: Positive Pathology of the terminal ileum: identified acid-fast bacilli
Kathryn et al	2022	Death of a 29-Year-Old Male from Undifferentiated Sepsis	M	Adult	Not reported	29	Sepsis	No	Death	Pulmonary and extrapulmonary Tuberculosis	Post-mortem pathology of lung, liver, spleen: giant cells, caseous necrosis and PCR confirmation of acid-fast bacilli

Table1. Overview of included studies and descriptive data (continued)

Authors	Years	Title	Sex	Category	BCG Vaccination	Age (Days for Infant/ Year for adult)	First diagnosis	Comorbidity	Treatment outcome	Site of tuberculosis infection	Bacteriological investigation
Vergara-sanchez et al	2022	A rare case of disseminated mycobacterial septicaemia (landouzy septicaemia) In an HIV-negative patient	F	Adult	Not reporter	33	Sepsis	No	Death	Pulmonary Tuberculosis	Bronchial aspiration PCR positive
Baljeet et al	2015	Septic Shock Due to Tuberculosis in Down Syndrome	M	Adult	Yes	16	Sepsis	Down syndrome	Discharged	Pulmonary Tuberculosis	Sputum microscopy examination revealed acid fast bacilli

Table 2. Clinical features and underlying conditions in 25 cases of tuberculosis sepsis

Variables	Adult, N = 24 (%)	Infant, N = 4 (%)
History of past illness		
Underlying conditions		
Bone marrow transplantation	1 (4.2)	Not applicable
Chronic kidney failure	1 (4.2)	0 (0)
Cirrhosis	1 (4.2)	Not applicable
Corticoid or immunomodulation therapies	2 (8.3)	0 (0)
Crohn's Disease	1 (4.2)	0 (0)
Down syndrome	1 (4.2)	
History of tuberculosis	1 (4.2)	1 (25)
Hypertension	2 (8.3)	0 (0)
Prematurity	Not applicable	1 (25)
Pregnancy	2 (8.3)	Not applicable
None	12 (50)	2 (50)
Chief complaint		
Abdominal pain	4 (17)	0 (0)
Confusion	2 (8.3)	0 (0)
Cough	2 (8.3)	0 (0)
Dyspnoea	7 (29)	1 (25)
Epistaxis	1 (4.2)	0 (0)
Fever	2 (8.3)	1 (25)
Anorexia	0 (0)	1 (25)
Weakness	6 (25)	1 (25)
Symptom and physical examination on admission*		
Cough	15 (62)	2 (50)
Night sweats	5 (21)	0 (0)
Diffuse adenopathy	9(43)	2 (50)
Fever	24 (100)	4 (100)
Altered states of consciousness	5 (24)	0 (0)
Hypotension	24(100)	Not reported
Hepatomegaly	5 (21)	2 (50)
Respiratory distress	24 (100)	4 (100)
Weakness	15 (62)	2 (50)
Laboratory examinations*		
Anaemia	9(38)	1 (25)
Leukopenia	12 (50)	3 (75)
Thrombocytopenia	10 (42)	2 (50)
Elevated C-reactive protein	8 (33)	2 (50)

Legend: No data was reported for erythrocyte sedimentation rates.
*Patients could have more than one sign or abnormality simultaneously; proportions were obtained by dividing the number of patients who showed the sign by the total number of patients (24 for adults and 4 for children).

Table 3. Summary of initial diagnosis and length of time between admission and confirmation or suspicion of tuberculosis sepsis diagnosis

Variables	Adults, N = 24(%)	Infants, N = 4(%)
Initial diagnosis		
Acute suppurative arthritis	1 (4.2)	0 (0)
Aggressive lymphoma	1 (4.2)	0 (0)
Cholecystitis	1 (4.2)	0 (0)
Chorioamnionitis	1 (4.2)	0 (0)
Cytomegalovirus reactivation	1 (4.2)	0 (0)
Immune thrombocytopenic purpura	1 (4.2)	0 (0)
Peritonitis	1 (4.2)	1 (25)
Pneumothorax	1 (4.2)	0 (0)
Sepsis	11 (46)	3 (75)
Severe community-acquired pneumonia	1 (4.2)	0 (0)
Tuberculosis	4 (17)	0 (0)
Time of TB sepsis diagnosis or suspicion (number of days after admission when the sepsis diagnosis was done), (SD)	6 (9)	4 (2)
Treatment outcome		
Death	17 (71)	1 (25)
Discharged	7 (29)	3 (75)

SD = Standard deviation

Supplementary Materials

Supplementary File S1: Search strategy

Supplementary File S2: Overview of excluded studies

Supplementary File S3: Risk of bias assessment

Supplementary File S1: Search strategy

PubMed
("tuberculosis"[All Fields] OR "tuberculosis"[MeSH Terms] OR "tuberculosis"[All Fields] OR "tuberculoses"[All Fields] OR "tuberculosis s"[All Fields]) AND ("sepsis"[MeSH Terms] OR "sepsis"[All Fields]) AND ((("ieee int conf automation sci eng case"[Journal] OR "case phila"[Journal] OR "case"[All Fields]) AND "report*"[All Fields]) OR (("ieee int conf automation sci eng case"[Journal] OR "case phila"[Journal] OR "case"[All Fields]) AND "serie*"[All Fields]))

Google Scholar
(Tuberculosis or Mycobacterium) AND sepsis AND (case series report OR case)

Web of Science (core collection)
Tuberculosis sepsis (All Fields) and case report OR case series (All Fields)

Embase
('tuberculosis sepsis' OR (('tuberculosis'/exp OR tuberculosis) AND ('sepsis'/exp OR sepsis))) AND ('case report'/exp OR 'case report' OR (case AND report) OR 'case series' OR (case AND series))

Table S2: Overview of excluded studies

Authors	Years	Title	Reason for exclusion
Toyoda et al	2010	A case of severe pulmonary tuberculosis with septic shock and ARDS	Not in English or French
Kanabus et al	1970	A case of tuberculosis diagnosed in the course of staphylococcal septicaemia in premature infants	Not tuberculosis sepsis
Karinauske et al	2018	A case report and literature review: previously excluded tuberculosis masked by amiodarone-induced lung injury	Not tuberculosis sepsis
Nunnet al	2022	A prospective study of pyogenic sepsis of the hip in childhood	Not a case report
Sehgal et al	2021	A Randomized Trial of Mycobacterium w in Severe Presumed Gram-Negative Sepsis	Not a case report
Gaubert et al	1958	A rare form of primary infection; tuberculous septicemia	Not tuberculosis sepsis
Kowalewski et al	2017	Abdominal tuberculosis after removal of an adjustable gastric band - report of an unusual case	Not tuberculosis sepsis
Islam et al	2017	Abdominal tuberculosis and spontaneous miscarriage	Not tuberculosis sepsis
Fu et al	2020	Abdominal Tuberculosis Managed Surgically in the Late Phase: A Case Report	Not tuberculosis sepsis
Frame et al	1987	Active tuberculosis in the medical intensive care unit: a 15-year retrospective analysis	Not a case report
Arum et al	2022	Acute Perforation of Small Intestine Due to Tuberculosis - Kakar - 1983 - Australia and New Zealand	Not tuberculosis sepsis
Lee et al	2011	Acute respiratory distress syndrome caused by miliary tuberculosis: a multicentre survey in South Korea	Not a case report
Peng et al	2022	Analysis of 170 cases of congenital TB reported in the literature between 1946 and 2009 -	Not a case report
Barber et al	1990	Bacteraemia due to Mycobacterium tuberculosis in patients with human immunodeficiency virus infection: A report of 9 cases and a review of the literature	Not in English or French
Joseph et al	2012	Bcg sepsis following intravesical bcg administration for the treatment of bladder cancer	Following BCG injection
Widger et al	2010	Breast milk causing neonatal sepsis and death	Not tuberculosis sepsis
Spronk et al	2019	Calculating incidence rates and prevalence proportions: not as simple as it seems	Not a case report

Table S2: Overview of excluded studies (continued)

Authors	Years	Title	Reason for exclusion
Kosheva et al	1985	Case of acute leukaemia complicated by tuberculous sepsis	Not in English or French
Rosas et al	2007	CD14 C(-159)T Polymorphism Is a Risk Factor for Development of Pulmonary Tuberculosis	Not a case report
Hogg et al	1999	Central Line Sepsis in a Child Due to a Previously Unidentified Mycobacterium	Not tuberculosis sepsis
Erbes et al	2022	Characteristics and outcome of patients with active pulmonary tuberculosis requiring intensive care	Not a case report
Hong et al	2003	Characterization of a Novel Rapidly Growing Mycobacterium Species Associated with Sepsis	Not a case report
Herné et al	1980	Chronic lymphocytic leukaemia, acute anergic tuberculosis, multiple caseous adenitis	Not tuberculosis sepsis
Byashalira et al	2022	Clinical outcomes of new algorithm for diagnosis and treatment of Tuberculosis sepsis in HIV patients	Not a case report
Aguado et al	1997	Clinical Presentation and Outcome of Tuberculosis in Kidney, Liver, And Heart Transplant Recipients in Spain1	Not a case report
Dudaka et al	2020	Coinfection of Typhoid Fever with Tuberculosis: A Challenge to Surgical Management	Not a case report
Sherwood et al	2005	Completion pneumonectomy for chronic mycobacterial disease	Not a case report
Oliveira de Araujo et al	2021	Complicated Lumbar Tuberculous Spondylodiscitis In Disseminated Tuberculosis, Treated Using A Non-Conventional Anterior Support System For Hydrostatic Distraction: A Case Report	Not tuberculosis sepsis
Shah et al	2014	Complications of tuberculosis	Not a case report
Kini et al	2002	Congenital tuberculosis associated with maternal asymptomatic endometrial tuberculosis	Not tuberculosis sepsis
Sosa et al	2007	Congenital tuberculosis associated with maternal disseminated miliary tuberculosis	Not in English or French
Ira et al	2022	Consumption Coagulopathy in Miliary Tuberculosis Annals of Internal Medicine	Not tuberculosis sepsis
Baldini et al	1988	Deep sepsis from mycobacterium tuberculosis after total hip replacement	Not tuberculosis sepsis

Table S2: Overview of excluded studies (continued)

Authors	Years	Title	Reason for exclusion
Xie et al	2022	Differential Adverse Event Profiles Associated with BCG as a Preventive Tuberculosis Vaccine or Therapeutic Bladder Cancer Vaccine Identified by Comparative Ontology-Based VAERS and Literature Meta-Analysis	Not a case report
Ziegler et al	2018	Disseminated Mycobacterium bovis infection post-kidney transplant following remote intravesical BCG therapy for bladder cancer	Following BCG injection
Kerkhoff et al	2017	Disseminated tuberculosis among hospitalised HIV patients in South Africa: a common condition that can be rapidly diagnosed using urine-based assays	Not a case report
Kandemir et al	2003	Elevation of procalcitonin level in patients with pulmonary tuberculosis and in medical staff with close patient contact	Not a case report
Jones et al	2010	Aetiology of Illness in Patients with Severe Sepsis Admitted to the Hospital from the Emergency Department	Not tuberculosis sepsis
Ritesh et al	2022	Experience with ARDS caused by tuberculosis in a respiratory intensive care unit	Not a case report
Hensel et al	2013	Fatal outcome of multiorgan tuberculosis with peritoneal involvement after abdominal surgery	Not in English or French
Bofinger et al	2007	Fever of Unknown Origin Caused by Tuberculosis	Not a tuberculosis sepsis
Oladiran et al	2022	Full article: Disseminated BCG sepsis following intravesical therapy for Bladder Carcinoma: A case report and review of literature	Following BCG injection
Padhi et al	2013	Hemophagocytic lymph histiocytosis: critical reappraisal of a potentially under-recognized condition	Not tuberculosis sepsis
Emanuel et al	2012	Hepatic tuberculosis presenting with extreme hyperserotonaemia masquerading as adult-onset Still's disease: a case report	Not tuberculosis sepsis
Koh et al	2013	Host Responses to Melioidosis and Tuberculosis Are Both Dominated by Interferon-Mediated Signalling	Not tuberculosis sepsis
Vandenbroucke et al	2012	Incidence rates in dynamic populations	Not a case report
Dettmeyer et al	2018	Lethal Infections, Sepsis, and Shock	Not a case report
Gardner et al	1949	Lymphocytic Leukemoid Reaction Of The Blood Associated With Miliary Tuberculosis	Not tuberculosis sepsis

Table S2: Overview of excluded studies (continued)

Authors	Years	Title	Reason for exclusion
van et al	2010	Maternal sepsis: epidemiology, aetiology and outcome	Not a case report
Colmenero et al	2012	Miliary pulmonary tuberculosis following intravesical BCG therapy: case report and literature review	Following BCG injection
Stanojevic et al	2018	Miliary tuberculosis complicated by staphylococcal sepsis	Not tuberculosis sepsis
Jog et al	2011	Mycobacterial Sepsis and Multiorgan Failure Syndrome	Not a case report
Legout et al	2001	Mycobacterial sepsis following instillation of intravesical bacillus. Is corticosteroid therapy necessary?	Following BCG injection
Thamthitiwat et al	2011	Mycobacterium bovis bacteremia in immunocompetent neonates following vaccination	Following BCG injection
Jacob et al	2013	Mycobacterium tuberculosis Bacteraemia in a Cohort of HIV-Infected Patients Hospitalized with Severe Sepsis	Not a case report
Kethireddy et al	2013	Mycobacterium tuberculosis Septic Shock	Not a case report
Figueroa et al	2001	Neonatal Outcome of Children Born to Women with Tuberculosis	Not a tuberculosis sepsis
Mehta et al	2004	Ocular lesions in acute disseminated tuberculosis	Not a tuberculosis sepsis
SÃ¡enz et al	2015	Perinatal tuberculosis	Not in English or French
Jin et al	2010	Procalcitonin: Uses in the Clinical Laboratory for the Diagnosis of Sepsis	Not a case report
Kim et al	2008	Pulmonary tuberculosis with acute respiratory failure	Not a case report
Trauner et al	1995	Recurrent Salmonella enteritidis sepsis and hepatic tuberculosis.	Not tuberculosis sepsis
Cofen et al	2020	Rifampicin induced shock during re-exposure for treatment of latent tuberculosis	Not tuberculosis sepsis
Giamarellos et al	2012	Risk assessment in sepsis: a new prognostication rule by APACHE II score and serum soluble urokinase plasminogen activator receptor	Not tuberculosis sepsis
Elton et al	2015	Sepsis in obstetrics	Not a case report
Gardner et al	2009	Sepsis in the Neonate	Not a case report
Japiass et al	2010	Sepsis is a major determinant of outcome in critically ill HIV/AIDS patients	Not a case report
Rafael Silva et al	2011	Sepsis tuberculosa gravissima	Not in English or French
Fichte et al	2018	Septic shock in a female patient with miliary tuberculosis	Not in English or French

Table S2: Overview of excluded studies (continued)

Authors	Years	Title	Reason for exclusion
Gachot et al	1990	Severe tuberculosis in patients with human immunodeficiency virus infection	Not tuberculosis sepsis
Dacombe et al	2013	Stage 3 pyomyositis of the gluteus minimums; Staphylococcus aureus sepsis, auto anticoagulation, proximal femoral osteomyelitis and the role of surgical intervention	Not tuberculosis sepsis
Morales et al	2007	Successful Recovery After Disseminated Infection Due to Mycobacterium Abscesses in a Lung Transplant Patient: Subcutaneous Nodule as First Manifestation	Not tuberculosis sepsis
Dewan et al	2010	Surgery for pulmonary tuberculosis	Not tuberculosis sepsis
Ye et al	2019	The clinical characteristics of patients with sepsis in a tertiary referral hospital in Yangon, Myanmar	Not tuberculosis sepsis
Kestler et al	2013	The development of an emergency sepsis care algorithme in Botswana	Not tuberculosis sepsis
Pillay et al	2001	The increasing burden of tuberculosis in pregnant women, new-borns and infants under 6 months of age in Durban, KwaZulu Natal	Not tuberculosis sepsis
Tanaka et al	2019	The most common causative bacteria in maternal sepsis-related deaths in Japan were group A Streptococcus: A nationwide survey	Not tuberculosis sepsis
Seymour et al	2017	Time to Treatment and Mortality during Mandated Emergency Care for Sepsis	Not tuberculosis sepsis
Alkhuja et al	2001	Tuberculosis and sudden death: A case report and review	Not tuberculosis sepsis
Lanoix et al	2014	Tuberculosis in the intensive care unit: a descriptive analysis in a low-burden country	Not a case report
Babhulkar et al	2022	Tuberculosis of the Hip: Clinical Orthopaedics and Related Research	Not tuberculosis sepsis
Castro et al	2007	Tuberculosis Surveillance: Data for Decision-Making	Not tuberculosis sepsis
Ündar et al	2006	Tuberculosis-Associated Hemophagocytic Syndrome: A Report of Two Cases and a Review of the Literature	Not tuberculosis sepsis
Hauch et al	2020	Tuberculosis-Associated HLH in an 8-Month-Old Infant: A Case Report and Review	Not tuberculosis sepsis
Ekaterina et al	2011	Urogenital Tuberculosis: Classification, Diagnosis, and Treatment – ScienceDirect	Not tuberculosis sepsis

Table S2: Overview of excluded studies (continued)

Authors	Years	Title	Reason for exclusion
Zhe Zhe et al	2022	Mycobacterium tuberculosis bacteraemia in a human immunodeficiency virus-negative patient with liver cirrhosis: A case report	Not tuberculosis sepsis
Ahmed et all	2022	Acute Cholecystitis Presenting With Septic Shock as the First Presentation in an Elderly Patient	Not tuberculosis sepsis
Pía Iglesias	2021	Acute cholecystitis, septic shock, and miliary tuberculosis	Not in English or French
Audulev et al	1984	Acute tuberculous sepsis	Not in English or French
Pesce et al	1999	Acute tuberculous septicaemia.	Not a tuberculosis sepsis
Kassapidis et al	2020	Diagnosing mycobacterium tuberculosis bacteraemia in an immunocompromised female	HIV positive patient
Vadilo et al	1994	AIDS presenting as septic shock caused by mycobacterium tuberculosis	HIV positive patient
Grigoru et al	2008	Disseminated tuberculosis with severe multi-organ failure in a patient with Aids	HIV positive patient
Nyirjesy et al	1993	Fulminant tuberculosis complicating pregnancy in a patient infected with the human immunodeficiency virus	HIV positive patient
Rodriguez et al	1997	Septic shock and multiple organ failure caused by Mycobacterium tuberculosis	Not in English or French
Cordtz et al	2005	Severe and sudden progress of septic shock related to infection with M. tuberculosis	Not in English or French
Silva et al	2011	Severe disseminated tuberculosis in a patient on immunosuppressive treatment. Report of one case	Not in English or French
Phelippeau et al	2015	Severe pulmonary tuberculosis in the ICU, diagnosis and treatment	Not a case report
Dziwiński et al	1970	Severe tuberculous septicemia	Not in English or French
Barmes et al	1987	Six Cases of Mycobacterium tuberculosis Bacteremia	Not a tuberculosis sepsis
X. Xiao	2020	Tuberculosis in patients with systemic lupus erythematosus–a 37-year longitudinal survey-based study	Not a case report
Mueller et all	1980	Unrecognized atypical tuberculosis sepsis in generalized hematologic neoplasms	Not in English or French
Khosa et al	2022	Tuberculous Tamponade With A Twist: A Case Of Tb And Covid-19	Not tuberculosis sepsis

Table S2: Overview of excluded studies (continued)

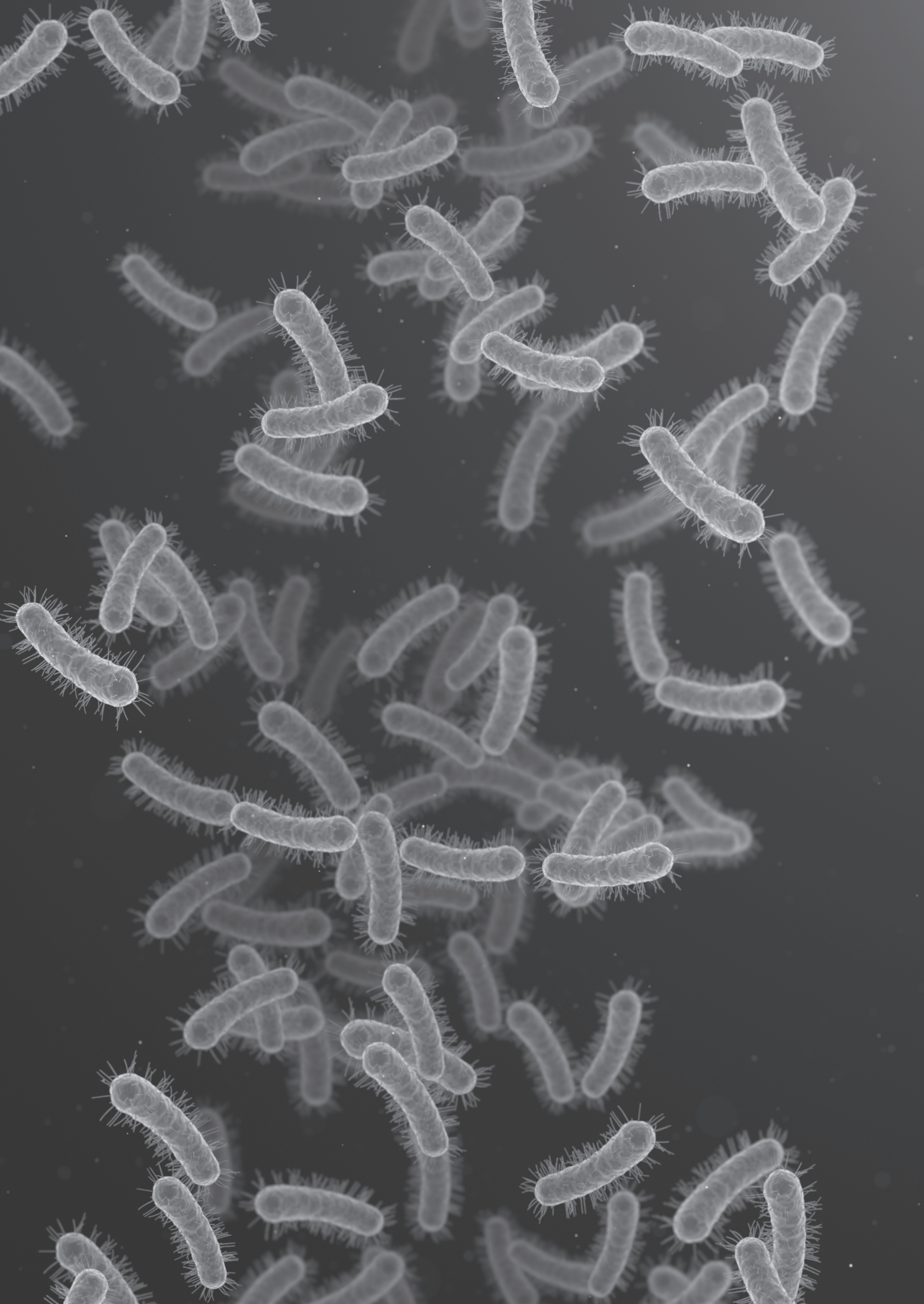
Authors	Years	Title	Reason for exclusion
Takeshi et al	2022	Uncommon Presentation of Tuberculosis as an Incidentally Discovered Solitary Pleural Tuberculoma	Not a tuberculosis sepsis
Tschöp et al	2012	Tuberculous encephalitis, Landouzy sepsis and Pott's disease. Complications after surgery for spinal stenosis	Not in English or French
Pasculle et al	1991	Tuberculous bacillemia, hyperpyrexia, and rapid death	Not tuberculosis sepsis
Naumov et al	1997	Tuberculous sepsis in expert practice	Not a case report
Krishnasamy et al	2013	Tuberculous pyomyositis: A rare but serious diagnosis	Not tuberculosis sepsis
Campo et al	1996	tuberculosis-associated hemophagocytic syndrome: A systemic process	Not a tuberculosis sepsis
Humbert et al	2015	Sepsis or not sepsis? The difficult diagnosis of azathioprine hypersensibility. A case report	Not a tuberculosis sepsis
Costanzo et al	2022	A rare presentation of tb-related septic shock	Abstract /conference publication with lack of information on inclusion criteria
Fiyad hanif et al	2022	A shocking case of disseminated tb	Abstract /conference publication with lack of information on inclusion criteria
Lauren Old et al	2020	a very rare presentation of miliary tuberculosis in mid-trimester pregnancy masquerading as sepsis and severe acute respiratory syndrome category: clinical lesson	Abstract /conference publication with lack of information on inclusion criteria
Debbie et al	2006	Severe Tuberculosis Sepsis in an Immunocompetent Patient	Abstract /conference publication with lack of information on inclusion criteria
Stephanie Hametner et al	2013	Tuberculous sepsis during antiviral HCV triple therapy	Abstract /conference publication with lack of information on inclusion criteria
Myles Rowe et al	2015	An unusual case of sepsis? A rare presentation of a common disease	Abstract /conference publication with lack of information on inclusion criteria

Table S3: Risk of bias assessment

Study	Criteria								
	1. Were patient's demographic characteristics clearly described?	2. Was the patient's history clearly described and presented as a timeline?	3. Was the current clinical condition of the patient on presentation clearly described?	4. Were diagnostic tests or assessment methods and the results clearly described?	5. Was the intervention(s) or treatment procedure(s) clearly described?	6. Was the post-intervention clinical condition clearly described?	7. Were adverse events (harms) or unanticipated events identified and described?	8. Does the case report provide takeaway lessons?	Overall appraisal
Artsiom et al	Yes	Yes	Yes	Yes	Yes	No	Not applicable	Yes	Include
Nakbanpot et al	Yes	No	Yes	Yes	Yes	Yes	Not applicable	Yes	Include
Barbosa et al	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	Yes	Include
Chun-Yuan et al	Yes	No	Yes	Yes	Yes	Yes	Not applicable	Yes	Include
Kindler et al	Yes	Yes	Yes	Yes	Yes	No	Not applicable	Yes	Include
Mitchon et al	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	Yes	Include
Sydow et al	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	Yes	Include
Okascharoenet al	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	Yes	Include
Eshiwe et al	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	Yes	Include
Mohamad et al	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	Yes	Include
Schroder et al	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	Yes	Include
Al Argan et al	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	Yes	Include
Reisinger et al	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	Yes	Include
sieamann et al	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	Yes	Include
Limin et al	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	Yes	Include
Mazade et al	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	Yes	Include
Mishra et al	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	Yes	Include

Table S3: Risk of bias assessment (continued)

Study	Criteria								
	1. Were patient's demographic characteristics clearly described?	2. Was the patient's history clearly described and presented as a timeline?	3. Was the current clinical condition of the patient on presentation clearly described?	4. Were diagnostic tests or assessment methods and the results clearly described?	5. Was the intervention(s) or treatment procedure(s) clearly described?	6. Was the post-intervention clinical condition clearly described?	7. Were adverse events (harms) or unanticipated events identified and described?	8. Does the case report provide takeaway lessons?	Overall appraisal
Mishra et al	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	Yes	Include
Pene et al	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	Yes	Include
Angoulvant et al	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	Yes	Include
Michel et al	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	Yes	Include
Michel et al	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	Yes	Include
Michel et al	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	Yes	Include
Colunche et al	Yes	Yes	Yes	Yes	Yes	No	Not applicable	Yes	Include
Sheldon et al	Yes	Yes	Yes	Yes	Yes	No	Not applicable	Yes	Include
Kathryn et al	Yes	Yes	Yes	Yes	Yes	No	Not applicable	No	Include
Vergara-Sanchez et al	Yes	Yes	Yes	Yes	Yes	No	Not applicable	No	Include
Baljeet et al	Yes	Yes	Yes	Yes	Yes	No	Not applicable	No	Include



Chapter 7

A Prospective Comparison of Quick Sequential Organ Failure Assessment, Systemic Inflammatory Response Syndrome Criteria, Universal Vital Assessment, and Modified Early Warning Score to Predict Mortality in Patients with Suspected Infection in Gabon

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ABSTRACT

The quick sequential organ failure assessment (qSOFA) score has been proposed for risk stratification of emergency room patients with suspected infection. Its use of simple bedside observations makes qSOFA an attractive option for resource-limited regions. We prospectively assessed the predictive ability of qSOFA compared with systemic inflammatory response syndrome (SIRS), universal vital assessment (UVA), and modified early warning score (MEWS) in a resource-limited setting in Lambaréné, Gabon. In addition, we evaluated different adaptations of qSOFA and UVA in this cohort and an external validation cohort from Malawi. We included 279 cases, including 183 with an ad hoc (suspected) infectious disease diagnosis. Overall mortality was 5%. In patients with an infection, oxygen saturation, mental status, human immunodeficiency virus (HIV) status, and all four risk stratification score results differed significantly between survivors and non-survivors. The UVA score performed best in predicting mortality in patients with suspected infection, with an area under the receiving operator curve (AUROC) of 0.90 (95% confidence interval [CI]: 0.78–1.0, $P < 0.0001$), outperforming qSOFA (AUROC 0.77; 95% CI: 0.63–0.91, $P = 0.0003$), MEWS (AUROC 0.72; 95% CI: 0.58–0.87, $P = 0.01$), and SIRS (AUROC 0.70; 95% CI: 0.52–0.88, $P = 0.03$). An amalgamated qSOFA score applying the UVA thresholds for blood pressure and respiratory rate improved predictive ability in Gabon (AUROC 0.82; 95% CI: 0.68–0.96) but performed poorly in a different cohort from Malawi (AUROC 0.58; 95% CI: 0.51–0.64). In conclusion, UVA had the best predictive ability, but multicenter studies are needed to validate the qSOFA and UVA scores in various settings and assess their impact on patient outcomes.

INTRODUCTION

In 2016, the Third International Consensus Definitions for Sepsis and Septic Shock proposed the use of a simplified Sequential Organ Failure Assessment (SOFA) score, termed quickSOFA (qSOFA), for suspected infection outside intensive care to rapidly identify high-risk patients [1,2]. The qSOFA score includes respiratory rate, altered mentation, and systolic blood pressure, which are readily available in any setting. As such, the qSOFA score could be of particular relevance in resource-limited regions. Since its original publication in 2016, several articles and reviews were published on the ability of the qSOFA to predict mortality [3-6]. However, few studies to date have been performed in low-resource settings.

In a retrospective study in the Albert Schweitzer Hospital, in Gabon, we previously found that a qSOFA score of 2 or greater had a sensitivity of 87% (95% confidence interval [CI]: 60–98%) and specificity of 75% (95% CI: 70–80%) with an area under the receiver operating curve (AUROC) of 0.83 (95% CI: 0.74–0.93) in patients with suspected infection (including bacterial infection and/or malaria) [7]. In addition, in a prospective observational study of patients with a suspected infection admitted to a tertiary hospital in Malawi, we observed a sensitivity of 72% (95% CI: 62–80%), a specificity of 68% (95% CI: 63–73%), and an AUROC of 0.73 (95% CI: 0.68–0.78) [8]. Other groups retrospectively evaluated the qSOFA score in patients with an infection presenting to the emergency department of a tertiary care hospital in Rwanda [9] and patients with suspected community-acquired infections presenting to the emergency department of a regional hospital in Tanzania [10]. In Rwanda, qSOFA had a sensitivity of 36% (95% CI: 29–44%) and a specificity of 83% (95% CI: 79–86%) with an AUROC of 0.70 (95% CI: 0.65–0.75) for in-hospital mortality [9]. In Tanzania, the sensitivity was 59% (95% CI: 41–76%) and specificity was 88% (95% CI: 84–91%) with an AUROC of 0.80 (95% CI: 0.73–0.87).[10] Finally, a multicentre retrospective secondary analysis on qSOFA was performed on nine studies in low- and middle-income countries from 2003 to 2017. The authors observed an AUROC of 0.70 (95% CI: 0.68–0.72), but predictive values differed highly between cohorts and settings [11]. This study also demonstrates that qSOFA can be used in a wide range of infections, including Lassa fever, malaria, and dengue [11]. Combined, the scarce number of studies available in resource-limited regions illustrates the potential for the use of qSOFA, but also high variation in performance, especially regarding sensitivity. Moreover, several studies in high-income settings observed limited sensitivity of qSOFA, so its added value compared with commonly used scores for diagnosis and risk stratification of sepsis, such as the systemic inflammatory response syndrome (SIRS) criteria [12] and modified early warning score (MEWS) [13], has been questioned [3,6].

More recently, a new risk stratification score, the universal vital assessment (UVA) score, based on data from hospital-based cohort studies in sub-Saharan Africa, and

thus potentially more suited to the African setting, was developed. The first article, a retrospective literature study, demonstrates a sensitivity and specificity of 71% and 59%, respectively, with an AUROC of 0.77 (95% CI: 0.75–0.79), which outperformed MEWS (AUROC 0.70 [95% CI: 0.67–0.71]) and qSOFA (AUROC 0.69 [95% CI: 0.67–0.72]) [14]. However, this score has not been prospectively evaluated.

Local validation of these scores in resource-limited settings is important to select a risk stratification score that is both practical and accurate. Therefore, we prospectively evaluated the ability of the qSOFA score to predict mortality in patients presenting to the emergency department of the Albert Schweitzer Hospital and compared the performance of qSOFA with the SIRS criteria, MEWS, and UVA scores. Furthermore, we reanalyzed our data by adapting details of the qSOFA and UVA scores to examine the potential for improving their performance characteristics beyond the limits of the existing score definitions.

METHODS

Study design and population.

We performed a single-center prospective observational study at the emergency department of the Albert Schweitzer Hospital in Lambaréné, Gabon. The Albert Schweitzer Hospital is a 150-bed referral hospital serving an estimated population of 75,500 patients throughout central Gabon. The emergency department is equipped to serve eight patients at a time, including a two-bed high-care unit adjacent to the emergency room. Data were collected from November 2017 to May 2018.

We included all consenting adults visiting the emergency department. The qSOFA, SIRS, MEWS, and UVA risk stratification scores were calculated and compared with one another to assess the ability to predict mortality. These scores were calculated using clinical parameters, obtained prospectively on admission to the emergency department (Table 1). Our primary analysis focused on patients with a suspected infection. Suspected infection was defined on presentation when available clinical, radiological, and laboratory findings suggest a most likely infectious cause (including bacterial infection, malaria, tuberculosis, and viral infections).

Table 1 Summary of information required for each prognostic scoring system discussed and maximum score allocated for each parameter

	Quick Sequential Organ Failure Assessment	Systemic inflammatory response syndrome	Modified early warning score	Universal vital assessment
Respiratory rate, breaths/minute	1: ≥ 22	1: > 20	0: 9–14	1: ≥ 30
			1: 15–20	
			2: 21–29 or < 9	
			3: ≥ 30	
Systolic blood pressure, mm Hg	1: ≤ 100	–	0: 101–199	1: < 90
			1: 81–100	
			2: 71–80 or ≥ 200	
			3: ≤ 70	
GCS or AVPU	1: GCS < 15	–	0: Alert	4: GCS < 15
			1: Reacts to voice	
			2: Reacts to pain	
			3: Unresponsive	
Temperature, °C	–	1: > 38 or < 36	0: 35–38.4	2: < 36
			2: <35 or ≥ 38.5	
Heart rate, beats/minute	–	1: > 90	0: 51–100	1: ≥ 120
			1: 101–110 or 41–50	
			2: 111–129 or <40	
			3: ≥ 130	
White blood cells, 10^9 g/L	–	1: >12 or <4	–	–
Oxygen saturation	–	–	–	2: < 92%
Source of infection	–	Yes/no	–	–
HIV status	–	–	–	2: seropositive
Maximum score	3 (≥ 2: high risk)	4 (≥ 2 and source of infection meets sepsis criteria)	14 (> 4: high risk)	13 (0–1 low risk, 2–4 medium risk, > 4 high risk

GCS = Glasgow Coma Scale; AVPU = alert, voice, pain, unresponsive.

Outcome.

The primary outcome was the ability of qSOFA to predict mortality in patients visiting the emergency department, specifically for patients with a suspected infection. All patients were followed up to determine the following possible outcomes: discharge, death, or loss to follow-up (due to absconded patients or transfer to another hospital with an unknown outcome). Final diagnoses, required hospitalization, in-hospital mortality, and length of stay in the hospital were recorded from patient files. For patients transferred to a

different hospital, the researcher made a phone call to retrieve information about the outcome of the patient.

Data collection.

All clinical parameters were collected within 12 hours after admission to the emergency department. Most parameters were measured as part of routine care and retrieved from patient files. Missing information was collected in the emergency department and on the wards. In patients with a known HIV status, this was recorded from the medical notes or patient interview. The training was given on the importance and correct measurement of the physiological parameters. Patients who absconded or were transferred to a different hospital received a follow-up phone call to determine their outcome. Study data were anonymized, collected, and managed using Research Electronic Data Capture (REDCap) tools hosted at Centre de Recherches Médicales de Lambaréné (CERMEL). REDCap is a secure, web-based application designed to support data capture for research studies. Data were verified by two separate researchers.

Sample size.

Because of limited data on the mortality, and sensitivity and specificity of qSOFA in our study population, a formal sample size calculation could not be performed before the start of the study. An interim analysis in March 2017 revealed that a total number of 3,144 and 6,880 patients would be needed to reliably assess specificity and sensitivity, respectively [15]. As this was not feasible in our setting, we analyzed the available data of this pilot study, which we intend to use as a template for a prospective multicentre study.

Data analysis.

Baseline characteristics are expressed as medians with interquartile ranges (IQRs). Comparisons were made using a Mann–Whitney U test for continuous variables and a chi-squared test for dichotomous variables. To assess the predictive ability of risk stratification scores, we analyzed AUROC, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), using a threshold of 2 for the qSOFA score; 2 and 5 for the middle and high UVA scores, respectively; 5 for the MEWS; and 2 for SIRS score. Missing or undetermined white blood cell counts were assumed to be normal in calculating SIRS. Missing information concerning HIV serostatus was recorded as unknown and not awarded a point in the UVA score. This is in accordance with the proposed use of the UVA score[14]. Patients who had unknown serostatus at the time-point of scoring, but were diagnosed with HIV after admission, were not allocated any UVA score points for HIV status. Patients with missing vital signs were excluded from the analysis. All statistical analyses were performed using GraphPad Prism 7 for Mac OS X (version 7.0d; GraphPad Software, La Jolla, CA).

Calculation of an amalgamated qSOFA/UVA score.

Retrospectively, data were analyzed to assess candidate amalgamated qSOFA/UVA scores possibly superior with regard to the outcome "best prognostic score" to inform possible further studies. The following options were calculated: 1) qSOFA with respiratory rate and systolic blood pressure (BP) thresholds according to UVA criteria, using a cutoff of ≥ 1 to identify high-risk patients; 2a) original qSOFA + oxygen saturation, 2b) adapted (see [1]) qSOFA + oxygen saturation; and 3) original qSOFA + 1 extra point for altered Glasgow Coma Scale (GCS). Next, we did a retrospective external validation of adapted qSOFA scores using data from a previous study in Malawi [8].

Ethics.

Ethical approval was obtained from the Institutional Review Board of CERMEL (CEI-CERMEL:014/2017). Informed consent was obtained from all patients. If patients were unable to understand the informed consent procedure because of illness, a legal representative was asked for informed consent. All patient data were kept confidential and only accessible to members of the study team.

RESULTS

During the study period, 277 patients were included in the study. Four patients visited the emergency department twice for the same problem for which the vital signs, corresponding scores, and outcomes were reported as separate cases. One patient was excluded because of missing data and one patient was lost to follow-up, leaving 279 cases for analysis, including 187 cases with an infectious diagnosis. The most common infectious diagnosis was malaria (*n* = 97), followed by gastrointestinal and intra-abdominal infections (*n* = 20), respiratory tract infections (*n* = 17), skin and soft tissue infections (*n* = 15), pulmonary tuberculosis (*n* = 13), suspected viral infections (*n* = 12), and urinary tract infections (*n* = 8). The most common diagnoses in patients without infection were musculoskeletal complaints (*n* = 19), abdominal pain (*n* = 17), hypertension (*n* = 14), anemia (*n* = 8), and heart failure (*n* = 8). Baseline characteristics are presented in Table 2. The median age of patients was 38 years (IQR 28–53) and 46% (*n* = 128) were male. Fourteen patients were known to be HIV positive (5%), including one who was diagnosed after admission to the hospital. Sixteen patients died (mortality 5.7%), including 11 with a suspected infection.

Table 2 Baseline characteristics

	All cases				Cases with infection			
	Total, *n* = 279	**Survivors, *n* = 263**	**Non-survivors, *n* = 16**	***P*-value**	**Total, *n* = 187**	**Survivors, *n* = 176**	**Non-survivors, *n* = 11**	***P*-value**
Demographics								
Gender–male, number (%)	128 (45.9)	121 (46.0)	7 (43.8)	1.0	93 (49.7)	88 (50.0)	5 (45.5)	1.0.
Age in years, median (IQR)	38 (28–53)	38 (27–51)	52 (34–61)	0.069	38 (26–50)	37 (25–49)	58 (35–60)	0.01
Admission, number (%)	134 (48)	118 (44.9)	16 (100)	Not applicable	103 (55.1)	92 (52.3)	11 (100)	Not applicable
Length of stay in days, median (IQR)	4 (3–6)	4 (3–6)	5 (2–12)	0.98	2 (1–5)	2 (1–4)	5 (2–12)	0.03
Clinical parameters								
Systolic blood pressure, mmHg, median (IQR)	120 (110–140)	120 (110–140)	105 (80–130)	0.019	120 (110–130)	120 (110–130)	110 (80–130)	0.10
Heart rate, beats/minutes, median (IQR)	91 (80–107)	90 (80–106)	112 (91–120)	0.003	96 (84–111)	96 (84–110)	104 (91–120)	0.09
Respiratory rate, breaths/minutes, median (IQR)	22 (18–26)	22 (18–26)	24 (23–34)	0.018	24 (20–28)	24 (20–28)	24 (24–48)	0.052
Temperature, °C, median (IQR)	37.2 (36.5–38.4)	37.2 (36.6–38.4)	36–4 (35.9–37.7)	0.005	37.8 (36.8–38.7)	37.8 (36.9–38.7)	36.5 (36.0–38.6)	0.07
Saturation, %, median (IQR)	97 (95–99)	98 (95–99)	93 (76–99)	0.028	97 (94–98)	97 (95–98)	92 (80–96)	0.01
White blood cells, 10^9g/L, median (IQR)*	7.2 (5.4–9.9)	7.1 (5.4–9.7)	10.5 (6.3–15.6)	0.028	7.2 (5.6–10.4)	7.2 (5.5–10.1)	12.0 (6.1–14.9)	0.10
Glasgow Coma Scale <15, number (%)	13 (4.7)	6 (2.3)	7 (43.8)	< 0.0001	10 (5.3)	5 (2.8)	5 (45.5)	< 0.0001
HIV infection, number (%)†	14 (5.0)	11 (4.2)	3 (18.8)	0.038	14 (7.5)	11 (6.3)	3 (27.3)	0.04
Risk stratification scores								
qSOFA, median (IQR)	1 (0–1)	1 (0–1)	1.5 (1–3)	< 0.0001	1 (0–1)	1 (0–1)	2 (1–3)	0.0009
qSOFA ≥ 2, number (%)	43 (15.4)	35 (13.3)	8 (50.0)	0.0009	37 (19.8)	31 (17.6)	6 (54.5)	0.009
SIRS, median (IQR)	2 (1–2)	2 (1–2)	2.5 (2–4)	0.0009	2 (1–3)	2 (1–3)	3 (2–4)	0.02

Table 2 Baseline characteristics (continued)

	All cases				Cases with infection			
	Total, *n* = 279	**Survivors, *n* = 263**	**Non-survivors, *n* = 16**	***P*-value**	**Total, *n* = 187**	**Survivors, *n* = 176**	**Non-survivors, *n* = 11**	***P*-value**
SIRS ≥ 2, number (%)	160 (57.3)	146 (55.5)	14 (87.5)	0.017	128 (68.4)	119 (67.6)	9 (81.8)	0.51
MEWS, median (IQR)	2 (2–4)	2 (1–4)	5 (3–9)	< 0.0001	3 (2–5)	3 (2–5)	5 (3–7)	0.01
MEWS ≥ 5, number (%)	62 (22.2)	52 (19.8)	10 (62.5)	0.0004	56 (29.9)	49 (27.8)	7 (63.6)	0.02
UVA, median (IQR)	0 (0–1)	0 (0–1)	4.5 (3–7)	< 0.0001	0 (0–2)	0 (0–1)	5 (3–7)	< 0.0001
UVA ≥ 2, number (%)	61 (21.9)	47 (17.9)	14 (85.7)	< 0.0001	48 (25.7)	38 (21.6)	10 (90.9)	< 0.0001
UVA ≥ 5, number (%)	13 (4.7)	5 (1.9)	8 (50.0)	< 0.0001	11 (5.9)	5 (2.8)	6 (54.5)	< 0.0001

As qSOFA is designed for risk stratification in sepsis patients, we focused our analyses on the subgroup of patients with suspected infection (n = 187). In this population, the clinical parameters that were significantly different between survivors and non-survivors were oxygen saturation, altered mental status, and HIV infection. Oxygen saturation was a median of 97% (95% CI: 95–98%) in survivors, compared with 92% (95% CI: 80–96%) in non-survivors (P = 0.01). A reduced GCS was observed in five (2.8%) survivors and five (45.5%) non-survivors (P < 0.0001). HIV infection was observed in 11 (6.3%) survivors and three (27.3%) non-survivors (P = 0.02). All risk stratification scores assessed in this study were significantly different between survivors and non-survivors (Table 2).

Next, we determined the predictive ability of different risk stratification scores in all cases and our subgroup of cases with an infectious diagnosis (Table 3). Although we focus our discussion here on cases with an infectious diagnosis, similar results were observed in unselected patients presenting to the emergency room. In patients with an infection, a qSOFA ≥ 2 had a sensitivity of 55% (95% CI: 23–83) and specificity of 82% (95% CI: 76–88). The positive predictive value was 16% and NPV was 97%. The AUROC was 0.77 (95% CI: 0.63–0.91). The qSOFA score was outperformed by the UVA score, with a sensitivity of 91% (95% CI: 59–100) and specificity of 78% (95% CI: 72–84%) for a cutoff value ≥ 2, with a PPV and NPV of 21% and 99%, respectively. When the cutoff was increased to a UVA score ≥ 5, sensitivity dropped to 55% (95% CI: 23–83%), similar to

Table 3 Predictive ability of risk stratification scores

	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Positive predictive value (%)	Negative predictive value (%)	Area under the receiver operating curve (95% CI)
All cases					
Existing risk stratification scores					
qSOFA ≥ 2	50 (25–75)	87 (82–91)	19	97	0.79 (0.69–0.89
SIRS ≥ 2	88 (62–98)	44 (38–51)	9	98	0.74 (0.62–0.86)
MEWS ≥ 5	63 (35–85)	80 (75–85)	16	97	0.80 (0.71–0.90)
UVA ≥ 2	88 (62–98)	82 (77–87)	23	99	0.89 (0.78–1.0)
UVA high ≥ 5	50 (25–75)	98 (96–99)	62	97	
Cases with an infection					
Existing risk stratification scores					
qSOFA ≥ 2	55 (23–83)	82 (76–88)	16	97	0.77 (0.63–0.91)
SIRS ≥ 2	82 (48–98)	32 (26–40)	7	97	0.70 (0.52–0.88)
MEWS ≥ 5	64 (31–89)	72 (65–79)	13	97	0.72 (0.58–0.87)
UVA ≥ 2	91 (59–100)	78 (72–84)	21	99	0.90 (0.78–1.0)
UVA high ≥ 5	55 (23–83)	97 (94–99)	55	97	
Adapted risk stratification scores					
qSOFA (1) ≥ 1	82 (48–98)	80 (73–86)	20	99	0.82 (0.68–0.96)
qSOFA (2a) ≥ 2	73 (39–94)	79 (72–85)	18	98	0.81 (0.69–0.94)
qSOFA (2b) ≥ 1	82 (48–98)	73 (66–79)	50	97	0.83 (0.68–0.98)
qSOFA (3) ≥2	55 (24–83)	82 (76–88)	16	97	0.78 (0.64–0.93)
UVA (1) ≥ 2	82 (48–98)	81 (75–87)	21	99	0.86 (0.70–1.0)
UVA (1) ≥ 5	55 (23–83)	99 (96–100)	75	97	
External validation of existing and adapted qSOFA in the Malawi cohort*					
qSOFA ≥ 2	72 (62–80)	68 (63–73)	40	50	0.73 (0.68–0.78)
qSOFA (1) ≥ 1	58 (48–67)	53 (48–59)	27	81	0.58 (0.51–0.64)
qSOFA (3) ≥ 2	79 (70–87)	63 (58–68)	39	91	0.77 (0.72–0.82)

qSOFA, whereas specificity increased to 97% (95% CI: 94–99%), with a PPV and NPV of 55% and 97%, respectively. The AUROC for the UVA score was 0.90 (95% CI: 0.78–1.0). The MEWS and SIRS score performed less well with an AUROC of 0.72 (95% CI: 0.58–0.87) and 0.70 (95% CI: 0.52–0.88), respectively (Table 3).

Following our primary analysis, we evaluated different amalgamated risk stratification scores, combining different aspects of qSOFA and UVA (Table 3). In Gabon, we observed that the predictive ability of qSOFA, and sensitivity, in particular, increased when the thresholds for blood pressure and respiratory rate in qSOFA were changed to those of the UVA (summarized as qSOFA [1] in Table 3), using a cutoff for the score of ≥ 1 to identify high-risk patients. Adding oxygen saturation as a parameter also increased the performance of qSOFA as a predictor of mortality. Allocating more points for an altered mental state did not change the performance of qSOFA in this cohort. We also evaluated the UVA score without taking HIV status into account. This did not affect the predictive ability of the UVA score. However, this may be because of the low number of HIV-positive cases in our cohort.

Next, we performed a retrospective external validation of qSOFA with respiratory rate and systolic BP thresholds according to UVA criteria, in a cohort of patients admitted with suspected infection in Malawi where we previously evaluated qSOFA[8]. Baseline characteristics of this cohort are presented in Supplemental Table 1 and demonstrate the demographic similarity between the two cohorts but a much higher mortality rate of 23%. The qSOFA score performed reasonably in Malawi with an AUROC of 0.73 (95% CI: 0.68–0.78), which could be increased to 0.77 (95% CI: 0.72–0.82) when an extra point was allocated for altered mental status. Strikingly, in this cohort, the amalgamated qSOFA score using UVA thresholds for respiratory rate and blood pressure performed poorly, with a sensitivity of 58% (95% CI: 48–67%), a specificity of 53% (95% CI: 48–59%), and an AUROC of 0.58 (95% CI: 0.51–0.64) (Table 3). This illustrates the heterogeneity in the performance of risk stratification scores between different cohorts.

DISCUSSION

We compared the ability to predict in-hospital mortality of the qSOFA score, UVA score, MEWS, and SIRS criteria in patients visiting the emergency department in a low-resource setting. Risk stratification scores performed similarly in the entire cohort and the subgroup with suspected infection, suggesting that these scores may be useful in an unselected patient population, with and without infection, presenting to emergency services. As qSOFA is designed for risk stratification in sepsis, the findings summarized in the following paragraphs represent the data for all cases with an infectious diagnosis.

Our main finding is that the UVA score yielded the best predictive ability with an AUROC of 0.90 (95% CI: 0.78–1.0), followed by qSOFA with an AUROC of 0.77 (95% CI: 0.63–0.91), whereas MEWS and SIRS had lower predictive values in our setting. Quick Sequential Organ Failure Assessment has previously been criticized for its low sensitivity, which was confirmed by our study (sensitivity 55% [95% CI: 23–83%]). Arguably, a risk stratification score should have high sensitivity to avoid overlooking critically ill patients. On the other hand, a score should be sufficiently specific to avoid overburdening of limited health services. The UVA score performed better with a sensitivity of 91% (95% CI: 59–100%), when using a cutoff value of ≥ 2, without losing much specificity (specificity 78% [95% CI: 72–84%], compared with 82% [95% CI: 76–88%] for qSOFA). The NPV was high for all risk stratification scores, whereas the PPV was low, likely related to the low mortality rate in our cohort. The UVA score also had the best PPV, with a PPV of 21% for scores ≥ 2 and a PPV of 55% for scores ≥ 5.

In the study presented here, qSOFA performance was in line with previous studies [7-9,11]. Regarding the UVA score, our study is, to the best of our knowledge, the first to perform a prospective validation of this score. In the original publication, Moore and others [14] describe an AUROC of 0.77 (95% CI: 0.75–0.79). Key differences between qSOFA and UVA are a higher cutoff value for respiratory rate (≥ 30 compared with ≥ 22) and a lower cut-off value for systolic blood pressure (< 90 compared with ≤ 100) in UVA as compared with qSOFA, which may increase specificity. Adding HIV status and saturation, and allocating four points for altered mental status may increase the sensitivity of the UVA score. We further evaluated this by using an amalgamated qSOFA score. Using UVA thresholds for blood pressure and respiratory rate increased the predictive ability of qSOFA to an AUROC of 0.82 (0.68–0.96). However, in a different cohort from Malawi where we previously evaluated qSOFA, the performance of qSOFA decreased with this adaptation. Hence, the optimal threshold for blood pressure and the respiratory rate remains uncertain and may not be universal. Adding oxygen saturation as a variable to qSOFA also increased performance in Gabon, but we were unable to evaluate this in our Malawi cohort. We previously found that adding two points for altered mental status improved the sensitivity of qSOFA in Malawi. However, this was not the case in Gabon, possibly because of a lower number of HIV-positive patients and, thus, fewer intracerebral infections in Gabon.

The HIV prevalence of 5% in our cohort is most likely an underestimate, as we previously observed a prevalence of 20% in hospitalized febrile patients in the same hospital [7]. Nevertheless, a known HIV status correlated with mortality and, thus, seems to be a useful parameter to incorporate in a risk stratification score. Because of the low number of patients with a known HIV status, we were unable to further examine the impact of HIV status on UVA performance.

The major strengths of our study are the prospective design and presence of study physicians in the emergency department. We included all patients presenting to the emergency room and later stratified our results according to the presence of an infection. As the source of infection is often unclear at presentation, especially in resource-limited settings where diagnostic tools may be unavailable, a risk stratification score should identify critically ill patients regardless of the source of infection. Therefore, we grouped patients with an infection, including bacterial infections, malaria, tuberculosis, and viral infections. Our presence in the emergency department facilitated the collection of vital parameters as soon as possible after the presentation before medical interventions had been performed. Other studies, including the pivotal publication by Seymour and others [2,11], allow for 24 hours between the presentation or onset of infection, and the collection of vital parameters to calculate qSOFA. We chose a smaller time frame of 12 hours after the presentation, which was both realistic and feasible, to assess qSOFA as a tool for triage. Being present also allowed us to observe the routine collection of clinical parameters. Although most parameters were collected by local staff, the respiratory rate was often missing. After training was given and a stopwatch was donated, the measurement frequency of the respiratory rate increased, but it remained hard to incorporate it into the standard practice of local staff. This illustrates the challenges of incorporating a risk stratification score in routine clinical practice. Finally, we were able to use a previous cohort for external validation of an amalgamated qSOFA score. This allowed us to illustrate the differences between settings and highlights the need for multicenter studies.

Our study was limited by the number of patients included. Therefore, we were unable to perform a statistically significant comparison between risk stratification scores, and CIs were wide. Our results, thus, need to be interpreted with caution and we recommend further prospective validation studies of both qSOFA and the UVA scores in low-resource settings to determine which score has the best predictive ability, and good applicability in clinical practice. Importantly, the differences we observed between Gabon and Malawi demonstrate that it is vital to perform multicenter studies on this subject.

CONCLUSION

We report here one of the few prospective studies on qSOFA in resource-limited settings and the first prospective evaluation of the UVA score. The UVA score was designed based on studies from sub-Saharan Africa and outperformed qSOFA, SIRS, and MEWS in the ability to predict mortality in our cohort. Multicenter studies are needed to validate qSOFA and the UVA score and variations thereof as suggested, in various settings, and assess whether the use of these scores can improve patient outcomes in resource-limited settings by rapid diagnosis and intervention for sepsis.

REFERENCES

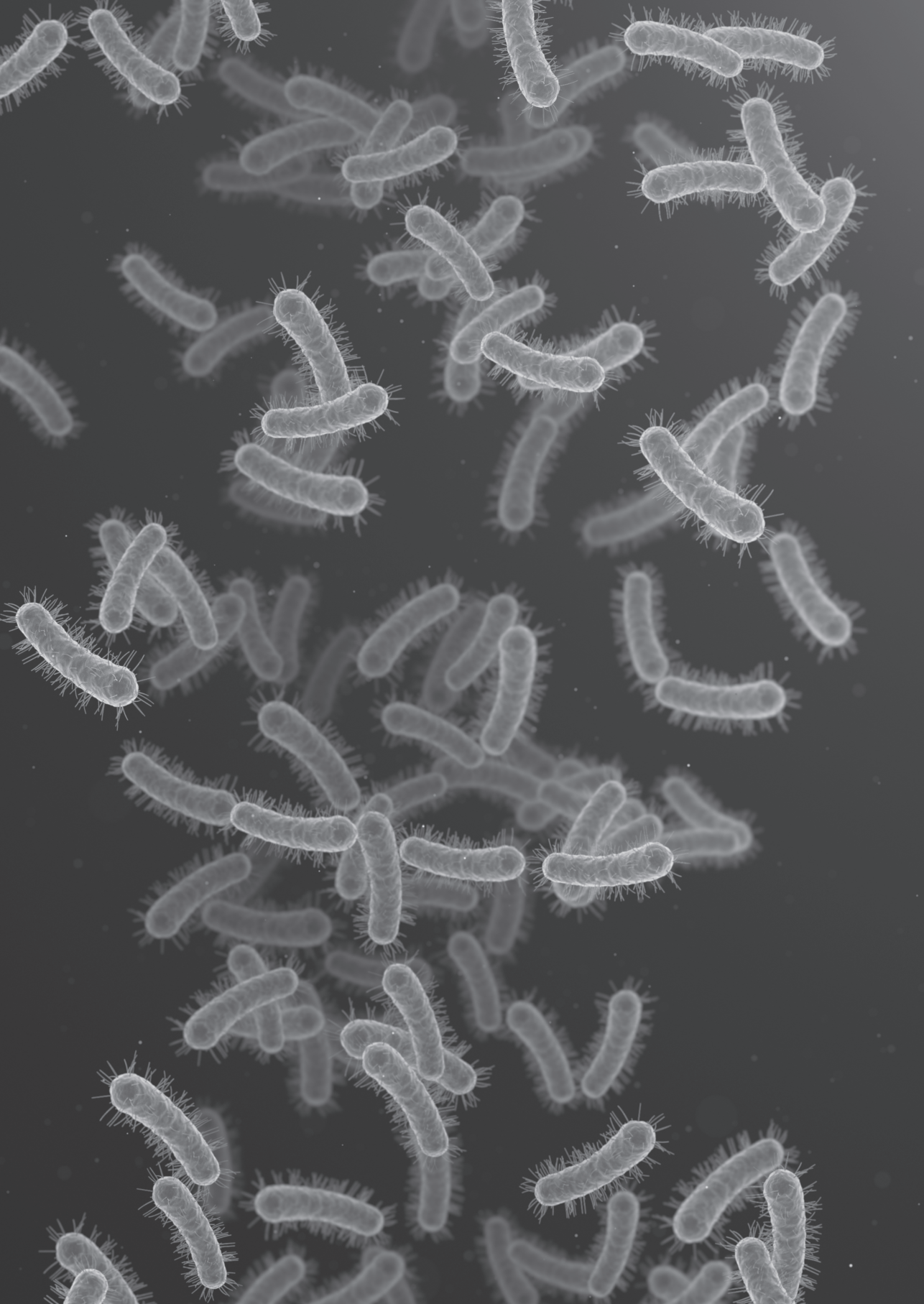
1. Singer M et al., 2016. The third international consensus definitions for sepsis and septic shock (sepsis-3). JAMA 315:801–810.
2. Seymour CW et al., 2016. Assessment of clinical criteria for sepsis: for the third international consensus definitions for sepsis and septic Shock (sepsis-3). JAMA 315: 762–774.
3. Song JU, Sin CK, Park HK, Shim SR, Lee J, 2018. Performance of the quick sequential (sepsis-related) organ failure assessment score as a prognostic tool in infected patients outside the intensive care unit: a systematic review and meta-analysis. Crit Care 22: 28.
4. Fernando SM, Tran A, Taljaard M, Cheng W, Rochwerg B, Seely AJE, Perry JJ, 2018. Prognostic accuracy of the quick sequential organ failure assessment for mortality in patients with suspected infection: a systematic review and meta-analysis. Ann Intern Med 168: 266–275.
5. Serafim R, Gomes JA, Salluh J, Povoa P, 2018. A comparison of the quick-SOFA and systemic inflammatory response syndrome criteria for the diagnosis of sepsis and prediction of mortality: a systematic review and meta-analysis. Chest 153:646–655.
6. Maitra S, Som A, Bhattacharjee S, 2018. Accuracy of quick sequential organ failure assessment (qSOFA) score and systemic inflammatory response syndrome (SIRS) criteria for predicting mortality in hospitalized patients with suspected infection: a meta-analysis of observational studies. Clin Microbiol Infect 24: 1123–1129.
7. Huson MA, Kalkman R, Grobusch MP, van der Poll T, 2017. Predictive value of the qSOFA score in patients with suspected infection in a resource-limited setting in Gabon. Travel Med Infect Dis 15: 76–77.
8. Huson MAM, Katete C, Chunda L, Ngoma J, Wallrauch C, Heller T, van der Poll T, Grobusch MP, 2017. Application of the qSOFA score to predict mortality in patients with suspected infection in a resource-limited setting in Malawi. Infection 45: 893–896.
9. Aluisio AR, Garbern S, Wiskel T, Mutabazi ZA, Umuhire O, Ch'ng CC, Rudd KE, D'Arc Nyinawankusi J, Byiringiro JC, Levine AC, 2018. Mortality outcomes based on ED qSOFA score and HIV status in a developing low-income country. Am J Emerg Med 36: 2010–2019.
10. Boillat-Blanco N, Mbarack Z, Samaka J, Mlaganile T, Mamin A,Genton B, Kaiser L, Calandra T, D'Acremont V, 2018. Prognostic value of quickSOFA as a predictor of 28-day mortality among febrile adult patients presenting to emergency departments in Dar es Salaam, Tanzania. PLoS One 13: e0197982.
11. Rudd KE et al., 2018. Association of the quick sequential (sepsis-related) organ failure assessment (qSOFA) score with excess hospital mortality in adults with suspected infection in low- and middle-income countries. JAMA 319: 2202–2211.
12. Bone RC, Sprung CL, SibbaldWJ, 1992. Definitions for sepsis and organ failure. Crit Care Med 20: 724–726.
13. Subbe CP, Kruger M, Rutherford P, Gemmel L, 2001. Validation of a modified early warning score in medical admissions. QJM 94:521–526.
14. Moore CC et al., 2017. Derivation and validation of a universal vital assessment (UVA) score: a tool for predicting mortality in adult hospitalised patients in sub-Saharan Africa. BMJ Glob Health 2: e000344.
15. Hajian-Tilaki K, 2014. Sample size estimation in diagnostic test studies of biomedical informatics. J Biomed Inform 48: 193–204.

Supplementary file

Table S1: Baseline characteristics of Malawi cohort

	Total n=458	Survivors n=352	Non-survivors n=106	p-value
Demographics				
Gender – male, number (%)	243 (53.1)	180 (51.1)	63 (59.4)	0.15
Age in years, median (IQR)	35 (26-47)	33.5 (25-45)	40 (30-52)	0.001
Length of stay in days, median (IQR)	4 (2-7)	5 (2-7)	3 (1-5)	< 0.0001
Clinical parameters				
Systolic blood pressure, mmHg, median (IQR),	110 (97122)	111 (98-121)	110 (91.5-129)	0.37
Heart rate, beats/min, median (IQR),	101 (86118)	101 (86-117)	102 (87-123)	0.46
Respiratory rate, breaths/min, median (IQR),	28 (20-32)	28 (24-37.75)	27 (20-32)	0.002
Glasgow Coma Scale <15, number (%)	15 (14-15)	15 (15-15)	14 (8-15)	< 0.0001
HIV infection, Number(%)	213 (53.7)	163 (53.4)	50 (54.3)	0.91
Risk stratification scores				
qSOFA, median (IQR)	2 (1-2)	1 (1-1)	2 (1-2)	< 0.0001
qSOFA ≥2, number (%)	188 (41)	112 (31.8)	76 (71.7)	< 0.0001

Abbreviations: IQR: inter quartile range, qSOFA : quick Sequential Organ Failure Assessment.



Chapter 8

A comparison of different scores for diagnosis and mortality prediction of adults with sepsis in Low-and-Middle-Income Countries: a systematic review and meta-analysis

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ABSTRACT

Background

Clinical scores for sepsis have been primarily developed for and applied in High-Income Countries. This systematic review and meta-analysis examined the performance of the quick Sequential Organ Failure Assessment (qSOFA), Systemic Inflammatory Response Syndrome (SIRS), Modified Early Warning Score (MEWS), and Universal Vital Assessment (UVA) scores for diagnosis and prediction of mortality in patients with suspected infection in Low-and-Middle-Income Countries.

Methods

PubMed, Science Direct, Web of Science, and the Cochrane Central Register of Controlled Trials databases were searched until May 18, 2021. Studies reporting the performance of at least one of the above-mentioned scores for predicting mortality in patients 15 years of age and older with suspected infection or sepsis were eligible. The Quality Assessment of Diagnostic Accuracy Studies tool was used for risk-of-bias assessment. PRISMA guidelines were followed (PROSPERO registration: CRD42020153906). The bivariate random-effects regression model was used to pool the individual sensitivities, specificities and areas under the curve (AUC).

Findings

Twenty-four articles (of 5669 identified) with 27,237 patients were eligible for inclusion. qSOFA pooled sensitivity was 0·70 (95% confidence interval [CI] 0·60–0·78), specificity 0·73 (95% CI 0·67–0·79), and AUC 0·77 (95% CI 0·72–0·82). SIRS pooled sensitivity, specificity and AUC were 0·88 (95% CI 0·79 -0·93), 0·34 (95% CI 0·25–0·44), and 0·69 (95% CI 0·50–0·83), respectively. MEWS pooled sensitivity, specificity and AUC were 0·70 (95% CI 0·57 -0·81), 0·61 (95% CI 0·42–0·77), and 0·72 (95% CI 0·64–0·77), respectively. UVA pooled sensitivity, specificity and AUC were 0·49 (95% CI 0·33 -0·65), 0·91(95% CI 0·84–0·96), and 0·76 (95% CI 0·44–0·93), respectively. Significant heterogeneity was observed in the pooled analysis.

Interpretation

Individual score performances ranged from poor to acceptable. Future studies should combine selected or modified elements of different scores.

Funding

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Keywords low-and-middle-income countries (LMICs) ; sepsis; severity scores;qSOFA;SIRS; MEWS;UVA

Research in context

Evidence before this study

There was no earlier systematic review reporting the performance comparison of the four scores, and previous systematic reviews and meta-analyses included predominantly studies from high-income countries (HICs). Variations in clinical presentation, aetiology of sepsis and limited access to intensive care units between HICs and low-and-middle-income countries (LMICs) settings may contribute to differences between the performance of the scores.

Added value of this study

The performance of four available scores, Sequential Organ Failure Assessment (qSOFA), Systemic Inflammatory Response Syndrome (SIRS), Modified Early Warning score (MEWS), and Universal Vital Assessment (UVA) in the diagnosis of sepsis and in-patient mortality prediction in patients with suspected infection in LMICs were systematically reviewed for the first time. Currently used scores yield variable performance, ranging from poor to acceptable, in predicting mortality or sepsis diagnosis when applied to adult patients hospitalised with infectious diseases in LMIC settings. The sensitivity of qSOFA might be higher in LMICs than that reported from HICs. However, further validation studies are needed.

Implications of all the available evidence

Our analysis suggests a two-step approach to better predict the worst outcome in patients with suspected infection in LMICs. The SIRS score has the best sensitivity; it could assist clinicians in making the first triage, followed by the qSOFA, MEWS, or UVA scores to inform decisions about the appropriate level of care.

INTRODUCTION

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection; it is responsible for twenty per cent of all-cause global mortality, the majority of which occurs in low-and-middle-income countries (LMICs) [1,2]. Sepsis is a syndrome that can manifest in affected patients as a broad constellation of symptoms and signs caused by the interplay of pathogens and host factors. To address the challenge of sepsis diagnosis, multiple sepsis diagnostic and mortality prediction models or scores have been developed.

The availability of sophisticated laboratory investigation tools and early warning scores are important instruments to improve the diagnosis and management of sepsis in high-income countries (HICs), but applying those to LMIC settings is complex. The first

early warning score published in 1997 was designed to enable the detection of changes in illness severity using aberrations in vital signs. In 2001, the Modified Early Warning Score (MEWS) was published. It was created by assigning weighted scores to five physiological parameters (systolic blood pressure, pulse rate, respiratory rate, temperature and level of consciousness) based on the severity of the abnormality [3]. Though not specific to sepsis, MEWS is intended to support medical staff in anticipating patients' clinical deterioration. Sepsis definitions have been modified significantly between 1991 and 2016 [4]. The current definition describes sepsis as organ dysfunction caused by the dysregulated host response to infection. For clinical operationalisation, organ dysfunction is represented by an increase in the Sequential (sepsis-related) Organ Failure Assessment (SOFA) score of two points or more [5]. The preceding sepsis screening tool utilised the systemic inflammatory response syndrome (SIRS) criteria but was suggested to be abandoned by the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) task force due to concerns about its lack of specificity in identifying patients with severe disease resulting in potential over-treatment of patients with the milder disease [5]. SOFA, however, requires laboratory values which may not be readily available outside of a highly resourced intensive care unit (ICU). Accordingly, the quick SOFA (qSOFA) score was proposed as a screening tool to identify patients at high risk of poor outcomes [5].

MEWS, SIRS and qSOFA were mainly developed in HICs. LMICs share a high burden of many infectious diseases, for which sepsis is the common final pathway. Studies validating these scores in LMICs are limited, with performances differing from one study to another [6-9]. Recently, the Universal Vital Assessment (UVA) score was developed, using multiple cohorts of patients from sub-Saharan African countries with suspected infection, demonstrating good performance in predicting in-hospital mortality [[10]]. The UVA score included points for systolic blood pressure, Glasgow Coma Scale score, temperature, oxygen saturation, respiratory and heart rates, and human immunodeficiency virus (HIV) serostatus [10]. Its performance has been assessed by now in several studies in Africa [7,11]. In LMICs, there are limited healthcare resources and ICU facilities. As a consequence, severe and critically-ill patients cannot always be admitted to an ICU. Therefore, an applicable triage score that is easily applied by frontline clinicians is paramount to prioritising care. Previous systematic reviews assessed the performance of the qSOFA, SIRS, and MEWS scores, but did not focus on LMICs [12]. Compared with SIRS, qSOFA showed better specificity for predicting mortality but lower sensitivity for identifying patients with sepsis in patients with suspected infection [6,13]. It is well-known that the setting and study population might influence the accuracy of screening and diagnostic testing [14]. This systematic review and meta-analysis assessed the performance of four available scores (qSOFA, SIRS, MEWS, UVA) in the diagnosis of sepsis and in-patient mortality prediction in adult non-pregnant and non-surgical patients with suspected infections in LMICs.

METHODS

2.1 Search strategy and selection criteria

This systematic review and meta-analysis followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement extension for Diagnostic Test Accuracy (DTA) [15]. An electronic search of the published literature was conducted on November 04, 2019, and updated on May 18, 2021, in PubMed, Science Direct, Web of Science, and the Cochrane Central Register of Controlled Trials. We used the following search terms: 'qsofa', 'sofa', 'sirs,' 'UVA', 'MEWS', 'sequential organ failure assessment', 'systemic inflammatory response syndrome, 'Universal Vital Assessment', 'Early Warning Score', 'sepsis', 'infections'. In addition, we used a filter suggested by the Cochrane Collaboration based on the World Bank list of low-income, lower-middle-income or upper-middle-income countries [16]. Articles resulting from these searches and relevant references cited in those articles were reviewed. The full search strategy used is reported in Supplementary File S1.

Studies which recruited patients 15 years of age and older with suspected infection or sepsis were eligible for inclusion using the following criteria: (1) full-length reports published in peer-reviewed journals; (2) observational studies or clinical trials of adult (>15 years old) patients; (3) studies that describe data about sepsis assessment using at least one of the four scores; and (4) studies that report the relationship between the sepsis screening criteria and at least one of the following outcomes: sensitivity or specificity for the diagnosis of sepsis (organ dysfunction, SOFA ≥2), deaths that occurred in hospital, or any post-hospital discharge outcomes. According to the published definitions, qSOFA was considered positive when at least two variables met fulfilment criteria'; SIRS when at least two criteria were met; MEWS when at least five score criteria were met; and UVA when at least five score criteria were met. The details of each score are provided in Supplementary File S2. We excluded studies which were not performed in LMICs, studies which did not report sensitivity, specificity, or data to calculate the score performance characteristics, and studies limited to specific patient populations (such as COVID-19 or pneumonia patients). Two investigators (WNN & LBD) independently screened studies for eligibility; disagreement was resolved by consensus. If WNN and LBD did not agree after discussion, a third investigator (BRA) was consulted. The study protocol was registered with the International Prospective Register of Systematic Reviews(PROSPERO;CRD42020153906;available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020153906) and amended once.

2.2 Data extraction and quality assessment

The following data were extracted from the original studies: first author; year of publication; country of origin; study design; sample size; mortality rate; patient selection

criteria; score evaluated, objectives and outcomes. In case of missing information, we contacted the respective corresponding authors. BRA and JRE independently extracted potentially relevant studies and reviewed each study according to the pre-defined eligibility criteria. The primary outcome was overall mortality (in-hospital or 28/30 days mortality). The secondary outcome was the diagnosis of sepsis (acute organ dysfunction).

The Quality Assessment of Diagnostic Accuracy Studies (QUADAS)-2 tool was used to assess the risk of bias in diagnostic test accuracy [17], as recommended by the Cochrane Collaboration. Consensus on the risk of bias was sought by two reviewers (BRA and WNN). A detailed quality assessment is provided in Supplementary File S3; articles rejected are listed in Supplementary File 4.

2.3 Data analysis

Statistical analysis was conducted using RevMan5.4 (Nordic Cochrane Center, Copenhagen, Denmark) [18] and RStudio 4.0.2 (250 Northern Ave, Boston, USA) [19]. We generated true positives, false negatives, false positives, and true negatives based on the sensitivity, specificity, and 95% confidence intervals (CIs) of each study using RevMan5.4. We used the packages 'meta' [20] and 'mada' (version 0.5.10) [21] in CRAN-R to produce the meta-analysis forest and funnel plots. Between studies, statistical heterogeneity was assessed using the I^2 statistic and Cochran's Q test; I^2 values of more than 50% indicated a significant level of heterogeneity. Funnel plots were used to assess publication bias (Supplementary File S5). Pooled sensitivity and specificity were calculated using a bivariate random-effects regression model. The summary receiver operator curves were constructed, and the area under the curve (AUC) was used to appreciate the discriminatory performance of each score.

2.4 Ethics information

No ethical clearance was required for this systematic review and meta-analysis.

2.5 Role of the funding source

The supporting funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author, Martin P. Grobusch accessed the dataset, and the decision to submit for publication was jointly taken by all authors.

RESULTS

In total, 8526 published articles were initially identified (3741 articles from PUBMED, 136 articles from Sci)ence Direct, 2093 articles from the Cochrane Library, and 2556 on

Web of Science). After removing duplicate articles, 5669 potentially eligible articles were screened. Of these articles, 5495 were excluded on the basis of title and abstract. A total of 174 articles underwent full-text review. One hundred fifty-five articles were excluded for the reasons presented in Figure 1. Finally, a total of 24 articles met our inclusion criteria for the systematic review and meta-analysis.

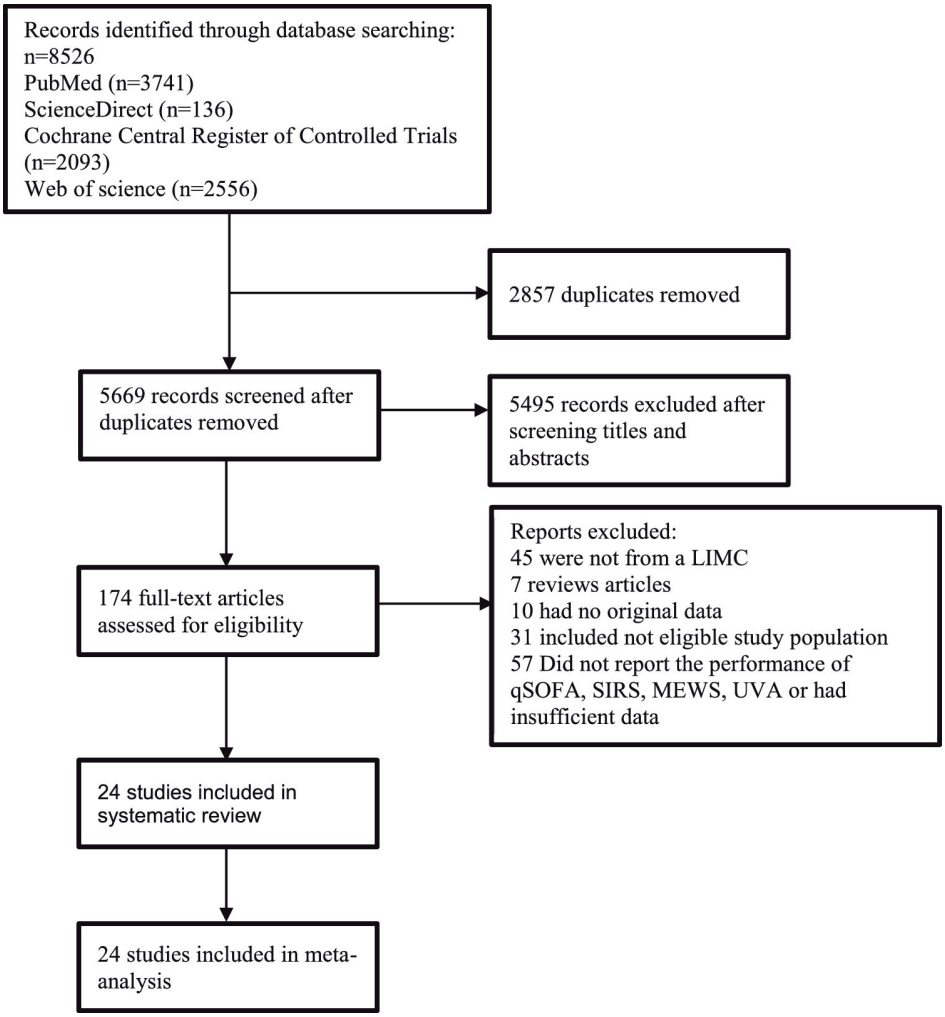

Figure 1 Diagram of the study selection process.

All studies were published between 2013 and 2021. Characteristics of the studies included are presented in Table 1. The number of patients per study ranged from 64 to 6218, and the overall mortality rate in each study ranged from 3·8 % to 61·0%. Across studies, the two most frequently reported conditions were respiratory tract infections and malaria.

Table 1 Characteristics of studies included

Author and year of publication [Reference]	Countries	Type of study	Department	Mean (SD)or Median age (Interquartile range) years	Mortality proportion (Number of death /Total number of patients, %)	Objectives of studies	Most-frequent infection n (%)	Score evaluated
Schmedding et al (2019)[30]	Gabon	Prospective	Emergency department	38 (28–53)	11/187(6)	To evaluated the ability of the qSOFA score to predict mortality in patients presenting to the emergency department, and compared the performance of qSOFA with the SIRS criteria, MEWS, and UVA scores.	Malaria 97 (51)	qSOFA, SIRS, UVA, MEWS
Boillat-Blanco et al (2018)[31]	Tanzania	Prospective	Emergency department	30 (23–40)	32/519(6)	To evaluate the prognostic accuracy of qSOFA for 28-day all-cause mortality in febrile adult patients treated at emergency departments and to compare it with SOFA and SIRS.	Respiratory tract infection 223 (43)	qSOFA, SIRS
Raphael_Kazidule et al (2020)[32]	Malawi	Prospective	General wards	40 (18–98)	44/413(10)	To evaluate the predictive value of a qSOFA score of 2 for mortality among hospitalised adults and among those with suspected infection.	Not reported	qSOFA
Luo et al (2019)[33]	China	Prospective	General wards	55(40-67)	32/409(7.8)	To evaluate the ability to diagnostic sepsis and predict 28-day mortality	Respiratory tract infection 234 (57)	qSOFA, SIRS
Yu et al (2019)[27]	China	Retrospective	Emergency department	62 (47–74)	178/1318(13.5)	To determine the ability of qSOFA to predict in hospital mortality in a multicenter cohort of patients who presented with clinical symptoms of systemic infection.	Respiratory tract infection 712 (54)	qSOFA, SIRS

Table 1 Characteristics of studies included (continued)

Author and year of publication [Reference]	Countries	Type of study	Department	Mean (SD)or Median age (Interquartile range) years	Mortality proportion (Number of death /Total number of patients, %)	Objectives of studies	Most-frequent infection n (%)	Score evaluated
Tian et al (2019)[34]	China	Retrospective	General wards	79(61–85)	353/1716(21)	1-To evaluate the accuracy of qSOFA for the diagnosis of sepsis-3 2-To evaluate the performance of qSOFA as one predictor of outcome in patients with suspicion of infection	Respiratory tract infection 1248 (73)	qSOFA
Wei et al (2019)[35]	China	Retrospective	Emergency department	44.5(18.3)	213/4857(4.4)	To evaluate the performance of MEWS in predicting the outcomes of adult patients presenting to the emergency department (ED)	Respiratory tract infection 1059 (22)	MEWS
Xie Xiaohua et al (2018) [36]	China	Prospective	Emergency department	59.6(18.3)	52/383(13.6)	To validate the performance of MEWS in a Chinese emergency department and to determine the best cut-off value for in-hospital mortality prediction	Respiratory tract infection 54 (14)	MEWS
Rudd et al (2018)[37]	Bangladesh, Haiti,India, Indonesia, Myanmar, Rwanda, Sierra Leone, Sri Lanka, Thailand, and Vietnam	Retrospective	General wards	38(36-55)	643/6218(10)	To assess the association of qSOFA with excess hospital death among patients with suspected infection in LMICs and to compare qSOFA with the systemic inflammatory response syndrome (SIRS) criteria	Malaria 1461 (24)	qSOFA, SIRS
Huson et al (2017)[38]	Malawi	Prospective	General wards	35(26-47)	106/458(23)	To determine the predictive value of qSOFA in Malawian patients with suspected infection	Not reported	qSOFA

Table 1 Characteristics of studies included (continued)

Author and year of publication [Reference]	Countries	Type of study	Department	Mean (SD)or Median age (Interquartile range) years	Mortality proportion (Number of death /Total number of patients, %)	Objectives of studies	Most-frequent infection n (%)	Score evaluated
Moore et al (2017)[29]	Gabon, Malawi, Sierra Leone, Tanzania, Uganda and Zambia	Retrospective	General wards	36(27-49)	966/5573(18)	To determine predictors of mortality UVA score and compare the performance of the UVA score in predicting mortality with that of MEWS and qSOFA.	Not reported	UVA, qSOFA, MEWS
Muhammad et al [a] (2018) [39]	Pakistan	Prospective	Intense care unit	60.2(17.9)	208/339(61)	To determine a comparison between the qSOFA score and SOFA when applied to septic shock patients in the Emergency Department for prediction of in-hospital mortality in the setting of a tertiary care hospital ED in a low-middle income country.	Respiratory tract infection 211 (62)	qSOFA
Muhammad et al [b] (2018) [39]	Pakistan	Prospective	Intense care unit	59.6(17.2)	242/421(57.5)	To determine a comparison between the qSOFA score and SOFA when applied to severe sepsis patients in the Emergency Department for prediction of in-hospital mortality in the setting of a tertiary care hospital ED in a low-middle income country.	Respiratory tract infection 187 (44)	qSOFA
Ergun et al [a](2013) [40]	Turkey	Prospective	Emergency department	Not reported	8/64(12.5)	To determine the ability of the mMEDS score, the MEWS score and the CCI to predict prognosis in patients presenting to the ED of our hospital who are diagnosed with sepsis	Not reported	MEWS

Table 1 Characteristics of studies included (continued)

Author and year of publication [Reference]	Countries	Type of study	Department	Mean (SD)or Median age (Interquartile range) years	Mortality proportion (Number of death /Total number of patients, %)	Objectives of studies	Most-frequent infection n (%)	Score evaluated
Ergun et al [b](2013) [40]	Turkey	Prospective	Emergency department	Not reported	66/166(39·8)	To determine the ability of the mMEDS score, the MEWS score and the CCI to predict prognosis in patients presenting to the ED of our hospital who are diagnosed with sepsis	Not reported	MEWS
Khwannimit et al (2018)[41]	Thailand	Retrospective	Intense care unit	62(44-75)	1045/2350(44·5)	To compare the SOFA score and qSOFA to SIRS criteria ability in predictive of in hospital mortality and organ failure	Respiratory tract infection 1174 (50)	qSOFA, SIRS
Huson et al (2016)[38]	Gabon	Retrospective	All wards	34 (24-46)	15/329(4·56)	To determine the predictive value of qSOFA in patients with suspected infection in a hospital with limited supportive care facilities, in Gabon.	Malaria 122 (37)	qSOFA
Sinto R, et al(2020)[42]	Indonesia	Prospective	Emergency department	51 (38-60)	454/1213(37·4)	To investigate the prognostic accuracy of the qSOFA and lactate criteria (defined as two or more qSOFA criteria, and venous lactate concentration higher than the defined cut-off) in an emergency department of a hospital with limited resources, in comparison with established prognosis criteria and screening criteria	Respiratory tract infection 808 (66·6)	qSOFA, SIRS

Table 1 Characteristics of studies included (continued)

Author and year of publication [Reference]	Countries	Type of study	Department	Mean (SD)or Median age (Interquartile range) years	Mortality proportion (Number of death /Total number of patients, %)	Objectives of studies	Most-frequent infection n (%)	Score evaluated
Prangsai et al(2020) [43]	Thailand	Retrospective	Emergency department	67 (53–79)	30/777(3.8)	To evaluate the accuracy of early warning scores (NEWS, MEWS, MEDS and SOS) and compare them with qSOFA and SIRS in detecting sepsis and predicting hospital admission and mortality in patients with suspected infection presenting at EDs	Primary bacteraemia 235 (30)	qSOFA, SIRS MEWS
Ruangsomboon et al (2021)[9]	Thailand	retrospectively	Emergency department	72.6 (15.4)	457/1622(28.18)	To validate and compare the clinical utility of REMS, SIRS, qSOFA, and NEWS in predicting in-hospital mortality and mortality within 7 days of admission in ED patients with suspected sepsis	Respiratory tract infection 982 (61)	qSOFA, SIRS
Pairattanakorn et al (2020)[44]	Thailand	prospective	all wards	65.74 (17.84)	117/409 (28.6)	To determine the diagnostic performance of SIRS score, qSOFA score, SOFA score, MEWS, and NEWS for sepsis detection and mortality prediction in adult patients suspected of having sepsis at Siriraj Hospital, Mahidol University, Bangkok, Tailand	Respiratory tract infection 138 (33·7)	Qsofa, SIRS MEWS

Table 1 Characteristics of studies included (continued)

Author and year of publication [Reference]	Countries	Type of study	Department	Mean (SD)or Median age (Interquartile range) years	Mortality proportion (Number of death /Total number of patients, %)	Objectives of studies	Most-frequent infection n (%)	Score evaluated
Minn et al (2021)[45]	Myanmar	prospective	General wards	48 (29-64)	75/434(17.28)	To determine the ability of several commonly used disease severity scores to predict the clinical course of patients with evidence of community-acquired sepsis in resource-limited tropical settings like Myanmar	Not reported	qSOFA UVA
Toker et al (2021)[46]	Turkey	prospective	Emergency department	72.5(13.7)	191/365(52.32)	To investigate the predictive capacity of the SOFA score, SIRS, qSOFA, and qSOFA + lactate criteria (qSOFA+L) criteria in the diagnosis and prognosis of sepsis	Not reported	qSOFA, SIRS
Fernandes et al (2020) [47]	India	prospective	Emergency department	47.5 (18.1)	54/180(30)	To assess the prognostic accuracy of qSOFA score in predicting adverse outcomes in patients with suspected infections and to compare it with the SIRS (Systemic Inflammatory Response Syndrome) and the SOFA (Sequential Organ failure Assessment Score)	Respiratory tract infection 56 (31)	qSOFA, SIRS

Twenty-three studies reported qSOFA (26,460 participants) score performance; twelve (15,401 participants) reported SIRS performance, nine reported MEWS (13,063 participants), and four reported UVA (6841 participants). Six studies compared the accuracy of qSOFA and SIRS, five studies compared qSOFA and MEWS, and three studies compared qSOFA and UVA criteria. One study compared all four scores. Two studies reported the performance of qSOFA in the diagnosis of sepsis. All studies included were observational. More than half were prospective. The studies were well-designed, the quality assessment demonstrated a low risk of bias. The detailed QUADAS-2 assessment is presented in Supplementary File S3.

For mortality, the pooled sensitivity of qSOFA across all included studies was 0·70 (95% CI 0·60–0·78); the pooled specificity was 0·73 (95% CI 0·67–0·79) (Figure 2A), and the pooled AUC was 0·77 (95% CI 0·72–0·82). SIRS pooled sensitivity and specificity for predicting mortality were 0·88 (95% CI 0·79 -0·93) and 0·34 (95% CI 0·25–0·44) (Figure 2B), respectively; the pooled AUC was 0·69 (95% CI 0·50–0·83). MEWS pooled sensitivity and specificity were 0·70 (95% CI 0·57 -0·81) and 0·61 (95% CI 0·42–0·77) (Fig. 2C), respectively; the pooled AUC was 0·72 (95% CI 0·64–0·77). UVA sensitivity and specificity were 0·49 (95% CI 0·33 -0·65) and 0·91 (95% CI 0·84–0·96) (Figure 2 D), respectively; the pooled AUC 0·76 (95% CI 0·44–0·93). In the subgroup analysis assessing the performance of qSOFA in ICU vs outside of ICU, the sensitivity and the AUC of qSOFA in predicting mortality was better in studies assessing its performance in ICU compared with non-ICU areas (sensitivity 0·96 [95% 0·90; 0·98] vs 0·61 [95% CI 0·52; 0·68]); AUC: 0·95 [95% CI 0·90- 0·97] vs 0·72 [95 % 0·68- 0·75] respectively). The specificity did not differ considerably (0·67 [95% CI 0·13; 0·87] vs 0·74 [95% CI 0·69; 0·79]). Due to a limited number of studies assessing the other scores, a subgroup analysis was not performed.

Table 2 Pooled performance characteristics comparison of qSOFA and SIRS criteria for predicting mortality in patients with suspected infection

Scores	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)
qSOFA vs SIRS			
qSOFA	0·72 (0·58-0·82)	0·67(0·55-0·79)	0·74(0·68–0·78)
SIRS	0·88(0·79- 0·93)	0·34(0·25- 0·44)	0·56(0·40-0·76)
qSOFA vs MEWS			
qSOFA	0·58(0·35-0·78)	0·78(0·62-0·88)	0·73(0·63-0·79)
MEWS	0·74(0·58-0·86)	0·55(0·35-0·74)	0·69(0·65-0·74)
	qSOFA vs UVA		
qSOFA	0·50 (0·17; 0·82)	0·79(0·51; 0·94)	0·69(0·53 -0·78)
UVA	0·45(0·24; 0·68)	0·92(0·82; 0·96)	0·77(0·47 -0·87)

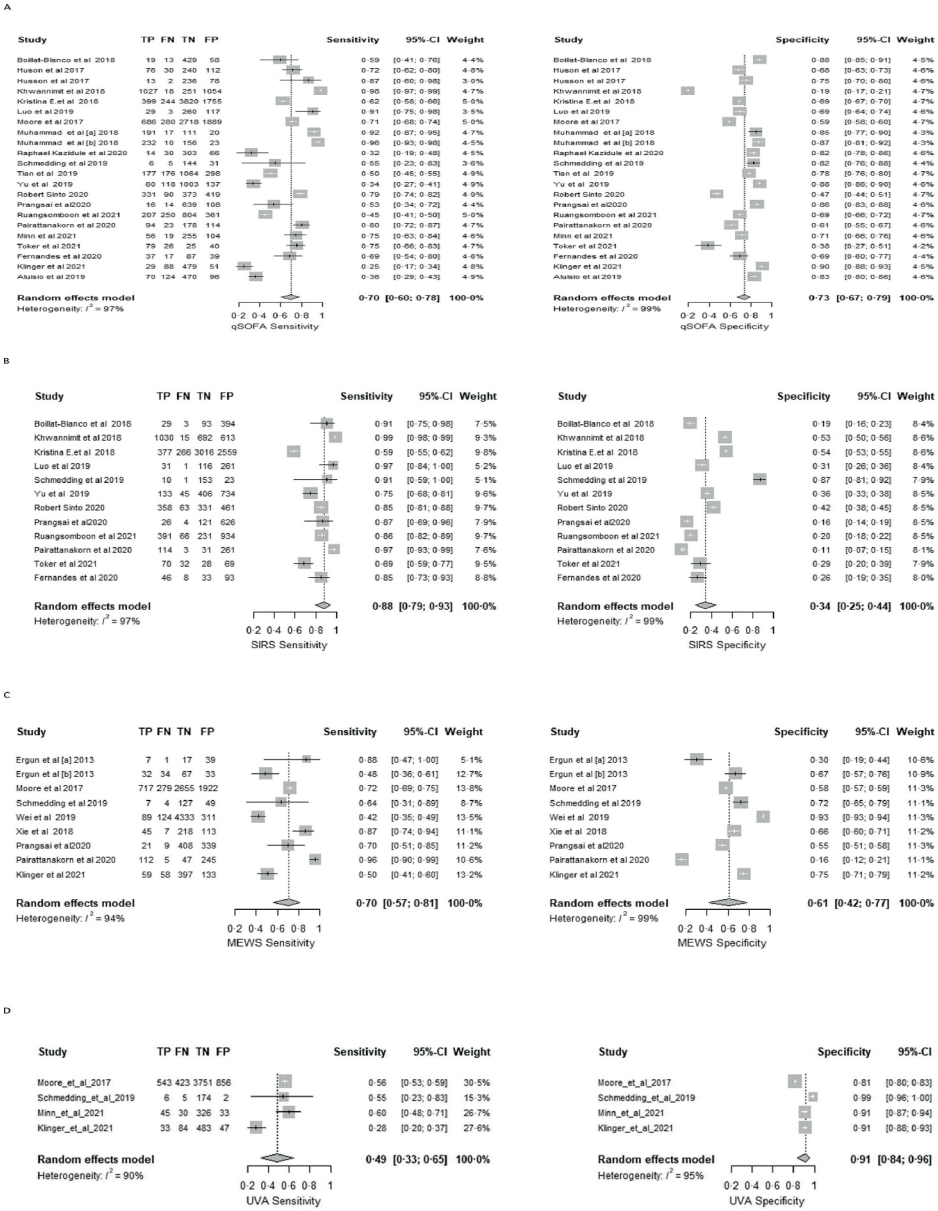

Figure 2 Forest plots for mortality by A qSOFA; B SIRS; C MEWS and D UVA scores.

In those studies simultaneously reporting the accuracy of a positive qSOFA score and positive SIRS criteria for predicting mortality, the qSOFA score was more specific but less sensitive than SIRS; qSOFA, MEWS, and UVA performed similarly (Table 2).

Three studies reported the prognostic performance of positive qSOFA scores in predicting acute organ dysfunction; the pooled sensitivity, specificity, and AUC were 0·43

(95% CI 0·30 -0·57), 0·85 (95% CI 0·78 -0·90), and 0·76 (95% CI 0·5 -0·86), respectively. The pooled performance of SIRS in the diagnosis of acute organ dysfunction was as follows: sensitivity 0·87 (95% CI 0·58 -0·97); specificity 0·30 (95% CI 0·11 -0·59); and AUC 0·62 (95% CI 0·35 -0·85).

4. DISCUSSION

In this systematic review and meta-analysis, the prognostic capability of qSOFA, SIRS, MEWS, and UVA for predicting mortality and organ dysfunction in adult patients with suspected infection or sepsis in LMICs was evaluated. The performance of qSOFA outside of ICU in our systematic review is lower than what was reported in the original study assessing the performance of qSOFA (0·72 (95% CI 0·68-0·75) vs 81(95% CI 0·80–0·82)) [22]. It is also lower than the performance (0·78 (95% CI, 0·72–0·84)) reported in 2018 in a systematic review including both HICs and LMICs [23]. The sensitivity of qSOFA in this systematic review, however, is higher than that determined by the systematic review which included studies from HICs only (0·76; 95% CI 0·59–0·88 vs 0·58; 95% CI 0·47–0·67) [24]. The difference in the performance of qSOFA in HICs as compared to LMICs could be due to patient characteristics and differences in the respective infectious disease burden, as well as variation in healthcare resources, and the degree to which definitive diagnostics are available (such as CT or MRI scans, bronchoscopy etc.). Furthermore, the mechanisms that lead to life-threatening acute organ dysfunction from infections such as malaria, tuberculosis, and HIV which are more prevalent in LMICs can differ from those of classic bacterial sepsis [25,26]. Some studies suggest the combination of qSOFA with biomarkers, such as C-reactive protein and procalcitonin, to increase its sensitivity [27]. The Sepsis 3.0 task force designed qSOFA criteria to replace SIRS to identify patients with suspected infection who would require early diagnosis and treatment. However, our meta-analysis demonstrates that qSOFA had poor sensitivity for predicting mortality as compared with SIRS. To that end, SIRS should not be abandoned as it could provide utility in a staged approach with qSOFA, whereby SIRS is used as a primary screening tool to identify patients requiring a high level of care, and qSOFA is applied subsequently for predicting mortality; an approach which to the best of our knowledge has not yet been investigated systematically.

The comparison of MEWS and qSOFA performance (AUC) in predicting mortality showed that they performed similarly (0·73 (95% CI 0·63-0·79) vs 0·69 (95% CI 0·65-0·74)). However, the sensitivity of MEWS is higher than that of qSOFA. When a high-sensitivity trigger is used, it is more likely that the patient will be identified sooner. However, if a 'sepsis bundle' is administered to patients who ultimately do not have sepsis, there is a risk of over-treatment, and there are substantial concerns about excessive

fluid administration and antibiotic use [28]. In LMIC settings, patients with HIV have an increased risk of developing sepsis [25]. In our meta-analysis, the UVA score had the highest specificity (0·92, 95% CI 0·82; 0·96). The UVA was reported as an appropriate score to assess in-hospital mortality risk in adults, and derived exclusively from data from six sub-Saharan African countries [29]; further prospective validation would be helpful.

Pathogen spectrum and clinical presentation of sepsis may be different between LMICs and high-income settings. Due to the lack of human resources and ICU facilities in LMICs, there is a need to develop reliable triage scores to determine who requires the highest available level of care. Our meta-analysis demonstrates that there is no single top-performing score. Future studies should investigate the performance of amalgamated (i.e. combining the best of different scores) and combined scores (staged using sensitivity score, followed by the more specific) in various countries.

Our review has several limitations. First, there was considerable heterogeneity between the studies included. Second, the definition of suspected infection varied among studies; and due to the retrospective design of many studies, these differences would have introduced selection bias. Third, we were unable to directly compare the four scores because there was one study simultaneously reporting the performance of these scores.

In conclusion, there is not a single score which ultimately identifies, with accuracy, patients with suspected infections or sepsis at high risk of death or clinical condition deterioration. Amongst the scores readily at hand, SIRS could be applied to the first screening to identify those patients requiring high-level care, followed by qSOFA, MEWS, or UVA scores, based both on published performance indicators and subject to local availability of data collection tools, for mortality prediction. There is a need to perform further studies to validate the UVA score. In general, future studies should investigate the performance of combined or sequential use of scores, or their amalgamation, i.e. optimisation by combining selected or modified elements of different scores. This altogether could help to further improve patient triage in resource-limited environments and serve as a standard for mortality risk in future studies.

Contributors

MPG and BRA conceptualised the study. BRA, MPG and AAA determined the methodological approach. BRA, JRE, WNN and LBN primarily investigated the data and conducted the formal data analysis. MPG and AAA provided and organised study resources. BRA, MPG, GMN curated the data. BRA wrote the original draft, with input from MPG. BRA, TH, JR, STJ, and MPG, together with all co-authors, did the editing and the writing of the final manuscript version. MPG supervised the project. MPG and AAA administered the project. All authors contributed to the writing of the final manuscript version, and have read and agreed to the published version of the manuscript.

Data sharing statement

Data will be made available upon request made to the corresponding author. The analysis code used in this study is available online.

Declaration of Competing Interest

None of the authors has any competing interests to declare.

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Supplementary materials Supplementary material associated with this article can be found in the online version at doi: 10.1016/j.eclinm.2021.101184.

REFERENCES

1. World Health Organization. Sepsis. Geneva: WHO; 2020 https://www.who.int/news-room/fact-sheets/detail/sepsis (accessed Aug 6.
2. Rudd KE, Johnson SC, Agesa KM, et al. Global, regional, and national sepsis incidence and mortality, 19902017: analysis for the Global Burden of Disease Study.Lancet 2020;395:200–11.
3. Ludikhuize Goossens A, Borgert J, Binnekade M, Dongelmans D, Subbe C. Standardized measurement of the Modified Early Warning Score results in enhanced implementation of a Rapid Response System: a quasi-experimental study. Resuscitation 2014;85:676–82.
4. Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest 1992;101:1644–55.
5. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315:801–10.
6. Jiang J, Yang J, Mei J, Jin Y, Lu Y. Head-to-head comparison of qSOFA and SIRS criteria in predicting the mortality of infected patients in the emergency department: a meta-analysis. Scand J Trauma Resusc Emerg Med 2018;26:56.
7. Schmedding M, Adegbite BR, Gould S, et al. A Prospective Comparison of Quick Sequential Organ Failure Assessment, Systemic Inflammatory Response Syndrome Criteria, Universal Vital Assessment, and Modified Early Warning Score to Predict Mortality in Patients with Suspected Infection in Gabon. Am J Trop MedHyg 2019;100:202–8.
8. Aluisio AR, Garbern S, Wiskel T, et al. Mortality outcomes based on ED qSOFA score and HIV status in a developing low-income country. Am J Emerg Med 2018;36:2010–9.
9. Ruangsomboon O, Boonmee P, Limsuwat C, Chakorn T, Monsomboon A. The utility of the rapid emergency medicine score (REMS) compared with SIRS, Qsofa and NEWS for Predicting in-hospital Mortality among Patients with suspicion of Sepsis in an emergency department. BMC Emerg Med 2021;21:2.
10. Moore CC, Hazard R, Saulters KJ, et al. Derivation and validation of a universal vital assessment (UVA) score: a tool for predicting mortality in adult hospitalised patients in sub-Saharan Africa. BMJ Glob Health 2017;2:0344.
11. Klinger A, Mueller A, Sutherland T, et al. Predicting mortality in adults with suspected infection in a Rwandan hospital: an evaluation of the adapted MEWS,qSOFA and UVA scores. BMJ Open 2021;11:e040361.
12. Stephen AH, Montoya RL, Aluisio AR. Sepsis and Septic Shock in Low- and middle income Countries. Surg Infect 2020;21:571–8.
13. Serafim R, Gomes JA, Salluh J, Povoa P. A Comparison of the Quick-SOFA and Systemic Inflammatory Response Syndrome Criteria for the Diagnosis of Sepsis and Prediction of Mortality. Chest 2018;153:646–55.
14. Leeflang MMG, Rutjes AWS, Reitsma JB, Hooft L, Bossuyt PMM. Variation of a test's sensitivity and specificity with disease prevalence. CMAJ Can Med Assoc J 2013;185:E537–44.

15. McInnes MDF, Moher D, Thombs BD, et al. Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies: The PRISMA-DTA Statement. JAMA 2018;319:388–96.

16. The Cochrane Collaboration. Filters for PubMed (NLM), MEDLINE (Ovid), Embase (Ovid), and CENTRAL (Cochrane Library) to help identify studies relevant to LMIC.https://epoc.cochrane.org/lmic-filters (accessed March 28, 2021).

17. Whiting PF, Rutjes AWS, Westwood ME, et al. QUADAS-2: A Revised Tool for the.Quality Assessment of Diagnostic Accuracy Studies. Ann Intern Med 2011;155:529–36.

18. The Cochrane Collaboration. Review Manager (RevMan) 2020.

19. Core Team. R:A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2020 https://www.R-project.org/.

20. Balduzzi S, Rucker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. Evidence-Based Mental Health 2019.

21. Philipp Doebler (2020). mada: Meta-Analysis of Diagnostic Accuracy. R package version 0.5.10. https://CRAN.R-project.org/package=mada. .

22. Seymour CW, Liu VX, Iwashyna TJ, et al. Assessment of Clinical Criteria for Sepsis:For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315:762–74.

23. Song J-U, Sin CK, Park HK, Shim SR, Lee J. Performance of the quick Sequential (sepsis-related) Organ Failure Assessment score as a prognostic tool in infected patients outside the intensive care unit: a systematic review and meta-analysis.Crit Care 2018;22:28.

24. Liu Y-C, Luo Y-Y, Zhang X, et al. Quick Sequential Organ Failure Assessment as a prognostic factor for infected patients outside the intensive care unit: a systematic review and meta-analysis. Intern Emerg Med 2019;14:603–15.

25. Lewis JM, Feasey NA, Rylance J. Aetiology and outcomes of sepsis in adults in subSaharan Africa: a systematic review and meta-analysis. Crit Care 2019;23:212.

26. Rudd KE, Seymour CW, Aluisio AR, et al. Association of the Quick Sequential (Sepsis-Related) Organ Failure Assessment (qSOFA) Score With Excess Hospital Mortality in Adults With Suspected Infection in Low- and Middle-Income Countries.JAMA 2018;319:2202–11.

27. Yu H, Nie L, Liu A, et al. Combining procalcitonin with the qSOFA and sepsis mortality prediction. Medicine (Baltimore) 2019;98:e15981.

28. McLymont N, Glover GW. Scoring systems for the characterization of sepsis and associated outcomes. Ann Transl Med 2016;4:527.

29. Moore CC, Hazard R, Saulters KJ, et al. Derivation and validation of a universal vital assessment (UVA) score: a tool for predicting mortality in adult hospitalised patients in sub- Saharan Africa. BMJ Glob Health 2017;2:e000344.

30. Schmedding M, Adegbite BR, Gould S, et al. A Prospective Comparison of Quick Sequential Organ Failure Assessment, Systemic Inflammatory Response Syndrome Criteria, Universal Vital Assessment, and Modified Early Warning Score to Predict Mortality in Patients with Suspected Infection in Gabon. Am J Trop Med Hyg 2019;100:202–8.

31. Boillat-Blanco N, Mbarack Z, Samaka J, et al. Prognostic value of quickSOFA as a predictor of 28-day mortality among febrile adult patients presenting to emergency departments in Dar es Salaam, Tanzania. PLOS ONE 2018;13:e0197982.

32. Kayambankadzanja RK, Schell CO, Namboya F, et al. The Prevalence and Outcomes of Sepsis in Adult Patients in Two Hospitals in Malawi. Am J Trop Med Hyg 2020;102:896–901.

33. Luo J, Jiang W, Weng L, et al. Usefulness of qSOFA and SIRS scores for detection of incipient sepsis in general ward patients: A prospective cohort study. J Crit Care 2019;51:13–8.

34. Tian H, Zhou J, Weng L, et al. Accuracy of qSOFA for the diagnosis of sepsis-3: a secondary analysis of a population-based cohort study. J Thorac Dis 2019;11:11.

35. Wei X, Ma H, Liu R, Zhao Y. Comparing the effectiveness of three scoring systems in predicting adult patient outcomes in the emergency department. Medicine (Baltimore) 2019;98:e14289.

36. Xie X, Huang W, Liu Q, et al. Prognostic value of Modified Early Warning Score generated in a Chinese emergency department: a prospective cohort study. BMJ Open 2018;8:e024120.

37. Rudd KE, Seymour CW, Aluisio AR, et al. Association of the Quick Sequential (Sepsis-Related) Organ Failure Assessment (qSOFA) Score With Excess Hospital Mortality in Adults With Suspected Infection in Low- and Middle-Income Countries.JAMA 2018;319:2202–11.

38. Huson MAM, Katete C, Chunda L, et al. Application of the qSOFA score to predict mortality in patients with suspected infection in a resource-limited setting in Malawi. Infection 2017;45:893–6.

39. Baig MA, Sheikh S, Hussain E, et al. Comparison of qSOFA and SOFA score for predicting mortality in severe sepsis and septic shock patients in the emergency department of a low middle-income country. Turk J Emerg Med 2018;18:148–51.

40. Cıldır E, Bulut M, Akalın H, Kocabas E, Ocako ˛ glu G, Ayd ın SA. Evaluation of the modified MEDS, MEWS score and Charlson comorbidity index in patients with community-acquired sepsis in the emergency department. Intern Emerg Med 2013;8:255–60.

41. Khwannimit B, Bhurayanontachai R, Vattanavanit V. Comparison of the performance of SOFA, qSOFA and SIRS for predicting mortality and organ failure among sepsis patients admitted to the intensive care unit in a middle-income country. J Crit Care 2018;44:156–60.

42. Sinto R, Suwarto S, Lie KC, Harimurti K, Widodo D, Pohan HT. Prognostic accuracy of the quick Sequential Organ Failure Assessment (qSOFA)-lactate criteria for mortality in adults with a suspected bacterial infection in the emergency department of a hospital with limited resources. Emerg Med J 2020;37:363–9.

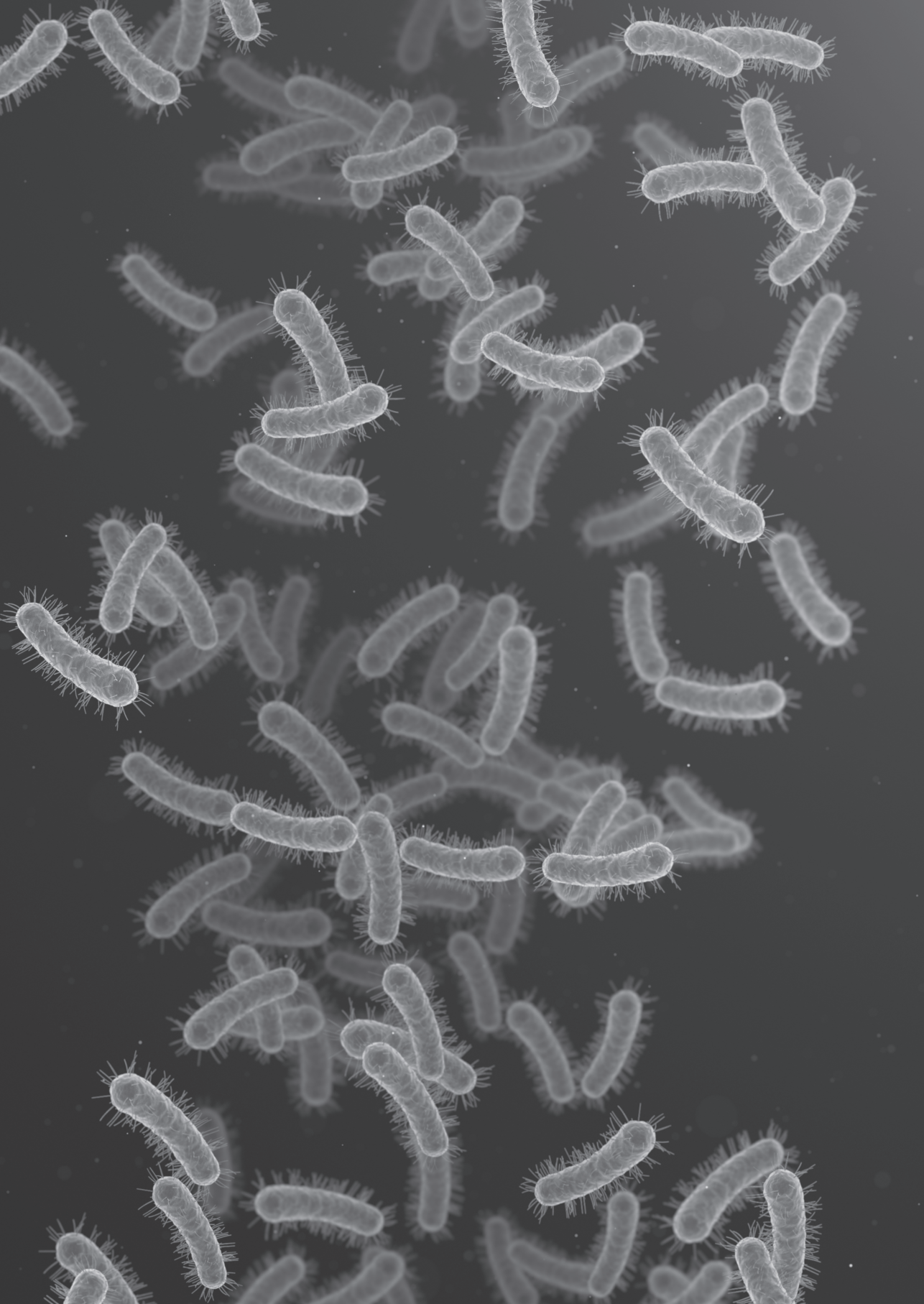
43. Wattanasit P, Khwannimit B. Comparison the accuracy of early warning scores with qSOFA and SIRS for predicting sepsis in the emergency department. Am J Emerg Med 2021;46:284–8. doi: 10.1016/j.ajem.2020.07.077.

44. Pairattanakorn P, Angkasekwinai N, Sirijatuphat R, Wangchinda W, Tancharoen L, Thamlikitkul V. Diagnostic and Prognostic Utility Compared Among Different Sepsis Scoring Systems in Adult Patients With Sepsis in Thailand: A Prospective Cohort Study. Open Forum Infect Dis 2021;8:ofaa573.

45. Mar Minn M, Aung NM, Kyaw DZ, et al. The comparative ability of commonly used disease severity scores to predict death or a requirement for ICU care in patients hospitalised with possible sepsis in Yangon, Myanmar. Int J Infect Dis 2021;104:543–50.

46. Kilinc Toker A, Kose S, Turken M. Comparison of SOFA Score, SIRS, qSOFA, and qSOFA + L Criteria in the Diagnosis and Prognosis of Sepsis. Eurasian J Med 2021;53:40–7.

47. Fernandes S, Wyawahare M. Utility of quick sepsis-related organ failure assessment (qSOFA) score to predict outcomes in out-of-ICU patients with suspected infections. J Fam Med Prim Care 2020;9:3251–5.



Chapter 9

Knowledge of health workers relating to sepsis awareness and management in Lambaréné, Gabon

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ABSTRACT

Background In 2016, the third international consensus definitions for sepsis and septic shock (Sepsis-3) task force provided revised definitions for sepsis and septic shock. This study explores knowledge regarding sepsis among health workers in Lambaréné, Gabon.

Methods We conducted a self-administered questionnaire-based survey about sepsis among health workers from the referral regional hospital, the research center, and primary care health facilities in the Lambaréné region. Participants were from the referral regional hospital, the research center, and primary healthcare facilities. A score of one was given to each correct answer. The global score out of a possible score of twenty was calculated, and the proportion of correct responses was determined.

Results A total of 115 health workers (physicians, nurses and assistant nurses) completed the questionnaire, of which 48.7% (56/115) provided a valid definition of sepsis, but 74% (85/115) had never heard about the quick Sequential Organ Failure Assessment (qSOFA) score. The proportion of correct answers was comparable across the three health profession categories. The median global score across all health workers was 11 [IQR, 9-14.5] out of 20. Physicians attained higher global scores [14 (IQR, 11-15)] than assistant nurses [11 (IQR, 8-13), P=0.007]; their global score was comparable to that of nurses.

Conclusion There are considerable knowledge gaps regarding sepsis among health workers in Lambaréné, potentially impairing the prompt recognition and management of sepsis. There is a need to establish periodic up-to-date training to improve sepsis knowledge.

Keywords

Health workers; Knowledge; Gabon; qSOFA; Sepsis

1. BACKGROUND

Nearly fifty million people worldwide are afflicted by sepsis every year, resulting in eleven million deaths annually (Rudd et al., 2020), and sub-Saharan African countries are amongst those most heavily affected (Rudd et al., 2020). The definition of sepsis has been revised recently, with sepsis now being defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection (Singer et al., 2016). Septic shock is clinically characterised by the vasopressor requirement to maintain a mean arterial pressure of 65 mmHg or higher, and a serum lactate level greater than 2 mmol/L (>18 mg/dL) in the absence of hypovolemia (Singer et al., 2016). The quick SOFA (qSOFA) score, consisting of a respiratory rate of 22/min or greater, altered mentation, and systolic blood pressure of 100 mmHg or less, was established as a bedside method for the prompt identification of severely ill patients who might have sepsis. The previous definition using the systemic inflammatory response syndrome (SIRS) criteria lead to the inclusion of an excess of patients with infection or inflammation and yielded a low specificity (Schmedding et al., 2019; Singer et al., 2016). In a cohort of patients recruited at the Albert Schweitzer Hospital (HAS) in Lambaréné, Gabon, sepsis (using the old definition based on SIRS criteria) was diagnosed in 28.1% of patients, with an associated mortality of 17.2% (Huson et al., 2015). Knowledge about the signs and symptoms of sepsis and prompt medical treatment is essential for the successful management of sepsis. While studies assessing the knowledge of sepsis have been performed in various settings (Eitze et al., 2018; Rubulotta et al., 2009; Watkins et al., 2020; Zaccone et al., 2017; Ziglam et al., 2006), few studies were performed in low-and-middle-income countries (LMICs) to date (Brizuela et al., 2019; Marshall-Brown et al., 2016). We hypothesise that in LMICs within Africa such as Gabon, knowledge about sepsis among health workers is sub-optimal. This study investigates knowledge regarding sepsis awareness and management among health workers in Lambaréné, Gabon.

2. METHODS

2.1. Study design and setting

From February 2020 to June 2020, we conducted a cross-sectional survey of health workers from seven health facilities, including a referral hospital (HAS), a medical research center (CERMEL), and five primary care health facilities (PHFs) in Lambaréné, in Moyen-Ogooué province of Gabon. While CERMEL and the PHFs have the capacity to manage cases of suspected infectious diseases, they refer patients to the regional referral hospital in case of severe infection or complication (Gabon's Ministry of Public Health, 2011). Participating care providers included in our study were physicians, nurses, and assistant nurses.

2.2. Survey instrument

We developed the questionnaire using World Health Organization (WHO) recommendations, Surviving Sepsis Campaign international guidelines (Dellinger et al., 2017; World Health Organization, n.d.), and content from previously published articles on the knowledge of sepsis among health care practitioners (Fleischmann et al., 2016; Marshall-Brown et al., 2016; Rahman et al., 2019). A panel comprising two local physician researchers and one senior expert reviewed the questionnaire. The questionnaire was submitted in a pilot test to ten health workers to check comprehension and clarity of the questions. The reliability of the questionnaire was tested, and the final questionnaire's Cronbach's alpha coefficient was 0.8. Each correct answer given to the question scored one point. The total correct answer score possible was 20 (Additional file 1).

2.3. Data collection

The researchers visited study sites to explain the study details to potential participants, who were subsequently approached individually. A self-administered questionnaire was distributed to all eligible health workers (physicians, nurses and assistant nurses).

2.4. Sample size

Due to the limited human resources of the health facilities of the Lambaréné region, we included all consenting health workers amongst those who were eligible and available.

2.5. Statistics

Study data were collected and doubly entered into a Research Electronic Data Capture (REDCap) database (Harris et al., 2009). Percentages were calculated for the categorical data. Fisher's exact test was used to compare proportions. In addition, the global score was calculated from the sum of correct answers to each question. The global score variable normality and variance homogeneity were tested using Shapiro-Wilk and Bartlett tests, respectively. Thus, in the analyses of subgroups, the Student's t-test was used. A two-sided p-value < 5% was considered statistically significant. The analysis was performed using Rstudio version 4.0.2 ("RStudio Team (2020). RStudio: Integrated Development for R. RStudio, PBC, Boston, MA URL," n.d.).

3. RESULTS

A total of 122 subjects were invited to participate in the study, of which 115 (94%) completed the entire questionnaire. A total of 57/115 (49.6%) participants were from the regional referral hospital; fifteen percent (17/115) were physicians and 53% (61/115)

were nurse assistants. The median length of service of the health worker included was 7 years [IQR 3-14] (Table1). Fifty-six of 115 (48.7%) responded that 'sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection'. The sign of sepsis recognised by the greatest proportion of participants was fever (92%, 106/115), followed by altered mental status (74.8%, 86/115) and tachycardia (67%, 77/115); the least recognised signs were tachypnoea and hypothermia. A large proportion agreed that securing large-bore intravenous access, initiation of blood cultures, and broad-spectrum antibiotic therapy are important for successful sepsis management. However, only 32% (37/115) responded that in case of hypotension, initial resuscitation with crystalloid fluids is important. While thirty (26%) interviewees reported knowledge of the qSOFA score, a total of 13% (15/115) recognised the three criteria that comprise it.

Table 1. Baseline characteristics of health workers.

Characteristics	[ALL]	Referral Hospital	Research center	Primary care health facilities
Empty Cell	***N=115 (%)***	***N=57 (%)***	***N=28(%)***	***N=30 (%)***
Gender				
F	82 (71.3)	42 (73.7)	21 (75.0)	19 (63.3)
M	33 (28.7)	15 (26.3)	7 (25.0)	11 (36.7)
Profession category				
Physicians	19 (16.5)	7 (12.3)	9 (32.1)	3 (10.0)
Nurses	29 (25.2)	19 (33.3)	0 (0.00)	10 (33.3)
Assistant nurses	67 (58.3)	31 (54.4)	19 (67.9)	17 (56.7)
Education level:				
Secondary	87 (75.7)	47 (82.5)	20 (71.4)	20 (66.7)
University	28 (24.3)	10 (17.5)	8 (28.6)	10 (33.3)
Length of service (years), Median [IQR]	7.00 [3.00-14.0]	7.00 [3.00-17.0]	4.00 [2.75-7.00]	14.0 [7.00-17.2]

3.1. Comparison of correct answer according to professional categories

The median global score across all health worker respondents was 11 [IQR, 9-14.5]; however, there were statistically significant performance differences across the three professional categories.

For individual questions, physicians provided correct responses more frequently than nurses and nurse assistants. However, the difference was not statically significant except for the questions related to the definition of qSOFA and the practical management of sepsis (Table 2). When comparing the global score of health worker per the type of health facilities, assistant nurses from the research center performed significantly better than their colleagues from PHFs (Fig. 2).

Table 2. Awareness and sepsis knowledge: distribution of correct, incorrect answers per item per professional group.

Questionnaire items	[ALL]	Assistant nurses	Nurses	Physicians	P-value*
Empty Cell	***N=115(%)***	***N=67(%)***	***N=29 (%)***	***N=19(%)***	Empty Cell
1. Have you ever heard about the qSOFA score?					0.914
No	85 (73.9)	49 (73.1)	21 (72.4)	15 (78.9)	
Yes	30 (26.1)	18 (26.9)	8 (27.6)	4 (21.1)	
2. What do you think is the most appropriate definition of sepsis?					
Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection *(Correct answer)*					0.233
No	59 (51.3)	31 (46.3)	15 (51.7)	13 (68.4)	
Yes (*Correct answer)*	56 (48.7)	36 (53.7)	14 (48.3)	6 (31.6)	
3. Do you think the following symptoms and signs could be associated with sepsis?					
a) Fever					0.700
No	9 (7.83)	6 (8.96)	1 (3.45)	2 (10.5)	
Yes *(Correct answer)*	106 (92.2)	61 (91.0)	28 (96.6)	17 89.5)	
b) Hypothermia					0.079
No	48 (41.7)	33 (49.3)	11 (37.9)	4 (21.1)	
Yes *(Correct answer)*	67 (58.3)	34 (50.7)	18 (62.1)	15 78.9)	
c) Tachycardia					0.074
No	38 (33.0)	25 (37.3)	11 (37.9)	2 (10.5)	
Yes *(Correct answer)*	77 (67.0)	42 (62.7)	18 (62.1)	15 (89.5)	
d) Tachypnoea					0.022
No	53 (46.1)	38 (56.7)	10 (34.5)	5 (26.3)	
Yes *(Correct answer)*	62 (53.9)	29 (43.3)	19 (65.5)	14 73.7)	
e) Hypotension					0.021
No	50 (43.5)	31 (46.3)	16 (55.2)	3 (15.8)	
Yes (Correct answer)	65 (56.5)	36 (53.7)	13 (44.8)	15 84.2)	
f) Alteration of consciousness					0.500
No	29 (25.2)	18 (26.9)	5 (17.2)	6 (31.6)	
Yes *(Correct answer)*	86 (74.8)	49 (73.1)	24 (82.8)	13 (68.4)	

Table 2. Awareness and sepsis knowledge: distribution of correct, incorrect answers per item per professional group. (continued)

Questionnaire items	[ALL]	Assistant nurses	Nurses	Physicians	P-value*
4. Which of the following is NOT a component of the qSOFA score?					
Tachycardia *(good answer)*					0.022
No	100 (87.0)	56 (83.6)	29 (100)	15 (78.9)	
Yes *(Correct answer)*	15 (13.0)	11 (16.4)	0 (0.00)	4 (21.1)	
5. The blood culture must be performed in case of sepsissuspicion					0.438
No	17 (14.8)	12 (17.9)	4 (13.8)	1 (5.26)	
Yes *(Correct answer)*	98 (85.2)	55 (82.1)	25 (86.2)	18 (94.7)	
6. Which patients do you think should be monitored for the onset of sepsis?					
a) Patients suffering from tuberculosis					0.456
No	59 (51.3)	37 (55.2)	12 (41.4)	10 (52.6)	
Yes *(Correct answer)*	56 (48.7)	30 (44.8)	17 (58.6)	9 (47.4)	
b) Patients admitted to the emergency room for severe infection					0.384
No	39 (33.9)	24 (35.8)	7 (24.1)	8 (42.1)	
Yes *(Correct answer)*	76 (66.1)	43 (64.2)	22 (75.9)	11 57.9)	
c) Patients infected with HIV					0.349
No	57 (49.6)	36 (53.7)	11 (37.9)	10 (52.6)	
Yes *(Correct answer)*	58 (50.4)	31 (46.3)	18 (62.1)	9 (47.4)	
d) All patients					0.506
No	88 (76.5)	51 (76.1)	24 (82.8)	13 (68.4)	
Yes	27 (23.5)	16 (23.9)	5 (17.2)	6 (31.6)	
7. Which of the following are appropriate for the management of sepsis?					
a) Secure large-bore IV access					0.018
No	35 (30.4)	26 (38.8)	8 (27.6)	1 (5.26)	
Yes *(Correct answer)*	80 (69.6)	41 (61.2)	21 (72.4)	18 (94.7)	
b) If hypotension, initially resuscitate with crystalloid					<0.001
No	78 (67.8)	56 (83.6)	15 (51.7)	7 (36.8)	
Yes(*Correct answer)*	37 (32.2)	11 (16.4)	14 (48.3)	12 (63.2)	

Table 2. Awareness and sepsis knowledge: distribution of correct, incorrect answers per item per professional group. (continued)

Questionnaire items	[ALL]	Assistant nurses	Nurses	Physicians	P-value*
c) Collect blood for blood culture and start broad-spectrum antibiotic therapy					0.059
No	29 (25.2)	21 (31.3)	7 (24.1)	1 (5.26)	
Yes *(Correct answer)*	86 (74.8)	46 (68.7)	22 (75.9)	15 (94.7)	
d) Maintain good oxygen saturation					<0.001
No	52 (45.2)	41 (61.2)	8 (27.6)	3 (15.8)	
Yes	63 (54.8)	26 (38.8)	21 (72.4)	16 (84.2)	
8. Do you think the following attitudes and practice may be essential for the management of sepsis?					
a) Use of antibiotics					0.493
No	9 (7.83)	6 (8.96)	3 (10.3)	0 (0.00)	
Yes *(Correct answer)*	106 (92.2)	61 (91.0)	26 (89.7)	15 100)	
b) Use of crystalloid					0.351
No	47 (40.9)	30 (44.8)	12 (41.4)	5 (26.3)	
Yes *(Correct answer)*	68 (59.1)	37 (55.2)	17 (58.6)	14 73.7)	
c) Use of vasopressor					0.004
No	89 (77.4)	57 (85.1)	23 (79.3)	9 (47.4)	
Yes *(Correct answer)*	26 (22.6)	10 (14.9)	6 (20.7)	10 (52.6)	
d) Earlier identification of the source of infection					0.232
No	78 (67.8)	44 (65.7)	18 (62.1)	16 (84.2)	
Yes *(Correct answer)*	37 (32.2)	23 (34.3)	11 (37.9)	3 (15.8)	

*Fisher's exact test for p-values comparing the number of correct responses in the three professional categories.

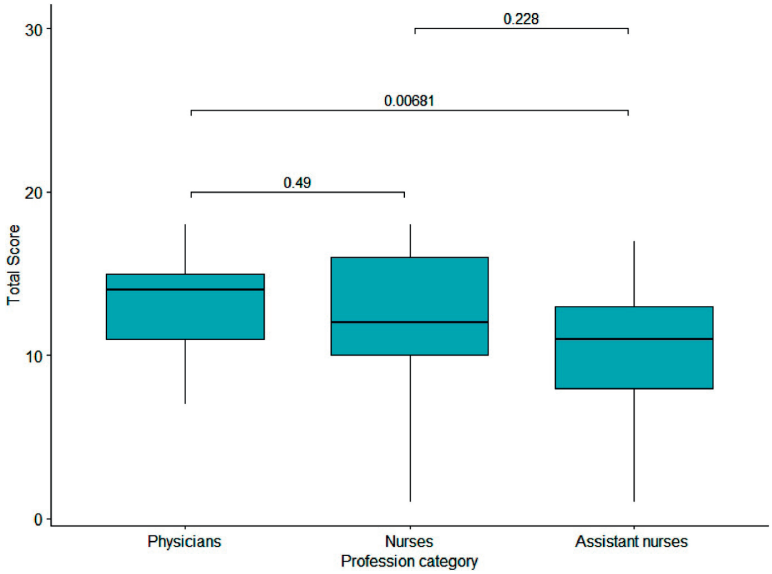

Fig. 1. Global score comparison according to the professional categories.

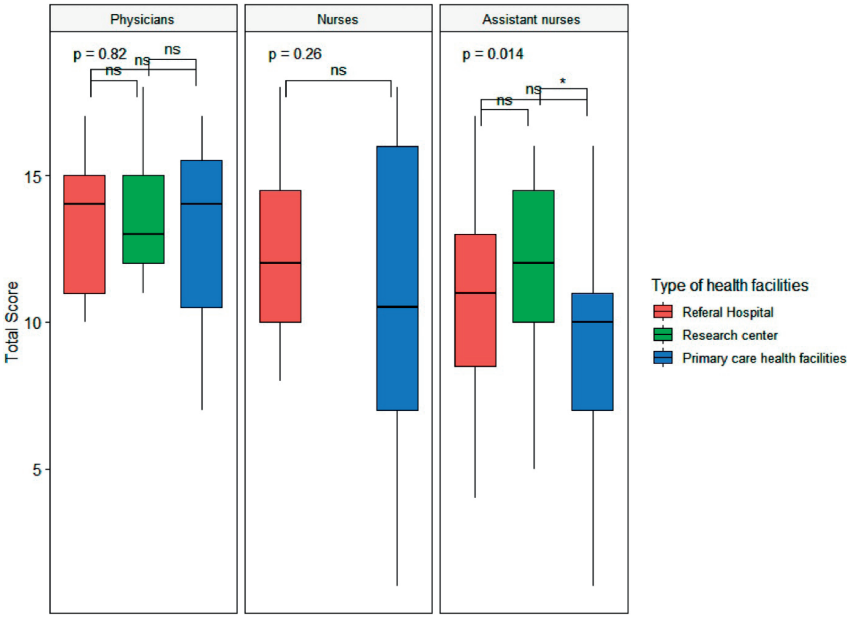

Fig. 2. Global score comparison of the professional categories with respect to type of health facilities.

Assistant nurse's profession category: Research center [12 (IQR,10-14.5)] vs referral hospital [11 (IQR 8.5-13)], P=0.432; Referral hospital [11 (IQR 8.5-13)] vs primary care health facility [10 (IQR 7-11)], P=0.055.; Research center [12 (IQR 10-14.5)] vs primary care health facilities [10 (IQR 7-11)], *P=0.016. There was no statistically significant difference when comparing global score of physicians or with respect to type of health facilities.

4. DISCUSSION

This study of sepsis knowledge among health workers representing all levels of health facilities from Lambaréné, Gabon, demonstrates important knowledge gaps in sepsis awareness and management. To the best of our knowledge, this study is the first of its kind from sub-Saharan Africa assessing the knowledge of health workers on sepsis, since the publication of the Sepsis-3 definitions.

While our results are similar to studies from Malawi (Marshall-Brown et al., 2016), Malaysia (Rahman et al., 2019), and Brazil (Assunção et al., 2010), which reported insufficient knowledge of health workers on sepsis, the proportion of correct responses in our study is lower compared with these studies. The difference between studies could be due to differences between the respective questionnaires applied. The knowledge assessment in our questionnaire is based on the Sepsis-3 definition, which was published four years ago. The lower number of infectious diseases and intensive care specialists in our study population offers an additional explanation.

As to be expected according to the level of formal education, physicians provided correct answers in higher frequency than nurses and nurse assistants. Overall, our findings were not unexpected because there were no recent specific training or educational activities related to sepsis for health workers in Lambaréné. Furthermore, there is no national guideline or recommendation for the management of sepsis. When comparing the performance of health workers across the type of health facilities, assistant nurses from the research center scored better than their counterparts from the PHFs, despite the fact that the research center does not often manage complicated infectious disease cases like sepsis. Though unexpected, this better performance of assistant nurses from the research center might be due to the shorter median period of service employment [4 years (IQR 2.75-7)], which reflects recent graduation from nursing school and therefore more recent exposure to formal teaching on sepsis.

A small number of participating health workers recognised tachypnoea and hypothermia as signs of sepsis. Moreover, only 32% of health workers responded that the crystalloid is appropriate for the management of sepsis. This illustrates the gap that exists in the management of sepsis by Gabon's health workers. The Surviving Sepsis Campaign (SSC) guidelines recommends to rapidly administer a minimum of 30 mL/kg crystalloid solution intravenously in patients with septic shock and those with elevated blood lactate levels (Levy et al., 2018). However, recent findings suggest an individualised, conservative and physiology-guided approach to fluid resuscitation (Marik et al., 2020). Due to the absence of national guidelines, the practitioners manage sepsis cases according to their own experience, knowledge, training and drugs and equipment available.

Our study also highlights the need for policymakers to contextualise international guidelines. Guidelines International Network (G-I-N) defines guideline adaptation as "the systematic approach to the modification of a guideline(s) produced in one ... setting for application in a different context" (Wang et al., 2018). It requires substantial time and resources to develop and update high-quality guidelines that are feasible and useful (Fervers et al., 2011). There are at least eight published frameworks for the adaptation of clinical, public health and health services guidelines (Darzi et al., 2017). Critical to the success of this process is collaboration and local ownership, engaging with key stakeholders to co-create guidelines that are relevant and responsive to contextual needs. Specifically, there is a need to ensure buy-in and input from the future guardians of the guidelines (district or provincial health offices); the future implementers of the guidelines (community health workers and health service providers); and future beneficiaries of the guidelines (community members). To ensure the guidelines' content, quality, consistency between sources and acceptability/applicability of the recommendations, these guidelines can be validated in accordance with the criteria of the Appraisal of Guidelines for Research and Evaluation (AGREE) checklist (Brouwers et al., 2016). Following such an adaptation process, there is a need to review the perceptions and challenges of adaptation and implementation of guidelines, which can use a modified method of the ADAPTE process (Fervers et al., 2011).

As with most surveys, our study has certain limitations. Despite delivering the survey similarly across respondents, there is a possibility that respondents felt compelled to provide 'socially acceptable answers' rather than answers that reflected their true opinion or awareness of the topic. This study was not performed on the full scale of a comprehensive Knowledge, Attitudes, and Practice (KAP) study, due to the shortened period available to conduct the study. Whilst we believe that our findings are most likely generalisable to a certain degree to other regions in Gabon because of shared context, we call for a national survey to fully assess and further understand the knowledge, attitudes and practice regarding sepsis among health workers in order to increase awareness.

5. CONCLUSION

There is a knowledge gap of Lambaréné health workers about sepsis. The majority of respondents were unaware about the new Sepsis-3 definition. In general, physician's knowledge is better than that of nurses and nurse assistants. There is an opportunity to introduce regular training programs in sepsis irrespective of the type of health facilities surveyed.

Acknowledgements

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ADDITIONAL FILES

Additional file 1.Sepsis KAP questionnaire (translated from the French original)

KAP SEPSIS QUESTIONNAIRE
SECTION A: Basic information
1. ID ……
2. Gender: M [] F []
3. Health facility ——————————-
4. Hospital service: ——————————————— ———–
5. Type of health facility
□ Referral hospital
□Secondary hospital (health center)
□ First level hospital (dispensary)
□Research center
□Other ……
6. Education level: O primary O secondary O university
7. Profession: Doctor O assistant nurse O nurse O Others O
8. Duration of medical career …… ……. .

SECTION B-KAP
Knowledge and perception of sepsis
1.Have you ever heard of the Third International Consensus on Definitions of Sepsis and Septic Shock (Sepsis-3) and qSOFA
□Yes □ No
2. What do you think is the most appropriate definition of sepsis?
a)Blood contamination by a microbe
b)life-threatening organ dysfunction caused by a dysregulated host response to infection.
c)Systemic inflammatory response caused by infection
d)Allergic reaction against germs
3. Do you think the following symptoms and signs are associated with sepsis?
a) Fever □ Yes □ No or not sure
b) Hypothermia □ Yes □ No or not sure
c) Tachycardia □ Yes □ No or not sure
d) Tachypnea □ Yes □ No or not sure
e) Hypotension □ Yes □ No or not sure
f) Altered state of consciousness □ Yes □ No or not sure

4. Which of the following is NOT a component of the qSOFA score?
   a)Glasgow score <15
   b)Respiratory rate ≥ 22 c / min
   c)Tachycardia> 90 beats / min
   d)Systolic blood pressure ≤100 mmHg
5. The blood culture must be requested in the event of any suspicion of sepsis
   True □False □
6. Which patients do you think should be monitored for the onset of sepsis?
   a) Patients suffering from tuberculosis
   b) Patients admitted to the emergency room for severe infection
   c) Patients infected with HIV
   d) All patients
   e) I don't know
7. Which of the following are urgently appropriate for the management of sepsis?
   a. Secure large-bore IV access
   b. If hypotension, initially resuscitate with crystalloid
   c. Collect blood for blood culture and start broad-spectrum antibiotic therapy
   d. Maintain good oxygen saturation
8. Do you think the following practice could be useful for the management of sepsis?
   a) using of antibiotics □ Yes □ No or not sure
   b) using of crystalloids □Yes □ No or not sure
   c) using of vasopressors □Yes □ No or not sure
   d) Earlier identification of the source of infection □Yes □ No or not sure

For section, where appropriate, single to multiple answers were correct:
2-b;3- a-b-c-d-e-f; 4-c; 5-True; 6-a-b-c; 7-a-b-c-d; 8-a-b-c-d

REFERENCES

1. Assunção, M., Akamine, N., Cardoso, G.S., Mello, P.V.C., Teles, J.M.M., Nunes, A.L.B.,Maia, M.O., Rea-Neto, A., ´ Machado, F.R., 2010. Survey on physicians' knowledge of sepsis: Do they recognize it promptly? J. Crit. Care 25, 545–552. https://doi.org/10.1016/j.jcrc.2010.03.012.
2. Brizuela, V., Bonet, M., Souza, J.P., Tunçalp, O., ¨ Viswanath, K., Langer, A., 2019. Factors influencing awareness of healthcare providers on maternal sepsis: a mixed-methods approach. BMC Public Health 19, 683. https://doi.org/10.1186/s12889-019-6920-0.
3. Brouwers, M.C., Kerkvliet, K., Spithof, K., 2016. The AGREE reporting checklist: A tool to improve reporting of clinical practice guidelines. BMJ Online 352, i1152. https:// doi.org/10.1136/bmj.i1152.
4. Darzi, A., Abou-Jaoude, E.A., Agarwal, A., Lakis, C., Wiercioch, W., Santesso, N.,Brax, H., El-Jardali, F., Schünemann, H.J., Akl, E.A., 2017. A methodological survey identified eight proposed frameworks for the adaptation of health-related guidelines. J. Clin. Epidemiol. https://doi.org/10.1016/j.jclinepi.2017.01.016.
5. Dellinger, R.P., Schorr, C.A., Levy, M.M., 2017. A Users' Guide to the 2016 Surviving Sepsis Guidelines. Crit. Care Med. 45, 381–385. https://doi.org/10.1097/CCM.0000000000002257
6. Eitze, S., Fleischmann-Struzek, C., Betsch, C., Reinhart, K., Betsch, C., Rossmann, C.,Pletz, M.W., Vollmar, H.C., Freytag, A., Wichmann, O., Hanke, R., Hanke, W.,Heinemeier, D., Schmid, P., Eitze, S., Weber, W., Reinhardt, A., Küpke, N.K.,Forstner, C., Fleischmann-Struek, C., Mikolajetz, A., Romhild, J., Neufeind, J., Rieck, T., Suchecka, K., Reinhart, K., the vaccination60+ study group, 2018. Determinants of sepsis knowledge: a representative survey of the elderly population in Germany. Crit. Care 22, 273. https://doi.org/10.1186/s13054-018-2208-5.
7. Fervers, B., Burgers, J.S., Voellinger, R., Brouwers, M., Browman, G.P., Graham, I.D., Harrison, M.B., Latreille, J., Mlika-Cabane, N., Paquet, L., Zitzelsberger, L., Burnand, B., Remy-Stockinger, M., Simon, A., Vlayen, J., 2011. Guideline adaptation: An approach to enhance efficiency in guideline development and improve utilisation. BMJ Qual. Saf. 20, 228–236. https://doi.org/10.1136/ bmjqs.2010.043257.
8. Fleischmann, C., Scherag, A., Adhikari, N.K.J., Hartog, C.S., Tsaganos, T.,Schlattmann, P., Angus, D.C., Reinhart, K., 2016. Assessment of Global Incidence and Mortality of Hospital-treated Sepsis. Current Estimates and Limitations. Am. J. Respir. Crit. Care Med. 193, 259–272. https://doi.org/10.1164/rccm.201504- 0781OC.
9. Gabon's Ministry of Public Health, 2011. Health Statistical Yearbook.Harris, P.A., Taylor, R., Thielke, R., Payne, J., Gonzalez, N., Conde, J.G., 2009.
10. Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support. J. Biomed. Inform.42, 377–381. https://doi.org/10.1016/j.jbi.2008.08.010.
11. Huson, M.A.M., Kalkman, R., Stolp, S.M., Janssen, S., Alabi, A.S., Beyeme, J.O., van derPoll, T., Grobusch, M.P., 2015. The impact of HIV on presentation and outcome of bacterial sepsis and other causes of acute febrile illness in Gabon. Infection 43,443–451. https://doi.org/10.1007/s15010-015-0753-2.
12. Levy, M.M., Evans, L.E., Rhodes, A., 2018. The Surviving Sepsis Campaign Bundle: 2018 update. Intensive Care Med 44, 925–928. https://doi.org/10.1007/s00134-018-5085-0.
13. Marik, P.E., Byrne, L., van Haren, F., 2020. Fluid resuscitation in sepsis: the great 30 mLper kg hoax. J. Thorac. Dis. 12, S37–S47. https://doi.org/10.21037/jtd.2019.12.84.

14. Marshall-Brown, P., Namboya, F., Pollach, G., 2016. Evaluating sepsis training for medical students and nonphysicians in Malawi. J. Clin. Anesth. 34, 352–357.https://doi.org/10.1016/j.jclinane.2016.05.013.

15. Rahman, N., Inayati, A., Chan, C.M., Zakaria, M.I., Jaafar, M.J., 2019. Knowledge and attitude towards identification of systemic inflammatory response syndrome (SIRS) and sepsis among emergency personnel in tertiary teaching hospital. Australas. Emerg. Care 22, 13–21. https://doi.org/10.1016/j.auec.2018.11.002.

16. RStudio Team, 2020. RStudio: Integrated Development for R. RStudio, PBC, Boston, MA.URL [WWW Document], n.d. URL. http://www.rstudio.com/.

17. Rubulotta, F.M., Ramsay, G., Parker, M.M., Dellinger, R.P., Levy, M.M., Poeze, M., Committee, on behalf of the S.S.C.S., 2009. An international survey: Public awareness and perception of sepsis*. Crit. Care Med. 37, 167–170. https://doi.org/ 10.1097/CCM.0b013e3181926883.

18. Rudd, K.E., Johnson, S.C., Agesa, K.M., Shackelford, K.A., Tsoi, D., Kievlan, D.R.,Colombara, D.V., Ikuta, K.S., Kissoon, N., Finfer, S., Fleischmann-Struzek, C.,Machado, F.R., Reinhart, K.K., Rowan, K., Seymour, C.W., Watson, R.S., West, T.E.,Marinho, F., Hay, S.I., Lozano, R., Lopez, A.D., Angus, D.C., Murray, C.J.L.,Naghavi, M., 2020. Global, regional, and national sepsis incidence and mortality,1990–2017: analysis for the Global Burden of Disease Study. Lancet Lond. Engl. 395,200–211. https://doi.org/10.1016/S0140-6736(19)32989-7.

19. Schmedding, M., Adegbite, B.R., Gould, S., Beyeme, J.O., Adegnika, A.A., Grobusch, M.P., Huson, M.A.M., 2019. A Prospective Comparison of Quick Sequential Organ Failure Assessment, Systemic Inflammatory Response Syndrome Criteria, Universal Vital Assessment, and Modified Early Warning Score to Predict Mortality in Patients with Suspected Infection in Gabon. Am. J. Trop. Med. Hyg. 100, 202–208. https://doi.org/10.4269/ajtmh.18-0577.

20. Singer, M., Deutschman, C.S., Seymour, C.W., Shankar-Hari, M., Annane, D., Bauer, M.,Bellomo, R., Bernard, G.R., Chiche, J.-D., Coopersmith, C.M., Hotchkiss, R.S.,Levy, M.M., Marshall, J.C., Martin, G.S., Opal, S.M., Rubenfeld, G.D., van der Poll, T., Vincent, J.-L., Angus, D.C., 2016. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 315, 801–810. https://doi.org/10.1001/jama.2016.0287.

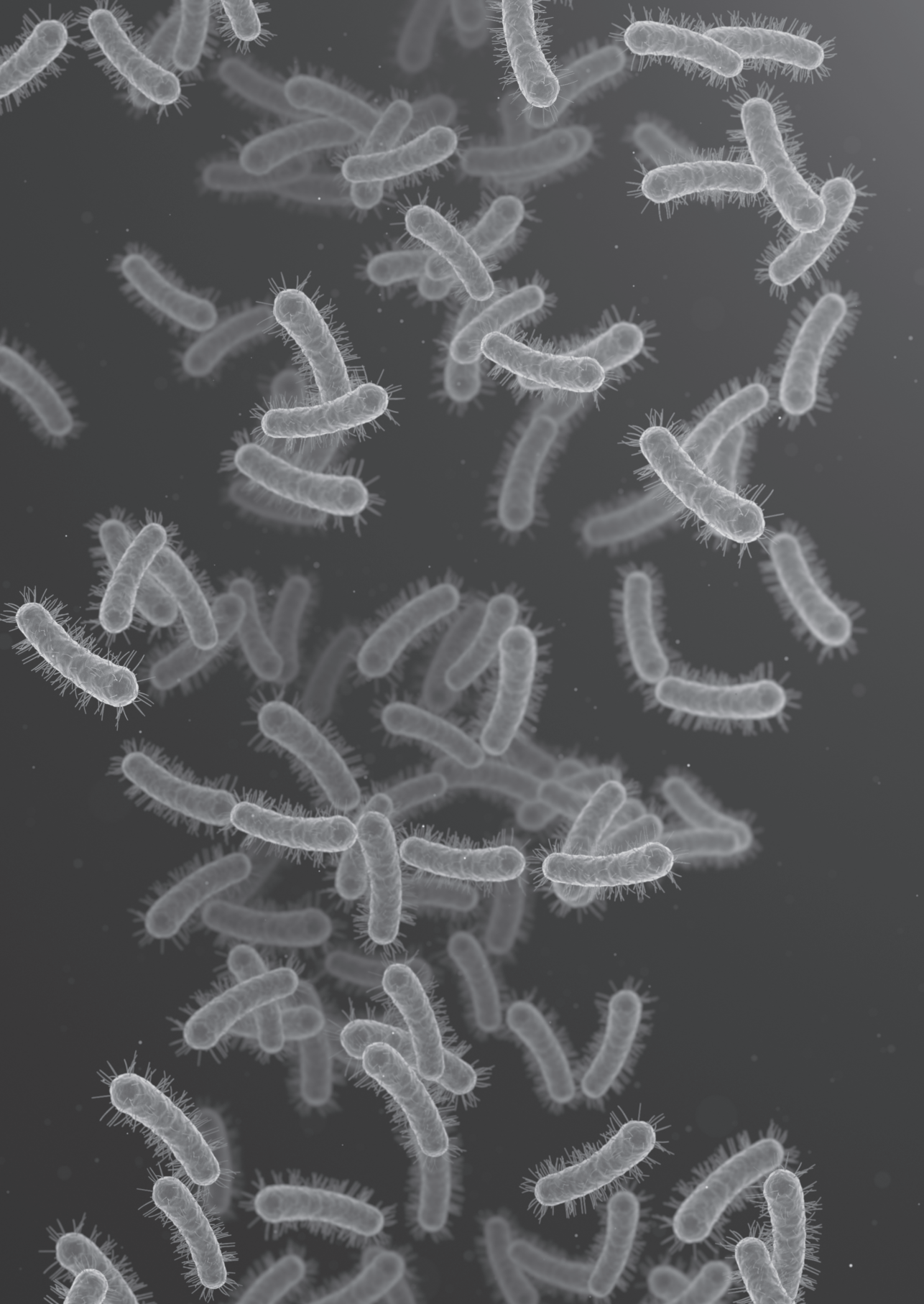
21. Wang, Z., Norris, S.L., Bero, L., 2018. The advantages and limitations of guideline adaptation frameworks. Implement. Sci. 13, 1–13. https://doi.org/10.1186/s13012-018-0763-4.

22. Watkins, R.R., Haller, N., Wayde, M., Armitage, K.B., 2020. A Multicenter Survey of House Staff Knowledge About Sepsis and the "Surviving Sepsis Campaign Guidelines for Management of Severe Sepsis and Septic Shock. J. Intensive Care Med. 35,187–190. https://doi.org/10.1177/0885066617737304.

23. World Health Organization, n.d. Sepsis. WHO, Geneva.

24. Zaccone, V., Tosoni, A., Passaro, G., Vallone, C.V., Impagnatiello, M., Li Puma, D.D., De Cosmo, S., Landolfi, R., Mirijello, A., 2017. Sepsis in Internal Medicine wards: current knowledge, uncertainties and new approaches for management optimization. Ann. Med. 49, 582–592. https://doi.org/10.1080/07853890.2017.1332776.

25. Ziglam, H.M., Morales, D., Webb, K., Nathwani, D., 2006. Knowledge about sepsis among training-grade doctors. J. Antimicrob. Chemother. 57, 963–965. https://doi.org/10.1093/jac/dkl042



Chapter 10

Recognising Sepsis as a Health Priority in Sub-Saharan African Country: Learning Lessons from Engagement with Gabon's Health Policy Stakeholders

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ABSTRACT

Sepsis has been recognised as a global health priority by the United Nations World Health Assembly, which adopted a resolution in 2017 to improve sepsis prevention, diagnosis, and management globally. This study investigated how sepsis is prioritised in Gabon. From May to November 2021, we conducted a qualitative study in healthcare stakeholders at the local, regional, and national levels. Stakeholders included the Ministry of Health (MOH), ethics/regulatory bodies, research institutions, academic institutions, referral hospitals, international funders, and the media. Twenty-three multisectoral stakeholders were interviewed. Respondents indicated that sepsis is not yet prioritised in Gabon due to the lack of evidence of its burden. They also suggest that the researchers should focus on linkages between sepsis and the countries' existing health sector priorities to accelerate sepsis prioritisation in health policy. Stakeholder awareness and engagement might be accelerated by involving the media in the generation of communication strategies around sepsis awareness and prioritisation. There is a need for local, regional and national evidence to be generated by researchers and taken up by policymakers, focusing on linkages between sepsis and a country's existing health sector priorities. The MOH should set sepsis reporting structures and develop appropriate sepsis guidelines for identification, management, and prevention.

Keywords: sepsis; policy engagement; prioritisation; health system; Lambaréné; Gabon

1. INTRODUCTION

Sepsis is a life-threatening organ dysfunction resulting from infection [1]. Sepsis kills 11 million people each year [2]. The term "sepsis" dates back to Hippocrates' time, when it was used to describe the process through which flesh rots and wounds fester [3]. Despite this long history, countless patients around the world continue to die of sepsis or suffer long-term disability [4,5]. The World Health Organization (WHO) recommends strengthening efforts to identify, document, prevent, and treat sepsis [6].

Recently, sepsis care has substantially improved due to extensive research efforts allowing for novel insights into the pathophysiology, treatment, and awareness of sepsis [7,-13]. In 2017, a WHO resolution recommended that member states recognise sepsis as a Global Health Priority [6,14]. The resolution also encourages health workers to increase sepsis awareness by using the term 'sepsis' in communication with patients, relatives, and other parties [6,14]. Many barriers delay the reduction in the global burden of sepsis, particularly in low-resource settings [15,16]. Many studies consistently report low community and stakeholder awareness of sepsis, its signs and symptoms, its causes, and resulting disability and death toll [17-20]. To be engaged, health leaders, researchers, and funding agencies need accurate quantification of sepsis incidence and mortality. We hypothesised that prioritising sepsis in Low-and-Middle-Income Countries (LMICs) such as Gabon might face many challenges or reticence from stakeholders. Using a qualitative approach, we collected Gabon's health system stakeholders' opinions on prioritising sepsis and used it as an indicator of the health system's performance. Furthermore, we aimed to elucidate baseline perceptions of key health workers on the burden of sepsis in Gabon and to identify opportunities for stakeholder engagement.

2. MATERIALS AND METHODS

2.1. Study Design and Study Site

From May to November 2021, we conducted a qualitative study at the Centre de Recherches Médicales de Lambaréné (CERMEL), Gabon. Participants included stakeholders at the local, regional, and national levels. They were from Ministry of Health (MOH), ethics/ regulatory bodies, research institutions, academic institutions, referral hospitals, international funders, and media. These stakeholder institutions have been selected based on their reported role in health policy in general, and on their contribution to improving and developing solution to health challenge at both local regional and national levels [21-24]. This study is part of the policy engagement component of the African Research Collaboration on Sepsis (ARCS), a multinational research initiative funded through the UK National Institute for Health Research (NIHR), which aims to: (1) deliver high-quality

sepsis research training; (2) establish commonly agreed sepsis care quality indicators for Gabon, which could form the bedrock of monitoring and evaluation programmes; (3) and pilot test innovative sepsis care interventions [25].

2.2. Participant Selection

Letters were sent to institutions identified as employing members of stakeholder groups representing the health sector, requesting that they suggest names of key informants who met the following eligibility criteria: being 18 years of age or more; having ever heard of sepsis; being willing to provide informed consent for the interview. These criteria were required to make sure that participants could provide their opinions based on their experience in their respective institutions.

2.3. Data Collection

A qualitative semi-structured questionnaire was used in face-to-face key informant interviews. The questionnaire was adapted from the sample Bellwether tool [26] (Supplementary Materials). Study participants were asked for: their perceptions of policy agenda priorities; characteristics and capacities of sepsis-related policymakers, policy implementers, advocates, opponents; and factors that might elevate sepsis on the policy agenda. These key informant interviews were audio-recorded, annotated, and transcribed. Study participants also completed a quantitative tool, which asked them to rate, for each stakeholder group, the likelihood of sepsis-related outcomes being realised in the next five years, on a scale of 1–5 (where 1 = highly unlikely; 2 = unlikely; 3 = neither likely or unlikely; 4 = likely, and 5 = highly likely). They took into consideration what influential MOH policymakers are saying about sepsis, what language they are using, how interested and open MOH policymakers are to sepsis, and what kind of evidence would convince them. They also took into consideration who, other than the MOH, is engaging in sepsis and how influential they are; what can be done to involve others; what influential stakeholders are saying about sepsis; and what new legislation, budgets, programmes, or strategies were being developed that could relate to sepsis. Regarding health workers specifically, participants considered who is involved in implementing sepsis-related policies among health workers; whether they have the skills, relationships, and incentives to deliver; whether different health workers are working coherently together to implement sepsis-related policy; and whether the necessary structures and incentives are in place to facilitate this (File S1).

2.4. Data Analysis

Framework Analysis was employed for the qualitative data collected from the key informant interviews. Analysis of the data was structured into five phases: familiarisation, identifying a thematic framework, indexing, mapping, and interpretation. During the

thematic framework identification phase, we used the interview guide in a deductive process of identifying broad themes. This thematic framework was refined inductively by identifying emerging themes. NVivo software [27] was used to summarise emerging themes.

3. RESULTS

3.1. Characteristics of Included Participants

Twenty-three stakeholders from seven institutions were interviewed. A total of 11/23 (48%) of the participants were aged between 31 and 40 years old, 16/23 (70%) were males, and 10/23 (43%) and 13/23 (57%) held Bachelor and Doctorate degrees, respectively. The distribution of stakeholder by interviewed institution is presented in **Table 1**

Table 1. Distribution of stakeholders interviewed according to institution.

Employing Body	Physicians	Nurses	Public Health Specialist	Laboratory Technician	Journalist	Economist	Total
Stakeholder Group	8	3	4	4	3	1	23
Ministry of Health	1		1	1			3
Ethics/ Regulatory Body		1	1	1			3
Research Institution	3						3
Training Institutions	2	2					4
Referral Hospital	1		1	2			4
International funder	1		1			1	3
Media					3		3

3.2. Health Priority in the Gabon Ministry of Health's Agenda

We asked participants to identify the top three priorities for the Ministry of Health. **Figure 1** shows the word cloud of participants' responses. Most respondents mentioned health promotion priorities for the prevention, diagnosis, and surveillance of infectious diseases (COVID-19, HIV, antimicrobial stewardship, tuberculosis, malaria); maternal and child health priorities; and chronic non-communicable diseases. None of the participants mentioned sepsis as a priority health issue. Malaria, tuberculosis, and COVID-19 are the three most frequently mentioned diseases with 30% (7/23), 22% (5/23), and 13% (3/23) proportions, respectively.

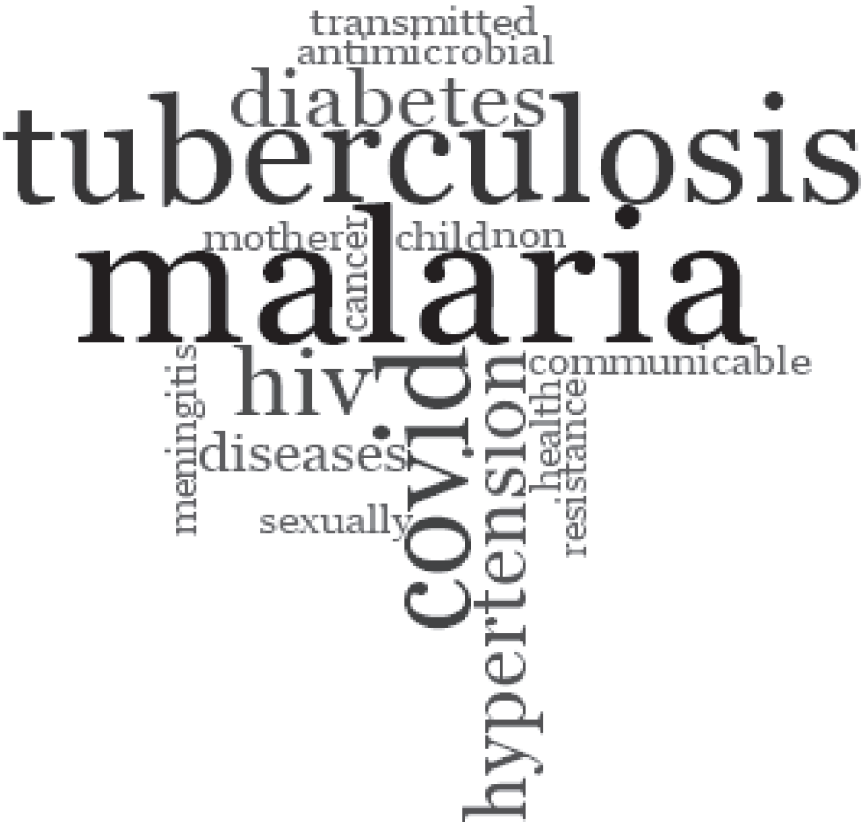

Figure 1. Perceptions of stakeholders on disease prioritisation in Gabon. The size of the writing of the disease is proportional to the number of participants who mentioned it as a health priority. Malaria, tuberculosis and COVID-19 were most frequently mentioned.

3.3. Gabon Sepsis Policy Strengthening

Study participants also estimated the likelihood of sepsis-related policy outcomes for stakeholder groups, as shown in **Table 2**. The participants responded that it is highly likely that the MOH will demand: evidence on sepsis; agreement by training institutions on a definition of sepsis; participation by health workers from central hospitals and health worker unions in sepsis training; permission granted by ethics committees for researchers to audit patients' clinical records; and resultant sepsis evidence supplied by researchers. Conversely, study participants perceived that the least likely outcome is that the MOH and regulatory bodies will recognise sepsis as a priority disease and put sepsis as an indicator of the quality of the health system.

Table 2. Participants' estimation of the likelihood of intervention to be pursued to elevate sepsis to a health priority in Gabon (*N* = 23).

Stakeholder Group (Number of Participants Interviewed)	Outcome	Likelihood of Intervention (Mode)		
		Unlikely	Neutral	Highly Likely
MOH (3)	Demand evidence on sepsis	0	0	3
	Organise training workshops on sepsis for health workers	0	0	3
	Put sepsis as the indicator of quality of health system	3	0	0
Referral hospitals (4)	Participate in training workshops on sepsis	0	0	4
	Accurately diagnose and report sepsis	0	0	4
	Recognition of sepsis as a priority disease	0	0	4
Ethics committees (3)	Give permissions for clinical audit of patient records for quality improvement	0	0	3
	More multi-disciplinary clinical research on sepsis	0	0	3
	Recognition of sepsis as a priority disease	1	0	2
Research organisations (3)	Supply evidence on sepsis	0	0	3
	Implement policy engagement activities on sepsis	0	0	3
	Organise conference tracks on sepsis	0	0	3
Training institutions (4)	Agree on a definition of sepsis	0	0	4
	Teach how to accurately diagnose and report sepsis	0	0	4
	Future health workers recognise sepsis as a priority disease	0	0	4
International funders (3)	Convene stakeholders' meetings on sepsis	0	0	3
	Put out calls for proposals around sepsis	1	0	2
	Put sepsis on international donors' agenda	0	0	3
Media (3)	Disseminate evidence on sepsis	0	0	3
	Implement public engagement activities on sepsis	0	0	3
	Commemorate World Sepsis Day	0	0	3

MOH: Ministry of Health.

The results from the qualitative interviews were further presented using three 'building blocks of WHO health system strengthening [28], namely, service delivery, leadership, governance, finance, and information.

3.3.1. Service Delivery

Respondents in our study indicated that referral hospitals lost many sepsis patients because there are no clear guidelines and indicators for reporting the various types of sepsis. Physicians and nurses use clinical judgment for diagnosis. Some participants acknowledged that they were aware of the recent sepsis score during the sepsis project performed in their hospital by CERMEL's research team. Training institution stakeholders estimated that it is highly likely (rated 5) for training institutions to agree on a definition of sepsis and teach how to accurately diagnose and report sepsis. As a result, most of the respondents from the health workers' group estimated that it is likely (rated 4) for them to accurately diagnose and report sepsis.

> *"I think it is important to train people, including the nurses, in the diagnosis of sepsis because it is not well known, as soon as someone has a fever, we go after malaria, we forget everything else. Sometimes, the thick blood smear is negative, but people are treated for malaria, so I think there is a problem with the training. And for those who are trained, knowledge updates are needed from time to time."*
> —Physician from a research institution.

3.3.2. Leadership and Governance

Respondents were not aware of a sepsis policy that includes prevention, treatment, and rehabilitation. They recommended advocating for the MOH to lead the development of national policy and guidelines. Most respondents indicated that it is unlikely (rated 1) for MOH to put sepsis care as an indicator of the quality of Gabon's health system. However, most of our respondents estimated the likelihood of state regulatory bodies to recognise sepsis as a priority disease to be highly likely (rated 5).

> *"As I said, it is first of all the evidence. Really to highlight the impact of sepsis in the management of child mortality. Once this is automatically demonstrated, these figures will push the ministry to put in place strategies to combat sepsis. And once the ministry has registered action as a priority in its program, there is no need to go to the National Assembly to set it. For now, we are not there. Sepsis could be set as an indicator for infection control program but not the whole health system."*
> —Medical microbiologist from MOH.

Most of the respondents also estimated that it was likely (rated 4) that research institutions will agree to conduct more multi-disciplinary clinical research on sepsis to address the lack of evidence of sepsis burden.

3.3.3. Finance

According to our respondents, funders might be interested in sepsis if there is evidence of the burden in the population. They estimated that funders are likely (rated 4) to convene stakeholders' meetings on sepsis.

> *"The first thing I think is to generate the data. From my point of view, the data exist since the hospital structures are confronted with this problem. It is, therefore, necessary to do this collection work at the national level in order to measure the extent of the problem. We must involve training and research institutions because there are two elements in Africa, the absence of data but also the support, and for this point, it is necessary that the institutions know that there is this problem in order to focus on initial and continuing training and research institutions to generate data. All this comes at a cost–therefore, the Ministry of Finance and Budget, the insurance companies that pay for these diseases, must be involved. Once these pre-requisites have been established, the funder will be able to financially support the Country."*
> —Participant from an international funder institution.

3.3.4. Information

The media participants estimated the likelihood of disseminating evidence on sepsis, implementing public engagement activities on sepsis, and commemorating World Sepsis Day at highly likely (rated 5). However, a lack of awareness of sepsis was noted by the public and media, as explained by this journalist:

> *"As a journalist, I do not have much knowledge in the field of sepsis. It is a bit difficult to assist you in the improvement of community awareness of sepsis without a minimum of knowledge from my side. You have to think about involving the journalists by improving our knowledge of sepsis."*
> —Journalist at a media institution.

Our respondents also cited patients, and survivors of sepsis, as the most appropriate advocates. They could inform the community about sepsis and improve awareness.

> *"In my opinion, if the thing is well explained to the population and if the population is well exposed to this condition, I think that people will buy in and maybe lift any reservations they may have. If I can rely on the experience of COVID-19, many people*

did not believe in COVID-19 because they did not see sick people. Basically, we said, we don't see anyone sick with COVID-19. We do not see COVID-19 deaths so COVID-19 does not exist. One of the ways to overcome this reluctance of the populations would be to demonstrate to the populations that the disease does exist, that there are patients who exist, that there are people who suffer from it and also that there are a people who can die of it. That is to say, make it much more tangible or concrete at the level of the population."
—Journalist at a media institution.

3.4. Prioritising Sepsis in Gabon's Health System

On considering sepsis as a health priority, all but one participant agreed. The exceptional stakeholder thought that there is not enough evidence for such a conclusion.

"Considering the number of cases I have been confronted with, I would say no. But I might not be aware of what happens with other hospitals. With regard to what the various health services declare sepsis might be a real problem but not a priority."
—Public health specialist from an international funder institution.

The respondents also identified the categories of people or groups as main advocates or opponents of sepsis being set as a health priority. Suggested advocates included medical doctors, nurses, paediatricians, infectious diseases specialists, microbiologists, intensive care specialists, non-governmental organisation representatives, and sepsis survivors.

Despite all participants reporting that it is highly likely that sepsis could be considered a health priority in Gabon, they were quick to state that there is a need for strong evidence/data to convince the MOH.

4. DISCUSSION

We collected stakeholder opinions on prioritising sepsis in the Gabon health system. Our study has found that sepsis is perceived to not be a priority among most health system stakeholders. Although the WHO has declared that sepsis is a global health problem, there is variation in critical care resource allocation for the management of sepsis in LMICs [29,30]. This indicates that regions and countries do not necessarily follow the same priorities. As reported previously by other studies, the absence of a harmonised definition contributes to delayed prioritisation in many LMICs' health systems [31,32]. The situation is aggravated by the lack of local or country-level evidence to justify the adoption of sepsis as a priority.

Our study shows that most of the stakeholders perceived it to be highly likely that sepsis could be considered a health priority by Gabon's MOH if the evidence of its burden as a public health issue is demonstrated. The Global Sepsis Alliance and African Sepsis Alliance have advocated for high-quality evidence on sepsis in Africa. In the coming years, robust data on sepsis from many African countries will be published [33-35]. The research center in Gabon CERMEL has provided local pieces of evidence on the burden of sepsis [36-42]; however, there is a need for national-level evidence. These data could serve as a baseline to guide public policy. The lack of evidence in LMICs affects all levels of healthcare delivery from individual patient management to strategic planning at the health-system level [19].

Stakeholders in our study estimated that sepsis would be unlikely to be set as a quality indicator of the health system in Gabon. While there is no single indicator of health system performance, sepsis is a common and final pathway of many infections causing death, including COVID-19. It could help to have a good overview of infectious disease prevention strategies, including hand hygiene, immunisation programme, chemoprophylaxis, food safety, safe water and sanitation, injection safety and sterilisation, blood safety, and vector control [43,44].

One of the major findings of our study was that health workers and stakeholders strongly advise involving the community, non-governmental organization representatives, sepsis survivors, and the media in policy engagement activities. Media participants were relatively unaware of sepsis as a public health issue. Interestingly, the three most-mentioned diseases (malaria, tuberculosis, COVID-19) as health priorities are those well mediated by the health authority and more prevalent in Gabon. Opportunities and vehicles for raising awareness such as World Sepsis Day could be used to engage the media, which would then feed to wider stakeholder awareness.

The strengths of our study were that we interviewed representative stakeholders from all levels of the Gabon health system and that the interviews were all carried out by the same interviewer, ensuring consistent questioning, but the open question format also allowed for insight into the actual awareness.

However, due to the face-to-face interview method, some participants might have been reluctant to answer questions openly. We did not perform a focus group discussion to further appreciate the opinions of stakeholders. These limitations would not significantly affect our findings. To the best of our knowledge, this study is the first in Gabon and the Central Africa region to assess the stakeholder opinion on prioritising sepsis in the health system. Our study calls for performing nationwide epidemiological quantitative studies to investigate the burden of sepsis in Gabon, the cost-effectiveness of considering sepsis as a health priority, and the role of the community in preventing sepsis or reducing sepsis mortality. Beyond the national level, our study shows the need for international advocacy

for more funding for research on sepsis in LMICs, for adding sepsis to the WHO Global Burden of Disease Report.

5. CONCLUSIONS AND RECOMMENDATIONS

Despite calls across the international public health community for positioning sepsis as a global health priority, our study illustrates that sepsis is not yet within the health priorities of Gabon. There is a need for local, regional and national evidence to be generated by researchers and taken up by policymakers, focusing on linkages between sepsis and a country's existing health sector priorities. We recommend that the MOH uses this evidence to set sepsis indicators and reporting structures and develop appropriate sepsis guidelines for identification, management, and prevention. The media should be involved in the generation of a communications strategy that will contribute to the acceleration of sepsis awareness by key stakeholders. Future perspectives include conducting cost-effectiveness studies for setting sepsis as a global health priority, as well as implementation studies for improving stakeholder awareness and routine hospital-based sepsis data reporting.

Supplementary Materials

The following supporting information can be downloaded at: **https://www.mdpi.com/article/10.3390/healthcare10050877/s1**, File S1: questionnaire.

Author Contributions

Conceptualization: P.K., B.R.A., M.P.G., S.T.J. and J.R.; formal analysis: B.R.A.; investigation: B.R.A.; methodology: P.K., L.K. and B.R.A.; project administration: M.P.G., B.R.A. and A.A.A.; supervision: M.P.G. and A.A.A.; writing—original draft: B.R.A.; writing—review and editing: P.K., M.P.G., S.T.J., L.K. and J.R. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki. Ethical approval for the study was obtained from the Liverpool School of Tropical Medicine Research Ethics Committee (protocol number 19-020) and the CERMEL institutional ethics Committee (CEI-013/2020).

Informed Consent Statement

The study information sheet was provided to the participants. After reading the study information sheet, study participants signed a consent form to be interviewed and audio-recorded.

Data Availability Statement

The data presented in this study are available from the corresponding author upon request.

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REFERENCES

1. Singer, M.; Deutschman, C.S.; Seymour, C.W.; Shankar-Hari, M.; Annane, D.; Bauer, M.; Bellomo, R.; Bernard, G.R.; Chiche, J.-D.; Coopersmith, C.M.; et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA* 2016, *315*, 801–810.
2. Word Health organization (WHO) Calls for Global Action on Sepsis—Cause of 1 in 5 Deaths Worldwide. Available online: https://www.who.int/news/item/08-09-2020-who-calls-for-global-action-on-sepsis---cause-of-1-in-5-deaths-worldwide (accessed on 30 December 2021).
3. Majno, G. The ancient riddle of sigma eta psi iota sigma (Sepsis). *J. Infect. Dis.* 1991, *163*, 937–945.
4. Rudd, K.E.; Johnson, S.C.; Agesa, K.M.; Shackelford, K.A.; Tsoi, D.; Kievlan, D.R.; Colombara, D.V.; Ikuta, K.S.; Kissoon, N.; Finfer, S.; et al. Global, regional, and national sepsis incidence and mortality, 1990–2017: Analysis for the global burden of disease study. *Lancet* 2020, *395*, 200–211.
5. Angus, D.C.; van der Poll, T. Severe Sepsis and Septic Shock. *New Engl. J. Med.* 2013, *369*, 840–851.
6. Improving the Prevention, Diagnosis and Clinical Management of Sepsis. Available online: https://apps.who.int/iris/handle/10665/273181 (accessed on 30 December 2021).
7. Baelani, I.; Jochberger, S.; Laimer, T.; Otieno, D.; Kabutu, J.; Wilson, I.; Baker, T.; Dünser, M.W. Availability of critical care resources to treat patients with severe sepsis or septic shock in Africa: A self-reported, continent-wide survey of anaesthesia providers. *Crit. Care* 2011, *15*, R10
8. Bruijns, S.R.; Green, R.; Wallis, L.A. Sepsis as a cause of rising health care casualties in Africa. *Afr. J. Emerg. Med.* 2012, *2*, 47–48.
9. Tupchong, K.; Koyfman, A.; Foran, M. Sepsis, severe sepsis, and septic shock: A review of the literature. *Afr. J. Emerg. Med.* 2015, *5*, 127–135.
10. Critical Care Society of South Africa Working Group. National library of medicine severe sepsis and the role of novel therapeutic agents. Position Statement of the Critical Care Society of South Africa on severe sepsis and the role of novel therapeutic agents such as drotrecogin alfa (activated). *South Afr. Med. J. Suid-Afrik. Tydskr. Vir Geneeskd.* 2003, *93*, 416–417.
11. Velaphi, S.C.; Westercamp, M.; Moleleki, M.; Pondo, T.; Dangor, Z.; Wolter, N.; Von Gottberg, A.; Shang, N.; Demirjian, A.; Winchell, J.M.; et al. Surveillance for incidence and etiology of early-onset neonatal sepsis in Soweto, South Africa. *PLoS ONE* 2019, *14*, e0214077
12. Jacob, S.T.; Banura, P.; Baeten, J.M.; Moore, C.C.; Meya, D.; Nakiyingi, L.; Burke, R.; Horton, C.L.; Iga, B.; Wald, A.; et al. The impact of early monitored management on survival in hospitalized adult ugandan patients with severe sepsis: A prospective intervention study. *Crit. Care Med.* 2012, *40*, 2050–2058. [
13. Bird, L. APOL1 variants contribute to racial disparity in sepsis. *Nat. Rev. Immunol.* 2021, *21*, 759.
14. Reinhart, K.; Daniels, R.; Kissoon, N.; Machado, F.R.; Schachter, R.D.; Finfer, S. Recognizing sepsis as a global health priority—A WHO resolution. *N. Engl. J. Med.* 2017, *377*, 414–417.
15. Morton, B.; Stolbrink, M.; Kagima, W.; Rylance, J.; Mortimer, K. The early recognition and management of sepsis in Sub-Saharan African adults: A systematic review and meta-analysis. *Int. J. Environ. Res. Public Health* 2018, *15*, 2017.

16. Kwizera, A.; Adhikari, N.K.J.; Angus, D.C.; Dondorp, A.M.; Dünser, M.W.; Festic, E.; Haniffa, R.; Kissoon, N.; Martin-Loeches, I.; Lundeg, G. Recognition of Sepsis in resource-limited settings. In *Sepsis Management in Resource-Limited Settings*; Dondorp, A.M., Dünser, M.W., Schultz, M.J., Eds.; Springer: Cham, Switzerland, 2019; ISBN 978-3-030-03142-8.

17. Adegbite, B.R.; Edoa, J.R.; Rylance, J.; Jacob, S.T.; Kawale, P.; Adegnika, A.A.; Grobusch, M.P. Knowledge of health workers relating to sepsis awareness and management in Lambaréné, Gabon. *Acta Trop.* 2021, *219*, 105914.

18. Rubulotta, F.M.; Ramsay, G.; Parker, M.M.; Dellinger, R.P.; Levy, M.M.; Poeze, M.; on behalf of the Surviving Sepsis Campaign Steering Committee. An International survey: Public awareness and perception of sepsis. *Crit. Care Med.* 2009, *37*, 167–170.

19. Keeley, A.J.; Nsutebu, E. Improving sepsis care in Africa: An opportunity for change? *Pan Afr. Med. J.* 2021, *40*, 204.

20. Otu, A.; Elston, J.; Nsutebu, E. Sepsis in Africa: Practical steps to stem the tide. *Pan Afr. Med. J.* 2015, *21*, 323.

21. *Sepsis Is a Policy Issue: Reshaping Stakeholders' Perceptions of Sepsis in Africa*; African Institute for Development Policy—AFIDEP: Nairobi, Kenya, 2019.

22. Hyder, A.; Syed, S.; Puvanachandra, P.; Bloom, G.; Sundaram, S.; Mahmood, S.; Iqbal, M.; Hongwen, Z.; Ravichandran, N.; Oladepo, O.; et al. Stakeholder analysis for health research: Case studies from low- and middle-income countries. *Public Health* 2010, *124*, 159–166

23. Masefield, S.C.; Msosa, A.; Chinguwo, F.K.; Grugel, J. Stakeholder engagement in the health policy process in a low-income country: A qualitative study of stakeholder perceptions of the challenges to effective inclusion in Malawi. *BMC Health Serv. Res.* 2021, *21*, 984.

24. Gilson, L.; Erasmus, E.; Borghi, J.; Macha, J.; Kamuzora, P.; Mtei, G. using stakeholder analysis to support moves towards universal coverage: Lessons from the SHIELD Project. *Health Policy Plan.* 2012, *27*, i64–i76.

25. The African Research Collaboration on Sepsis (ARCS). Available online: https://www.arcsepsis.com/ (accessed on 30 December 2021).

26. Blair, E. Evaluating an Issue's Position on the Policy Agenda: The Bellwether Methodology. Available online: https://archive.globalfrp.org/evaluation/the-evaluation-exchange/issue-archive/advocacy-and-policy-change/evaluating-an-issue-s-position-on-the-policy-agenda-the-bellwether-methodology. (accessed on 30 December 2021).

27. QSR International Pty Ltd. *NVivo*, Released in March 2020; QSR International Pty Ltd.: Melbourne, Australia, 2020. Available online: https://www.qsrinternational.com/nvivo-qualitative-data-analysis-software/home(accessed on 17 February 2022).

28. Word Health Organization. *Strengthen Health Systems to Improve Health Products*; Word Health Organization: Geneva, Switzerland, 2007.

29. Austin, S.; Murthy, S.; Wunsch, H.; Adhikari, N.K.J.; Karir, V.; Rowan, K.; Jacob, S.T.; Salluh, J.; Bozza, F.A.; Du, B.; et al. Access to urban acute care services in high- vs. middle-income countries: An analysis of seven cities. *Intensive Care Med.* 2014, *40*, 342–352.

30. Mendsaikhan, N.; Begzjav, T.; Lundeg, G.; Brunauer, A.; Dünser, M.W. A nationwide census of ICU capacity and admissions in Mongolia. *PLoS ONE* 2016, *11*, e0160921.

31. Vincent, J.-L. The clinical challenge of sepsis identification and monitoring. *PLoS Med.* 2016, *13*, e1002022.

32. Adegbite, B.R.; Edoa, J.R.; Ndzebe Ndoumba, W.F.; Dimessa Mbadinga, L.B.; Mombo-Ngoma, G.; Jacob, S.T.; Rylance, J.; Hänscheid, P.T.; Adegnika, P.A.A.; Grobusch, P.M.P. A comparison of different scores for diagnosis and mortality prediction of adults with sepsis in low-and-middle-income countries: A systematic review and meta-analysis. *EClinicalMedicine* 2021, *42*, 101184

33. Global Sepsis Alliance. Available online: https://www.global-sepsis-alliance.org/ (accessed on 30 December 2021).

34. Rylance, J.; Nsutebu, E.; Mergani, K.O.; Grobusch, M.P.; Jacob, S.T. African sepsis alliance the african sepsis alliance: Making a difference in the fight against sepsis in Africa. *Infection* 2018, *46*, 733–734.

35. African Sepsis Alliance. Available online: https://www.africansepsisalliance.org/ (accessed on 30 December 2021).

36. Schmedding, M.; Adegbite, B.R.; Gould, S.; Beyeme, J.O.; Adegnika, A.A.; Grobusch, M.P.; Huson, M.A.M. A prospective comparison of quick sequential organ failure assessment, systemic inflammatory response syndrome criteria, universal vital assessment, and modified early warning score to predict mortality in patients with suspected infection in Gabon. *Am. J. Trop. Med. Hyg.* 2019, *100*, 202–208.

37. Moore, C.C.; Hazard, R.; Saulters, K.J.; Ainsworth, J.; Adakun, S.A.; Amir, A.; Andrews, B.; Auma, M.; Baker, T.; Banura, P.; et al. Derivation and validation of a Universal Vital Assessment (UVA) score: A tool for predicting mortality in adult hospitalised patients in sub-Saharan Africa. *BMJ Glob. Health* 2017, *2*, e000344.

38. Huson, M.A.M.; Wouters, D.; van Mierlo, G.; Grobusch, M.P.; Zeerleder, S.S.; van der Poll, T. HIV coinfection enhances complement activation during sepsis. *J. Infect. Dis.* 2015, *212*, 474–483.

39. Huson, M.A.M.; Zeerleder, S.S.; van Mierlo, G.; Wouters, D.; Grobusch, M.P.; van der Poll, T. HIV infection is associated with elevated nucleosomes in asymptomatic patients and during sepsis or Malaria. *J. Infect.* 2015, *71*, 266–269.

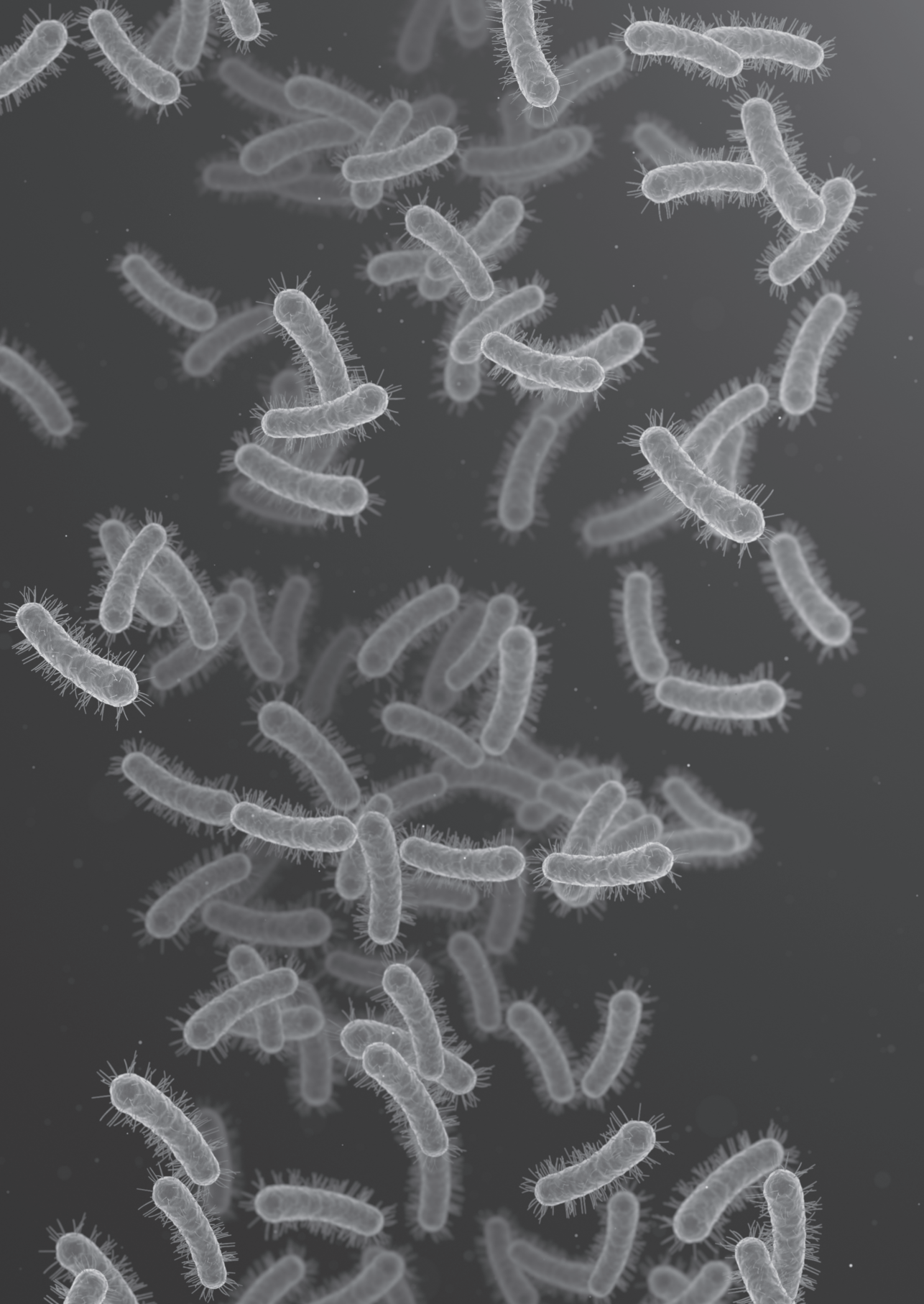
40. Huson, M.A.M.; Kalkman, R.; Grobusch, M.P.; van der Poll, T. Predictive value of the QSOFA score in patients with suspected infection in a resource-limited setting in Gabon. *Travel Med. Infect. Dis.* 2017, *15*, 76–77.

41. Huson, M.A.M.; Scicluna, B.P.; van Vught, L.A.; Wiewel, M.A.; Hoogendijk, A.J.; Cremer, O.L.; Bonten, M.J.M.; Schultz, M.J.; Franitza, M.; Toliat, M.R.; et al. The impact of HIV Co-infection on the genomic response to Sepsis. *PLoS ONE* 2016, *11*, e0148955.

42. Huson, M.A.M.; Kalkman, R.; Stolp, S.M.; Janssen, S.; Alabi, A.S.; Beyeme, J.O.; van der Poll, T.; Grobusch, M.P. The impact of HIV on presentation and outcome of bacterial sepsis and other causes of acute febrile illness in Gabon. *Infection* 2015, *43*, 443–451.

43. World Health Organization. *Geneva Recommended Strategies for the Prevention and Control of Communicable Diseases*; World Health Organization: Geneva, Switzerland, 2001.

44. Scherbaum, M.; Kösters, K.; Mürbeth, R.E.; Ngoa, U.A.; Kremsner, P.G.; Lell, B.; Alabi, A. Incidence, pathogens and resistance patterns of nosocomial infections at a rural hospital in Gabon. *BMC Infect. Dis.* 2014, *14*, 124.



Chapter 11

Summary and General Discussion

Summary and Discussion

In **Chapter 2,** we reported the higher prevalence of accessed non-communicable diseases in tuberculosis patients, with diabetes and hypertension being the most prevalent comorbidities. Almost half of the tuberculosis patients had at least dyslipidaemia, hypertension, diabetes, or obesity, with a majority newly diagnosed with hypertension and diabetes. Smoking was significantly associated with patient-related diagnostic delay (adjusted odds ratio [AOR] = 8.18; 95% CI = 3.67-19.56), a higher number of pulmonary TB signs and symptoms (AOR = 2.74; 95% CI = 1.18-6.73), and a higher sputum mycobacterial load (AOR = 3.18; 95% CI = 1.33-8.11), **Chapter 3**. Based on the finding of these studies, it is clear that clinicians should screen NCDs and their risk factors in TB patients. The association between non-communicable disease and tuberculosis treatment outcome and control has been reported by several studies [1–3]. NCDs comorbidity in tuberculosis patients is the second cause (after HIV) of mortality in tuberculosis patients [4–6]. There is more evidence that infectious diseases should be a pathway for earlier diagnosis of NCDs [7, 8]. The WHO recommends collaborative care for people with TB and NCDs [9]. **Chapters 2 and 3** of this thesis demonstrated the need for integrating the systematic screening of highly prevalent NCDs and risk factors such as diabetes, hypertension, obesity, and smoking in routine tuberculosis activities. In the community, regular screening of tuberculosis in smokers living in the endemic area such as Gabon should be initiated for earlier TB diagnosis to reduce its transmission. Smoking prevention or cessation activities' should be associated with TB control activities. Feasibility and cost-effectiveness studies would help to identify the most appropriate integration system according to country specificity.

In **Part 2** of this thesis, we reported the drug-resistant tuberculosis epidemiology in Gabon, and the lesson learned when implementing the short regiment treatment for the MDR-TB. The analysis of eight years of surveillance data of drug-resistant tuberculosis in Gabon (**Chapter 4**) showed a cumulative incidence of RR-TB at 17 (95% CI 15-19)/100,000 population over eight years with a worryingly high rate of primary drug-resistant tuberculosis (31% of cases). Many reasons explain this epidemic crisis of MDR-TB in Gabon. These reasons include the difficulty of implementing DOT outside of the hospital, the drug stock-outs, and the discontinuation of the treatment by patients. The inappropriate use of fluoroquinolones by health workers in tuberculosis patients is an additional reason for the increasing number of drug-resistant tuberculosis. Furthermore, the same difficulty (difficulty to implement DOT outside of the hospital, discontinuation due to lack of funds to cover transport and other treatment-related fees) accounted by patients on treatment for drug-sensitive TB were reported by those under second-line drug treatment. The Gabon National Tuberculosis Programme extended and decentralised the diagnosis of rifampicin resistance by providing each region with a GeneXpert machine.

This has improved the case finding, but there is a need to decentralise MDR-TB treatment, which so far is done only in Libreville (the capital) and in the south of the country at Bongolo and Lambaréné. The decentralisation should be followed by rigorous training and mentorship of health workers in charge of MDR-TB to avoid an exponential increase of XDR-TB due to inappropriate monitoring of MDR-TB treatment. We report in **Chapter 5** the lessons learned after the first short regimen treatment implementation of MDR-TB in Gabon. The short regimen showed 64% of treatment success with limited adverse events. This treatment was implemented by a mixed team of local and European medical researchers and physicians. The experience learned from the first MDR-TB patients is shared with the national referral TB hospital and would be used for extending the MDR-TB treatment to other regional hospitals in the country. There is a need to sustain case finding strategy and good quality treatment management and implementation. Since injectable drugs have been removed from the MDR-TB treatment,home-based DOT is one of the options to be considered. Most importantly, ongoing TB control activities in Gabon such as the BCG vaccine in newborns, laboratory diagnosis capacity improvement, free TB drug supply to patients and treatment adherence improvement strategies, HIV prevention and good management, and detection of TB cluster and sensitisation for earlier consultation in case of chronic coughing should be sustained.

In **Part 3,** we discussed improving the diagnosis and awareness of sepsis in Gabon. The systematic review and meta-analysis of clinical features, treatment outcomes, and mortality risk in **Chapter 6** confirmed how deadlier sepsis could be in general, specifically tuberculosis sepsis. We further reported how difficult the diagnosis of tuberculosis sepsis could be for HIV-non-infected patients. We found that 64% of tuberculosis sepsis patients succumbed to their disease, and in most of them, the diagnosis was confirmed only post-mortem. This is likely because the tuberculosis aetiology of sepsis is not coming earlier to the mind of clinicians as an alternative causative agent of a sepsis-like picture. On the other hand, its diagnosis is not easy without modern laboratory tools such as blood culture and molecular biology, which are still simply not available in many LMICs settings. Clinically, early signs of sepsis might be discrete and the road to worsening not obvious, with only the onset of complications or worsening of vital parameters alerting the non-proactive clinicians when it might already be too late. Hence – apart from strengthening the awareness and knowledge base of healthcare workers (**see Chapter 9**), there is a need to continue more research to improve earlier recognition of evolving sepsis in general, as there is, and probably will not be, a unique biomarker for the diagnosis of sepsis. The combination of many signs and scores is used to identify patients with sepsis. In **Chapters 7 and 8** we investigated the best score for the diagnosis of sepsis or predicting with accuracy its occurrence in adult patients. In **Chapter 7**, we compared the performance of qSOFA, SIRS, MEWS, and UVA scores in identifying patients with sepsis. This study showed that the UVA score performed best with an area under the receiving operator

curve (AUROC) of 0.90 (95% confidence interval [CI]: 0.78-1.0, P < 0.0001), outperforming qSOFA (AUROC 0.77; 95% CI: 0.63-0.91, P = 0.0003), MEWS (AUROC 0.72; 95% CI: 0.58-0.87, P = 0.01), and SIRS (AUROC 0.70; 95% CI: 0.52-0.88, P = 0.03). A composite qSOFA score applying the UVA thresholds for blood pressure and respiratory rate improved predictive ability in Gabon (AUROC 0.82; 95% CI: 0.68-0.96) but performed poorly in a different cohort from Malawi (AUROC 0.58; 95% CI: 0.51-0.64). We concluded that multicentre studies are needed to validate the qSOFA and UVA scores in various settings. To this end, in **Chapter 8**, we performed a meta-analysis including 27,237 patients from LMICs where we compared the performance of qSOFA, SIRS, MEWS, and UVA scores in identifying patients with sepsis. The results showed that qSOFA pooled sensitivity was 0.70 (95% CI 0.60-0.78), specificity 0.73 (95% CI 0.67-0.79), and AUC 0.77 (95% CI 0.72-0.82). SIRS pooled sensitivity, specificity and AUC were 0.88 (95% CI 0.79 -0.93), 0.34 (95% CI 0.25-0.44), and 0.69 (95% CI 0.50-0.83), respectively. MEWS pooled sensitivity, specificity and AUC were 0.70 (95% CI 0.57 -0.81), 0.61 (95% CI 0.42-0.77), and 0.72 (95% CI 0.64-0.77), respectively. UVA pooled sensitivity, specificity and AUC were 0.49 (95% CI 0.33 -0.65), 0.91(95% CI 0.84-0.96), and 0.76 (95% CI 0.44-0.93), respectively. We concluded that individual bedside scores could not identify sepsis patients with accuracy but could be combined to improve their performance. Based on these results, the combination of SIRS and qSOFA might improve the diagnosis of sepsis. We suggest using SIRS as the first triage score, followed by the qSOFA or UVA score. However, this needs to be confirmed through a well-designed multicentre study. The finding from **Chapters 7** and **8** showed the need to conduct further research to identify the best bedside tool for the early diagnosis of sepsis. Studies from LMCs should be encouraged in general as they would consider the epidemiological specificities. To this end, it is important to raise the awareness of health workers and stakeholders about the diagnosis, and management of sepsis as reported in **Chapter 9,** where we found that 74% (85/115) of health workers had never heard about the quick Sequential Organ Failure Assessment (qSOFA) score. Fifty-six of 115 (48.7%) responded that sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection'. While thirty health workers interviewed reported knowledge of the qSOFA score, 13% (15/115) recognised its three criteria. The study showed considerable knowledge gaps regarding sepsis among health workers. The consequences of a lack of knowledge of the diagnostic criteria of sepsis are misdiagnosis and, more important, a high risk of mortality of patients due to the absence of close monitoring of vital signs or delay in management [10, 11]. The lack of health workers' awareness is due to the absence of national guidelines for managing sepsis in Gabon. We suggested establishing periodic up-to-date training to improve sepsis knowledge. This will be better done if sepsis is considered a global health priority. Knowing the role of health policy authorities in enhancing the understanding and awareness of health workers and the community, the qualitative study (**Chapter 10**) collecting the opinions of health policy

stakeholders on prioritising sepsis confirmed sepsis is not yet a global health priority in Gabon. Most health workers recognised that sepsis could be prioritised only based on the evidence of its burden at the local and national levels. **Chapters 9 and 10** call for performing many other epidemiological studies and, most importantly, advocating for standardised sepsis data reports in hospitals. This thesis serves as a baseline for initiating national-level sepsis advocacy. Continuous training of health workers on sepsis care and its codification data report system would reduce its burden. In the meantime, effective vaccinations, infection control and prevention activities, against deadlier infectious diseases causing sepsis such as COVID-19, Ebola and Lassa fever, malaria, tuberculosis, HIV and others should be improved and sustained.

FUTURE PERSPECTIVE

Despite being known for decades, tuberculosis and sepsis remain health problems. Therefore, efforts to reduce their burden in Gabon deserve to be questioned. This thesis has clearly shown the areas not yet sufficiently explored to reduce the burden of tuberculosis and sepsis in Gabon.

Regarding tuberculosis,
The future perspective would be to perform feasibility and cost-effectiveness studies on integrating NCDs screening in TB routine activities in all referral hospitals in Gabon. A follow-up study should be conducted to assess the effect of diabetes and other NCDs on the treatment outcome of TB.

Given the worrying prevalence of drug-resistant TB in Gabon, the perspective will be to conduct:

- Studies to identify barriers to treatment adherence and interventions to improve adherence to TB treatment, particularly among patients with MDR-TB;
- Feasibility studies of decentralising the treatment of sensitive and drug-resistant tuberculosis in all regions of the country; and
- Feasibility and cost-effectiveness studies of implementing home-based DOT for MDR-TB.

Regarding sepsis, further research is still needed to facilitate the diagnosis of sepsis, especially in countries with limited resources where it is not always possible to obtain all laboratory results and/or in a reasonable time. However, the awareness would be significantly improved if health policymakers and stakeholders were engaged. Therefore, future research should be interesting:

- To identify interventions, communication, and evidence needed to engage health policy stakeholders to consider sepsis as a global health priority;

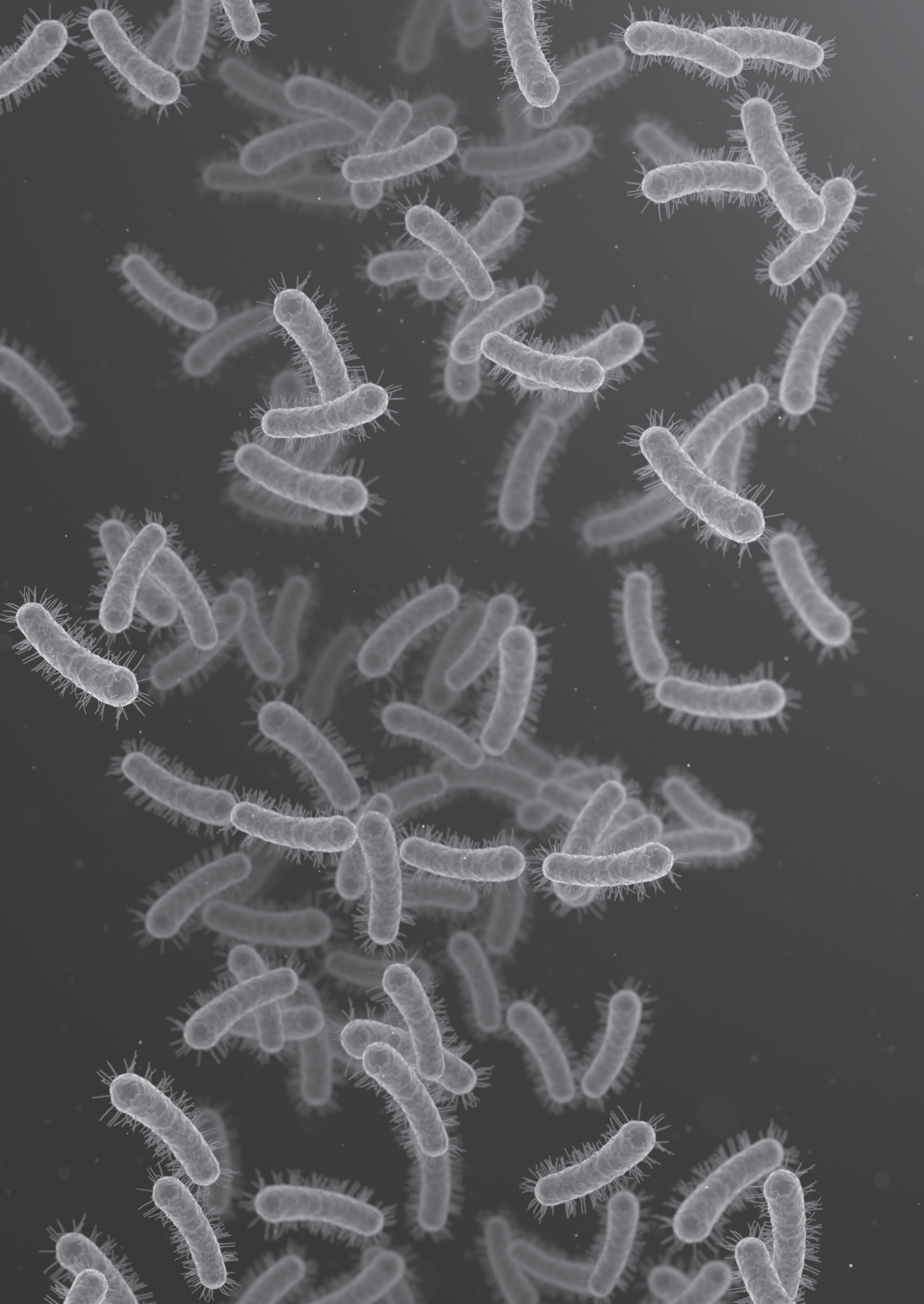
- To perform national or regional level studies on the incidence of sepsis in Gabon; and
- To contribute to international, multi-centre studies aiming to identify the best biomarkers that can unequivocally identify a patient with sepsis and their likely outcome.

CONCLUSION

We described in this thesis the burden of some TB epidemiological contributing factors that are so far under-controlled in Gabon. To reach the objective of "end the global TB epidemic" by 2035, WHO suggests strategies that target a 90% reduction in patients suffering from TB, and a 95% reduction in deaths. Integrating patient-centred care and prevention, and bold policies and supportive systems are two essential pillars that could be used. The high burden of NCDs and factors in TB patients requires urgently integrating of patient-centred care into TB management activities. Screening of NCDs in TB patients would detect earlier comorbidities and improve the patient's treatment outcomes. Screening TB in smokers and patients consulting for NCDs such as diabetes might improve case findings. This is mainly important to reduce the transmission of drug-resistant tuberculosis. Case findings combined with good management of MDR-TB treatment would significantly reduce the burden of drug-resistant tuberculosis in Gabon. Similar strategies apply to reduce the burden of sepsis. It is underdiagnosed or underreported in many LMICs. This thesis confirms the need to raise awareness of sepsis and engage policymakers for bold policies and report systems, as this would improve sepsis management and its burden in Gabon.

REFERENCES

1. Puchner KP, Rodriguez-Fernandez R, Oliver M, Solomos Z. Noncommunicable diseases and tuberculosis: Anticipating the impending global storm. Glob Public Health. 2019;14:1372–81.
2. Asturiningtyas IP, Mulyantoro DK, Kusrini I, Ashar H. Non-communicable disease comorbidity and multimorbidity among people with tuberculosis in Indonesia. Ann Trop Med Public Health. 2021;24.
3. White LV, Edwards T, Lee N, Castro MC, Saludar NR, Calapis RW, et al. Patterns and predictors of comorbidities in Tuberculosis: A cross-sectional study in the Philippines. Sci Rep. 2020;10:4100.
4. Viana PV de S, Paiva NS, Villela DAM, Bastos LS, Bierrenbach AL de S, Basta PC. Factors associated with death in patients with tuberculosis in Brazil: Competing risks analysis. PLOS ONE. 2020;15:e0240090.
5. Alavi-Naini R, Moghtaderi A, Metanat M, Mohammadi M, Zabetian M. Factors associated with mortality in tuberculosis patients. J Res Med Sci Off J Isfahan Univ Med Sci. 2013;18:52–5.
6. Simonovska L, Trajcevska M, Mitreski V, Simonovska I. The causes of death among patients with tuberculosis. Eur Respir J. 2015;46 suppl 59.
7. Foo CD, Shrestha P, Wang L, Du Q, García-Basteiro AL, Abdullah AS, et al. Integrating tuberculosis and non-communicable diseases care in low- and middle-income countries (LMICs): A systematic review. PLOS Med. 2022;19:e1003899.
8. Ogoina D, Onyemelukwe GC. The role of infections in the emergence of non-communicable diseases (NCDs): Compelling needs for novel strategies in the developing world. J Infect Public Health. 2009;2:14–29.
9. Word Health Organization. TB and diabetes. WHO. Geneva; 2021. https://www.who.int/publications/digital/global-tuberculosis-report-2021/featured-topics/country-success-stories
10. Holanda AMC, de Amorim MMR, Bezerra SMB, Aschoff LMS, Katz L. Risk factors for death in patients with sepsis admitted to an obstetric intensive care unit. Medicine (Baltimore). 2020;99:e23566.
11. Whiles BB, Deis AS, Simpson SQ. Increased Time to Initial Antimicrobial Administration Is Associated With Progression to Septic Shock in Severe Sepsis Patients. Crit Care Med. 2017;45:623–9.



Chapter 12

Summary in Dutch/ Nederlandse Samenvatting

Samenvatting en discussie

In **deel 1** bespraken we de last van niet-overdraagbare ziekten bij tuberculose (tbc)-patiënten.

In **hoofdstuk 2** rapporteerden we de hogere prevalentie van niet-overdraagbare ziekten bij tbc-patiënten, met diabetes en hypertensie als meest voorkomende co-morbiditeiten. Bijna de helft van de tbc-patiënten had dyslipidemie, hypertensie, diabetes of obesitas, waarbij een meerderheid gediagnosticeerd werd met zowel hypertensie als diabetes. Roken was significant geassocieerd met patiënt gerelateerde factoren leidend tot het verlaat stellen van de tbc-diagnose (adjusted odds ratio [AOR] = 8,18; 95% CI = 3,67-19,56), een hoger aantal pulmonale tbc-symptomen en diagnostische kenmerken (AOR = 2,74; 95% CI = 1,18-6,73) en een hogere mycobacteriële belasting in het sputum (AOR = 3,18; 95% CI = 1,33-8,11) (**Hoofdstuk 3**). Op basis van de bevindingen van deze studies is het duidelijk dat clinici tbc-patiënten moeten screenen op niet-overdraagbare ziekten en bijbehorende risicofactoren. Het verband tussen niet-overdraagbare ziekten en het resultaat van de behandeling voor en de screening op tbc is door verschillende studies gerapporteerd [1–3]. Co-morbiditeiten ten gevolge van niet-overdraagbare ziekten bij tbc-patiënten is na het humaan immunodeficiëntievirus (hiv) de tweede oorzaak van sterfte onder tbc-patiënten [4–6]. Er zijn meer aanwijzingen dat infectieziekten een aanleiding moeten zijn voor vroegdiagnostiek naar niet-overdraagbare ziekten [7, 8]. De Wereldgezondheidsorganisatie (WHO) beveelt gezamenlijke zorg aan voor mensen met tbc en niet-overdraagbare ziekten [9]. De **hoofdstukken 2 en 3** van dit proefschrift hebben de noodzaak aangetoond van de integratie van de systematische screening van veel voorkomende niet-overdraagbare ziekten en risicofactoren zoals diabetes, hypertensie, obesitas en roken in routinematige tbc-zorg. Haalbaarheids- en kosteneffectiviteitsstudies zouden helpen bij het vaststellen van de meest geschikte manier van integreren van deze zorg, afhankelijk van de specifieke omstandigheden van het land.

In **deel 2** van dit proefschrift hebben wij verslag uitgebracht over de epidemiologie van resistente tbc in Gabon en over de lessen die zijn geleerd bij de toepassing van korte behandelregimes voor multiresistente tuberculose (mdr-tbc).

In **hoofdstuk 4** hebben wij verslag gedaan van een gegevensanalyse van acht jaar resistente tbc in Gabon. Hieruit bleek een cumulatieve incidentie van rifampicine resistente tuberculose (rr-tbc) van 17 (95% CI 15-19)/100.000 inwoners over acht jaar met een toename van mdr-tbc-gevallen en een verontrustend aantal pre-extensieve resistente (xdr) - en xdr-tbc-gevallen in de loop van de tijd. Meerdere redenen verklaren het vele voorkomen van mdr-tbc in Gabon. Deze redenen zijn onder meer de beperkte mogelijkheid om *direct observed treatment* (DOT) buiten het ziekenhuis toe te passen, de beperkte voorraad geneesmiddelen en het afbreken van de behandeling door patiënten. Het ongepaste gebruik van fluorochinolonen door gezondheidswerkers bij

tbc-patiënten is een bijkomende reden voor de toename van het aantal resistente tbc-gevallen. Bovendien werden dezelfde barrières (beperkte mogelijkheden om DOT buiten het ziekenhuis toe te passen en het stoppen van de behandeling wegens gebrek aan middelen om vervoer- en andere behandeling gerelateerde kosten te dekken) gemeld door patiënten die werden behandeld voor drugsgevoelige tbc en degenen die een tweedelijnsbehandeling met geneesmiddelen ondergingen. Het nationale tbc-programma van Gabon heeft de diagnose van rifampicineresistentie uitgebreid en gedecentraliseerd door elke regio te voorzien van een GeneXpert-machine. Hierdoor is de opsporing van gevallen verbeterd, maar de mdr-tbc-behandeling, die tot dusver alleen in Libreville (de hoofdstad) en in het zuiden van het land in Bongolo en Lambaréné plaatsvindt, moet worden gedecentraliseerd. De decentralisatie moet worden gevolgd door een rigoureuze opleiding en begeleiding van gezondheidswerkers betrokken bij mdr-tbc zorg, om een exponentiële toename van xdr-tbc als gevolg van een onjuiste monitoring van de mdr-tbc-behandeling te voorkomen. In **hoofdstuk 5** wordt verslag gedaan van de lessen die zijn geleerd na de eerste implementatie van een kort behandelregime voor mdr-tbc in Gabon. Het korte behandelregime was succesvol in 64% van de gevallen met een beperkt aantal bijwerkingen. De behandeling werd geïmplementeerd door een team van lokale en Europese medische onderzoekers en artsen. De ervaring die met de nieuwe behandeling bij de mdr-tbc-patiënten is opgedaan wordt gedeeld met het nationale verwijzingsziekenhuis voor tbc en zal naar verwachting worden gebruikt om de mdr-tbc-behandeling uit te breiden in andere regionale ziekenhuizen in het land. Er is verder behoefte aan een strategie voor het opsporen van tbc-gevallen en een kwalitatief goed beheer en uitvoering van de behandeling. Thuis uitgevoerde DOT is een van de opties die in haalbaarheids- en implementatiestudies moeten worden overwogen.

In **deel 3** bespraken we het verbeteren van de diagnose en het bewustzijn van sepsis in Gabon. De systematische review en meta-analyse van klinische kenmerken, behandelingsresultaten, en mortaliteitsrisico in **hoofdstuk 6** bevestigden hoe moeilijk de diagnose van sepsis in het algemeen kan zijn en specifiek bij tbc-sepsis bij niet-hiv geïnfecteerde patiënten. Wij vonden dat 64% van de tbc-sepsis patiënten aan hun ziekte bezweken en bij de meesten van hen werd de diagnose pas post-mortem bevestigd. Dit is waarschijnlijk omdat de etiologie van tbc-sepsis beperkt bekend is bij clinici en tbc niet wordt overwogen als een veroorzaker van een sepsisachtig beeld. Bovendien is de diagnose niet gemakkelijk zonder moderne laboratoriuminstrumenten zoals bloedkweek en moleculaire biologie te stellen en deze zijn in vele lage- en middeninkomenslanden (LMIL) nog niet beschikbaar. Klinisch gezien kunnen de eerste tekenen van sepsis discreet zijn en is initiële verslechtering niet altijd evident zichtbaar, waardoor pas het optreden van complicaties of de verslechtering van vitale parameters de niet-proactieve clinici waarschuwen op een laat moment in het ziekteverloop. Vandaar dat er naast het verbeteren van kennis van zorgverleners (zie **hoofdstuk 9**) behoefte is aan meer

onderzoek om de vroegtijdige herkenning van zich ontwikkelende sepsis in het algemeen te verbeteren. Dit zeker gezien er geen unieke bio marker voor de diagnose van sepsis is en deze er waarschijnlijk ook niet zal komen. De combinatie van vele tekenen en scores wordt gebruikt om patiënten met sepsis te identificeren. In de **hoofdstukken 7 en 8** hebben wij onderzocht wat de beste score is voor de diagnose van sepsis om met nauwkeurigheid het optreden van sepsis bij volwassen patiënten vast te kunnen stellen. In **hoofdstuk 7** vergeleken we de prestaties van qSOFA, SIRS, MEWS, en UVA-scores bij het identificeren van patiënten met sepsis. Deze studie toonde aan dat de UVA-score het beste presteerde met een *area under the receiving operator curve (*AUROC) van 0.90 (95% betrouwbaarheidsinterval [CI]: 0.78-1.0, P < 0.0001), beter dan qSOFA (AUROC 0,77; 95% CI: 0,63-0,91, P = 0,0003), MEWS (AUROC 0,72; 95% CI: 0,58-0,87, P = 0,01) en SIRS (AUROC 0,70; 95% CI: 0,52-0,88, P = 0,03). Een samengestelde qSOFA-score die de UVA-drempels voor bloeddruk en ademhalingsfrequentie toepaste, verbeterde de voorspellende waarde in Gabon (AUROC 0,82; 95% CI: 0,68-0,96), maar presteerde slecht in een ander cohort uit Malawi (AUROC 0,58; 95% CI: 0,51-0,64). Wij concluderen dat multicentrische studies nodig zijn om de qSOFA en UVA-scores in verschillende populaties en omstandigheden te valideren. Hiertoe hebben wij in **hoofdstuk 8** een meta-analyse uitgevoerd met 27.237 patiënten uit LMIL, waarbij wij de qSOFA, SIRS, MEWS, en UVA-scores hebben vergeleken wat betreft het accuraat identificeren van patiënten met sepsis. De resultaten toonden aan dat qSOFA gepoolde sensitiviteit 0,70 (95% CI 0,60-0,78) was, specificiteit 0,73 (95% CI 0,67-0,79) en AUC 0,77 (95% CI 0,72-0,82). SIRS gepoolde sensitiviteit, specificiteit en AUC waren respectievelijk 0,88 (95% CI 0,79 -0,93), 0,34 (95% CI 0,25-0,44) en 0,69 (95% CI 0,50-0,83). MEWS gepoolde sensitiviteit, specificiteit en AUC waren respectievelijk 0,70 (95% CI 0,57 -0,81), 0,61 (95% CI 0,42-0,77) en 0,72 (95% CI 0,64-0,77). De gepoolde sensitiviteit, specificiteit en AUC van de UVA waren respectievelijk 0,49 (95% CI 0,33 -0,65), 0,91 (95% CI 0,84-0,96) en 0,76 (95% CI 0,44-0,93). Wij concludeerden dat individuele scores uitgevoerd aan bed sepsis patiënten niet met nauwkeurigheid konden identificeren, maar wel gecombineerd konden worden om hun prestatie te verbeteren. Gebaseerd op deze resultaten zou de combinatie van SIRS en qSOFA de diagnose van sepsis kunnen verbeteren. Wij stellen voor om SIRS als eerste triage score te gebruiken, gevolgd door de qSOFA of UVA-score. Dit moet echter worden bevestigd door een goed opgezette multicentrische studie. Uit de bevindingen van de **hoofdstukken 7 en 8** blijkt dat verder onderzoek nodig is om het beste instrument aan het bed voor de vroege diagnose van sepsis te bepalen. Studies van LMIL moeten in het algemeen worden aangemoedigd, aangezien zij rekening houden met de specifieke epidemiologische kenmerken van de setting. Ook is het van belang dat gezondheidswerkers en andere betrokkenen zich meer bewust worden van sepsis.

In **hoofdstuk 9** beschreven we de kennis van zorgmedewerkers over het bewustzijn van en omgaan met sepsis in Lambaréné. We ontdekten dat 74% (85/115) van de

zorgmedewerkers nog nooit had gehoord over de *quick Sequential Organ Failure Assessment* (qSOFA) score. 56 van de 115 gezondheidswerkers (48,7%) antwoordden dat sepsis "een levensbedreigende orgaanschade is die wordt veroorzaakt door een ontregelde reactie van de gastheer op infectie". Dertig ondervraagde gezondheidswerkers gaven aan op de hoogte te zijn van de qSOFA-score en maar 13% (15/115) herkenden de drie criteria. De studie toonde aan dat de kennis over sepsis bij zorgmedewerkers aanzienlijk tekortschiet. De gevolgen van een gebrek aan kennis van de diagnostische criteria van sepsis leidt tot een verkeerde diagnose met mogelijk een hoger risico op sterfte van patiënten als gevolg van het niet nauwlettend in de gaten houden van de vitale functies of vertraging in de behandeling [10, 11]. Het gebrek aan kennis bij de zorgmedewerkers is te wijten aan het ontbreken van nationale richtlijnen voor sepsis in Gabon. Wij stelden voor om periodieke bijscholing te organiseren om de kennis van sepsis te verbeteren. Dit zal beter lukken als sepsis als een wereldwijde gezondheidsprioriteit wordt beschouwd. Wetende welke rol autoriteiten op het gebied van gezondheidsbeleid spelen bij het vergroten van het begrip van zorgmedewerkers en de algemene populatie over sepsis, bevestigde de kwalitatieve studie (**Hoofdstuk 10**). In deze studie werden de meningen van belanghebbenden op het gebied van gezondheidsbeleid over het prioriteren van sepsis verzameld en werd duidelijk dat sepsis nog geen nationale gezondheidsprioriteit is in Gabon. De meeste gezondheidsmedewerkers erkenden dat er alleen prioriteit aan sepsis kan worden gegeven op basis van het bewijs van de last ervan op lokaal en nationaal niveau. **Hoofdstuk 9** roept op tot het uitvoeren van vele andere epidemiologische studies en als belangrijkste voor het pleiten voor gestandaardiseerde sepsis gegevensrapporten in ziekenhuizen. Deze dissertatie dient als basis voor het initiëren van pleitbezorging op nationaal niveau voor verbeteren van zorg voor sepsis. Voortdurende scholing van gezondheidswerkers op het gebied van sepsiszorg en het verbeteren van het coderingssysteem voor gegevensrapportage van sepsis zou de last van deze ziekte verminderen.

TOEKOMSTPERSPECTIEF

Ondanks het feit dat tbc en sepsis al tientallen jaren bekende ziektebeelden zijn blijven zij impactvolle gezondheidsproblemen. Daarom moeten de inspanningen om hun last in Gabon te verminderen kritische worden geëvalueerd. Deze dissertatie heeft duidelijk aangetoond welke gebieden uitgebreider onderzocht moeten worden om de impact van tbc en sepsis in Gabon te verminderen.

Met betrekking tot tbc, in de toekomst zouden haalbaarheids- en kosteneffectiviteitsstudies kunnen worden uitgevoerd met betrekking tot de integratie van screening op niet-overdraagbare ziekten in de routine zorg voor tbc in alle verwijzingsziekenhuizen in Gabon.

Gezien de verontrustende prevalentie van resistente tbc in Gabon, zal het perspectief zijn:

- Studies ter identificatie van belemmeringen voor therapietrouwheid en interventies om therapietrouwheid bij tbc-behandeling te verbeteren, met name bij patiënten met mdr-tbc;
- Haalbaarheidsstudies gericht op de decentralisatie van de behandeling van gevoelige en resistente tbc in alle regio's van het land;
- Haalbaarheids- en kosteneffectiviteitsstudies van de implementatie van thuis uitgevoerde DOT voor mdr-tbc.

Wat sepsis betreft is verder onderzoek nodig om de diagnose van sepsis te vergemakkelijken, vooral in landen met beperkte middelen waar het niet altijd mogelijk is alle laboratoriumresultaten te verkrijgen en/of binnen een redelijke termijn te verzamelen. De bekendheid van sepsis zou aanzienlijk worden verbeterd als beleidsmakers op het gebied van de gezondheidszorg en belanghebbenden meer betrokken zouden zijn. Toekomstig onderzoek dat in die context interessant zou zijn:

- Het identificeren van interventies, communicatie en bewijsmateriaal dat nodig is om belanghebbenden bij het gezondheidsbeleid ertoe te bewegen sepsis als een gezondheidsprioriteit te beschouwen;
- Het verrichten van studies op nationaal of regionaal niveau over de incidentie van sepsis in Gabon;
- Bijdragen aan internationale, multicenter studies die gericht zijn op het identificeren van de beste bio markers die een patiënt met sepsis ondubbelzinnig kunnen identificeren en hun waarschijnlijke uitkomst.

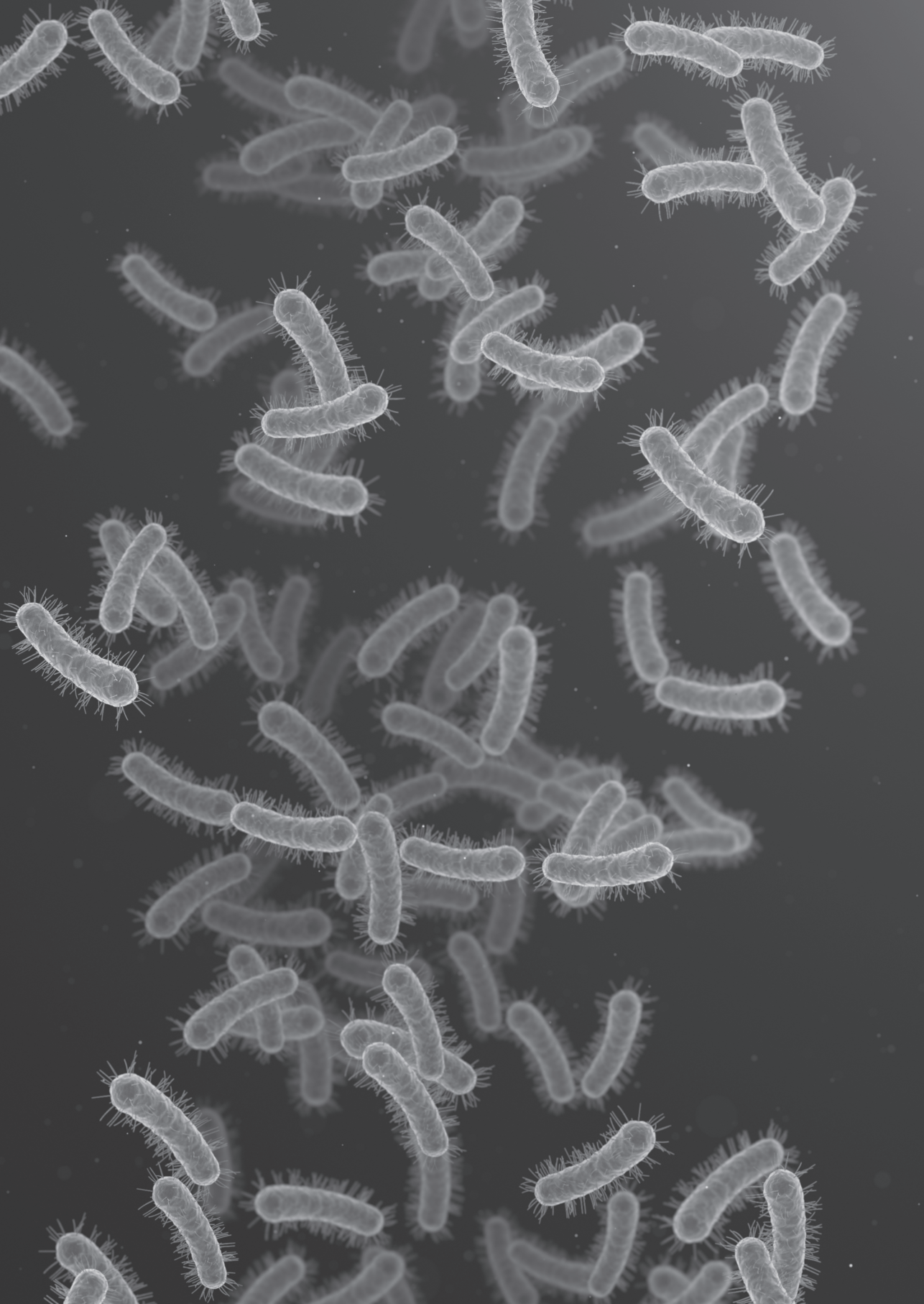
CONCLUSIE

In deze dissertatie hebben we de last beschreven van een aantal epidemiologische factoren die tot tbc bijdragen en die tot dusver in Gabon onvoldoende onder controle zijn. Om de doelstelling van "beëindiging van de wereldwijde tbc-epidemie" tegen 2035 te bereiken, stelt de WHO strategieën voor die gericht zijn op een vermindering van het aantal tbc-patiënten met 90% en van het aantal sterfgevallen door tbc met 95% in 2035. Integratie van patiëntgerichte zorg en preventie en doortastend beleid en ondersteunende systemen zijn twee essentiële pijlers die kunnen worden gebruikt. De hoge last van niet-overdraagbare aandoeningen en bijbehorende risicofactoren bij tbc-patiënten vereisen dringend de integratie van patiëntgerichte zorg voor tbc. Screening voor niet-overdraagbare ziekten bij tbc-patiënten zou co-morbiditeiten in een vroeger stadium opsporen en de behandelingsresultaten voor de patiënt verbeteren. Screening voor tbc

bij rokers en patiënten die worden behandeld voor een niet-overdraagbare aandoeningen, zoals diabetes, kan leiden tot betere tbc-casusbevindingen. Dit is vooral van belang om de overdracht van geneesmiddelenresistente tbc te beperken. Betere casusbevinding in combinatie met een goed beheer van de mdr-tbc-behandeling zou de last van resistente tbc in Gabon aanzienlijk kunnen verminderen. Soortgelijke strategieën gelden om de last van sepsis te verminderen. Deze wordt in veel LMIL onder gediagnosticeerd of gerapporteerd. Deze dissertatie bevestigt de noodzaak om het bewustzijn van sepsis te vergroten en beleidsmakers te betrekken bij verbeterd beleid en rapportagesystemen, aangezien dit de last van sepsis in Gabon zou verminderen.

REFERENCES

1. Puchner KP, Rodriguez-Fernandez R, Oliver M, Solomos Z. Noncommunicable diseases and tuberculosis: Anticipating the impending global storm. Glob Public Health. 2019;14:1372–81.
2. Asturiningtyas IP, Mulyantoro DK, Kusrini I, Ashar H. Non-communicable disease comorbidity and multimorbidity among people with tuberculosis in Indonesia. Ann Trop Med Public Health. 2021;24.
3. White LV, Edwards T, Lee N, Castro MC, Saludar NR, Calapis RW, et al. Patterns and predictors of comorbidities in Tuberculosis: A cross-sectional study in the Philippines. Sci Rep. 2020;10:4100.
4. Viana PV de S, Paiva NS, Villela DAM, Bastos LS, Bierrenbach AL de S, Basta PC. Factors associated with death in patients with tuberculosis in Brazil: Competing risks analysis. PLOS ONE. 2020;15:e0240090.
5. Alavi-Naini R, Moghtaderi A, Metanat M, Mohammadi M, Zabetian M. Factors associated with mortality in tuberculosis patients. J Res Med Sci Off J Isfahan Univ Med Sci. 2013;18:52–5.
6. Simonovska L, Trajcevska M, Mitreski V, Simonovska I. The causes of death among patients with tuberculosis. Eur Respir J. 2015;46 suppl 59.
7. Foo CD, Shrestha P, Wang L, Du Q, García-Basteiro AL, Abdullah AS, et al. Integrating tuberculosis and non-communicable diseases care in low- and middle-income countries (LMICs): A systematic review. PLOS Med. 2022;19:e1003899.
8. Ogoina D, Onyemelukwe GC. The role of infections in the emergence of non-communicable diseases (NCDs): Compelling needs for novel strategies in the developing world. J Infect Public Health. 2009;2:14–29.
9. Word Health Organization. TB and diabetes. WHO.Geneva; 2021. https://www.who.int/publications/digital/global-tuberculosis-report-2021/featured-topics/country-success-stories
10. Holanda AMC, de Amorim MMR, Bezerra SMB, Aschoff LMS, Katz L. Risk factors for death in patients with sepsis admitted to an obstetric intensive care unit. Medicine (Baltimore). 2020;99:e23566.
11. Whiles BB, Deis AS, Simpson SQ. Increased Time to Initial Antimicrobial Administration Is Associated With Progression to Septic Shock in Severe Sepsis Patients. Crit Care Med. 2017;45:623–9.



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List of publication

First and last authorships

1. Schmedding M, **Adegbite BR***, Gould S, Beyeme JO, Adegnika AA, Grobusch MP, Huson MAM. A Prospective Comparison of Quick Sequential Organ Failure Assessment, Systemic Inflammatory Response Syndrome Criteria, Universal Vital Assessment, and Modified Early Warning Score to Predict Mortality in Patients with Suspected Infection in Gabon. Am J Trop Med Hyg. 2019 Jan;100(1):202-208
2. Ateba-Ngoa U, Edoa JR, **Adegbite BR***, Rossatanga EG, Madiou D, Mfoumbi A, Mevyann C, Achimi Agbo P, Mahoumbou J, Gould S, Lell B, Adegnika AA, Köhler C, Kremsner PG, Massinga-Loembe M, Alabi A, Grobusch MP. Implementation of multidrug-resistant tuberculosis (MDR-TB) treatment in Gabon: lessons learnt from the field. Infection. 2019 Oct;47(5):811-816
3. **Adegbite BR**, Edoa JR, Honkpehedji YJ, Zinsou FJ, Dejon-Agobe JC, Mbong-Ngwese M, Lotola-Mougueni F, Koehne E, Lalremruata A, Kreidenweiss A, Nguyen TT, Kun J, Agnandji ST, Lell B, Safiou AR, Obone Atome FA, Mombo-Ngoma G, Ramharter M, Velavan TP, Mordmüller B, Kremsner PG, Adegnika AA. Monitoring of efficacy, tolerability and safety of artemether-lumefantrine and artesunate-amodiaquine for the treatment of uncomplicated Plasmodium falciparum malaria in Lambaréné, Gabon: an open-label clinical trial. Malar J. 2019 Dec 16;18(1):424
4. **Adegbite BR**, Edoa JR, Achimi Agbo P, Dejon-Agobé JC, N Essone P, Lotola-Mougeni F, Mbong Ngwese M, Mfoumbi A, Mevyann C, Epola M, Zinsou JF, Honkpehedji YJ, Agnandji ST, Kremsner PG, Alabi AS, Adegnika AA, Grobusch MP.Epidemiological, Mycobacteriological, and Clinical Characteristics of Smoking Pulmonary Tuberculosis Patients, in Lambaréné, Gabon: A Cross-Sectional Study. Am J Trop Med Hyg. 2020 Dec;103(6)
5. **Adegbite BR**, Edoa JR, Ndzebe Ndoumba WF, Dimessa Mbadinga LB, Mombo-Ngoma G, Jacob ST, Rylance J, Hänscheid T, Adegnika AA, Grobusch MP A comparison of different scores for diagnosis and mortality prediction of adults with sepsis in Low-and-Middle-Income Countries: a systematic review and meta-analysis. EClinicalMedicine. 2021 Oct 30;42:101184
6. **Adegbite BR**, Edoa JR, Rylance J, Jacob ST, Kawale P, Adegnika AA, Grobusch MP. Knowledge of health workers relating to sepsis awareness and management in Lambaréné, Gabon. Acta Trop. 2021 Jul;219:105914.
7. **Adegbite BR**, Edoa JR, Agbo Achimi Abdul J, Epola M, Mevyann C, Dejon-Agobé JC, Zinsou JF, Honkpehedji YJ, Mpagama SG, Alabi AS, Kremsner PG, Klipstein-Grobusch K, Adegnika AA, Grobusch MP. Non-communicable disease comorbidity and associated factors in tuberculosis patients: A cross-sectional study in Gabon. EClinicalMedicine. 2022 Feb 27;45:101316.
8. **Adegbite BR**, Edoa JR, Schaumburg F, Alabi AS, Adegnika AA, Grobusch MP.Knowledge and perception on antimicrobial resistance and antibiotics prescribing attitude among physicians and nurses in Lambaréné region, Gabon: a call for setting-up an antimicrobial stewardship program. Antimicrob Resist Infect Control. 2022 Mar 3;11(1):44.
9. **Adegbite BR**, Kawale P, Kalitsilo L, Jacob ST, Rylance J, Adegnika AA, Grobusch MP.Recognising Sepsis as a Health Priority in Sub-Saharan African Country: Learning Lessons from Engagement with Gabon's Health Policy Stakeholders. Healthcare (Basel). 2022:10(5):877.

10. Essone PN, **Adegbite BR***, Mbadinga MJM, Mbouna AV, Lotola-Mougeni F, Alabi A, Edoa JR, Lell B, Alabi AS, Adegnika AA, Ramharter M, Siawaya JFD, Grobusch MP, Kremsner PG, Agnandji ST.Creatine kinase-(MB) and hepcidin as candidate biomarkers for early diagnosis of pulmonary tuberculosis: a proof-of-concept study in Lambaréné, Gabon. Infection. 2022;50(4):897-905.

11. Vigenschow A, **Adegbite BR*,** Edoa JR, Alabi A, Adegnika AA, Grobusch MP, Massinga-Loembe M..Tuberculosis infection control measures in healthcare facilities in Moyen-Ogooué Province, Gabon. BMC Health Serv Res. 2021 Nov 5;21(1):1200

12. Jabar Babatunde Pacome Achimi Agbo Abdul, **Bayode Romeo Adegbite*** Micheska Epola Dibamba Ndanga, Jean Ronald Edoa, Rhett Chester Mevyann, Guy Rogue Arnault Ibinda Mfoumbi, Tshisekedi Jean de Dieu, Jocelyn Mahoumbou, Christopher Mebiame Biyogho, Sankarganesh Jeyaraj, Stefan Niemann, Bertrand Lell,, Peter G. Kremsner, Abraham Sunday Alabi, Ayola Akim Adegnika, Martin Peter Grobusch. Resistance patterns among drug-resistant tuberculosis patients and trends-over-time analysis of national surveillance data in Gabon, Central Africa. *Infection. 2022 Oct 28:1-8.*

13. **Bayode R Adegbite**, Nadege OM Elegbede-Adegbite, Jean R Edoa, Yabo J Honkpehedji, Jeannot F Zinsou ,Jean Claude Dejon-Agobé, Ayola A Adegnika, Martin P Grobusch. Clinical features, treatment outcomes and mortality risk of tuberculosis sepsis in HIV-negative patients: a systematic review and meta-analysis of case reports *Infection 2022 Nov 16.*

14. Sandesh Gautam , Rajeev Shrestha 2, Mohammad R Ghani , Mahmoud M Ali , Manish Kc , Yomna A Elfert , Vanessa Chong , **Bayode Romeo Adegbite** .Efficacy and safety of different therapies of non-steroidal anti-inflammatory drugs against antibiotic monotherapy in the treatment of uncomplicated lower urinary tract infection: A systematic review. SAGE Open Med. 2022 Sep 4; 1(10): 1–12

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Other publications

1. Honkpéhèdji YJ, **Adegbite BR**, Zinsou JF, Dejon-Agobé JC, Edoa JR, Zoleko Manego R, McCall M, Mbong Ngwese M, Lotola Mougeni F, Mombo-Ngoma G, Ramharter M, Kremsner PG, Lell B, Yazdanbakhsh M, Esen M, Adegnika AA.Association of low birth weight and polyparasitic infection during pregnancy in Lambaréné, Gabon. Trop Med Int Health. 2021 Aug;26(8):973-981.

2. Dejon-Agobé JC, Zinsou JF, Honkpehedji YJ, Ateba-Ngoa U, Edoa JR, **Adegbite BR**, Mombo-Ngoma G, Agnandji ST, Ramharter M, Kremsner PG, Lell B, Grobusch MP, Adegnika AA. Schistosoma haematobium effects on Plasmodium falciparum infection modified by soil-transmitted helminths in school-age children living in rural areas of Gabon. PLoS Negl Trop Dis. 2018 Aug 6;12(8)

3. Elion Assiana DO, Abdul JBPA, Linguissi LSG, Epola M, Vouvoungui JC, Mabiala A, Biyogho CM, Ronald Edoa J, **Adegbite BR**, Adegnika AA, Elton L, Canseco JO, McHugh TD, Ahombo G, Ntoumi F.Epidemiological profile of multidrug-resistant and extensively drug-resistant Mycobacterium Tubrculosis among Congolese patients. Ann Clin Microbiol Antimicrob. 2021 Dec 17;20(1):84

4. Vigenschow A, Edoa JR, **Adegbite BR**, Agbo PA, Adegnika AA, Alabi A, Massinga-Loembe M, Grobusch MP.Knowledge, attitudes and practices regarding tuberculosis amongst healthcare workers in Moyen-Ogooué Province, Gabon. BMC Infect Dis. 2021 May 27;21(1):486

5. Dejon-Agobé JC, Zinsou JF, Honkpehedji YJ, Edoa JR, **Adegbité BR,** Beh-Mba R, Kremsner PG, Adegnika AA, Grobusch MP. Knowledge, attitudes and practices pertaining to urogenital schistosomiasis in Lambaréné and surrounding areas, Gabon. Parasit Vectors. 2021 Sep 22;14(1):486

6. Manouana GP, Byrne N, Mbong Ngwese M, Nguema Moure A, Hofmann P, Bingoulou Matsougou G, Lotola Mougeni F, Nnoh Dansou E, Agbanrin MD, Mapikou Gouleu CS, Ategbo S, Zinsou JF, **Adegbite BR**, Edoa JR, Kremsner PG, Mordmüller B, Eibach D, McCall M, Abraham A, Borrmann S, Adegnika AA.Prevalence of Pathogens in Young Children Presenting to Hospital with Diarrhea from Lambaréné, Gabon. PLoS Negl Trop Dis 2020 Jul 13;14(7):

7. Koehne E, Kreidenweiss A, **Adegbite BR**, Manego RZ, McCall MBB, Mombo-Ngoma G, Adegnika AA, Agnandji ST, Mordmüller B, Held J.In vitro activity of eravacycline, a novel synthetic halogenated tetracycline, against the malaria parasite Plasmodium falciparum. J Glob Antimicrob Resist. 2021 Mar;24:93-97

8. Nouatin O, Mengue JB, Dejon-Agobé JC, Fendel R, Ibáñez J, Ngoa UA, Edoa JR, **Adégbité BR**, Honkpéhédji YJ, Zinsou JF, Hounkpatin AB, Moutairou K, Homoet A, Esen M, Kreidenweiss A, Hoffman SL, Theisen M, Luty AJF, Lell B, Agnandji ST, Mombo-Ngoma G, Ramharter M, Kremsner P, Mordmüller B, Adegnika AA. Exploratory analysis of the effect of helminth infection on the immunogenicity and efficacy of the asexual blood-stage malaria vaccine candidate GMZ2. PLoS Negl Trop Dis. 2021 Jun 1;15(6):e0009361

9. Epola Dibamba Ndanga M, Achimi Agbo Abdul JBP, Edoa JR, Chester Mevyann R, **Adegbite BR**, Mfoumbi A, Mebiame Biyogho C, Beh Mba R, Mahoumbou J, McCall MBB, Grobusch MP, Adegnika AA, Alabi AS. Non-tuberculous mycobacteria isolation from presumptive tuberculosis patients in Lambaréné, Gabon. Trop Med Int Health. 2022 Apr;27(4):438-444.

10. Dejon-Agobé JC, Edoa JR, Honkpehedji YJ, Zinsou JF, **Adégbitè BR**, Ngwese MM, Mangaboula A, Lell B, Woldearegai TG, Grobusch MP, Mordmüller B, Adegnika AA. Schistosoma haematobium infection morbidity, praziquantel effectiveness and reinfection rate among children and young adults in Gabon. Parasit Vectors. 2019 Dec 10;12(1):577

11. Zoleko Manego R, Koehne E, Kreidenweiss A, Nzigou Mombo B, **Adegbite BR**, Dimessa Mbadinga LB, Akinosho M, Matthewman J, Adegnika AA, Ramharter M, Mombo-Ngoma G Description of Plasmodium falciparum infections in central Gabon demonstrating high parasite densities among symptomatic adolescents and adults. Malar J. 2019 Nov 21;18(1):371

12. Pugliese CM, **Adegbite BR**, Edoa JR, Mombo-Ngoma G, Obone-Atome FA, Heuvelings CC, Bélard S, Kalkman LC, Leopold SJ, Hänscheid T, Adegnika AA, Huson MA, Grobusch MP Point-of-care ultrasound to assess volume status and pulmonary oedema in malaria patients. Infection. 2022 Feb;50(1):65-82

13. Dejon-Agobé JC, Honkpehedji YJ, Zinsou JF, Edoa JR, **Adégbitè BR**, Mangaboula A, Agnandji ST, Mombo-Ngoma G, Ramharter M, Kremsner PG, Lell B, Grobusch MP, Adegnika AA. Epidemiology of Schistosomiasis and Soil-Transmitted Helminth Coinfections among Schoolchildren Living in Lambaréné, Gabon. Am J Trop Med Hyg. 2020 Jul;103(1):325-333

14. Suzuki TA, Fitzstevens JL, Schmidt VT, Enav H, Huus KE, Mbong Ngwese M, Grießhammer A, Pfleiderer A, **Adegbite BR**, Zinsou JF, Esen M, Velavan TP, Adegnika AA, Song LH, Spector TD, Muehlbauer AL, Marchi N, Kang H, Maier L, Blekhman R, Ségurel L, Ko G, Youngblut ND, Kremsner P, Ley RE. Codiversification of gut microbiota with humans.Science. 2022 Sep 16;377(6612):1328-1332

PhD PORTFOLIO

Name : ADEGBITE Bayodé Romeo
PhD period 2019 -2023
Name PhD supervisors: Prof GROBUSCH Peter Martin & Prof ADEGNIKA Ayola Akim

	Year	Workload (Hours/ECTS)
1. PhD training		
General courses		
- Scientific Writing in English for Publication	2020	1.5
- Practical Biostatistics	2021	1.4
- Randomised Controlled Trials	2021	0.6
- Evaluation of Medical Tests	2021	0.6
- Research Data Management (eLearning & optional workshop)	2021	0.5
Specific courses		
- Design and Interpretation of Clinical Trials courses: Johns Hopkins University	2019	3.8
- Short course on POCUS ultrasound by Prof Elisabeth Joekes and Ingeborg Welters, Malawi and Gabon course series	2019	2.8
- Grant writing and scientific review course by Africa Research Excellence Fund	2020	2.6
- Qualifying the Workforce for AMR Surveillance in Africa and Asia (QWARS) Training: African Society for Laboratory Medicine	2021	4.0
Seminars, workshops and master classes		
- ASAP Digital Career Event	2021	0.2
- Amsterdam institute for Infection and Immunity annual symposium	2021	0.2
- VERSA: Video Games for PhD Soft Skills Training	2022	0.3
Presentations		
- Tuberculosis and smoking, oral presentation (PanACEA annual physical meeting)	2020	0.5
- Sepsis definitions and challenges of diagnosing sepsis in Africa, Oral presentation (African Sepsis Alliance online conference)	2021	0.5
- Resistance patterns among multidrug-resistant tuberculosis patients and trends-over-time analysis of national surveillance data in Gabon, poster (DZIF annual meeting)	2022	0.5
- Resistance patterns among multidrug-resistant tuberculosis patients and trends-over-time analysis of national surveillance data in Gabon(Oral presentation, ASTMH annual meeting)	2022	0.5
(Inter)national conferences		
- Annual online World Sepsis Congress	2020	0.2
- Annual online World Sepsis Congress	2021	0.2
- Rethinking Sepsis in Resource Variable/Constrained Settings	2021	0.2
- Sepsis Alliance Leadership Conference: Empowering Improvements in Care	2022	0.2

	Year	Workload (Hours/ECTS)
2. Teaching		
Lecturing		
Tutoring, Mentoring		
Supervising		
Manus Schmedding's Medical degree: Performance of qSOFA, MEWS, UVA, and SIRS in Lambaréné (co-supervision under the guidance of MP Grobusch)	2019	0.3
Christina Pugliese 's Master's degree: " Point-of-care ultrasound to assess volume status and pulmonary oedema in malaria patients" (co-supervision under the guidance of MP Grobusch)	2021	0.3
Emily Henning 's Medical degree: Epidemiology of severe malaria in Lambarene(co-supervision under the guidance of AA Adegnika)	2022	0.3
Other: Organisation of a workshop on the epidemiology and management of sepsis and antimicrobial resistance in Lambaréné Albert Schweitzer Hospital	2021	0.3
3. Parameters of Esteem		
Grants		
- Tuberculosis and diabetes comorbidity in Gabon (14500 EUR)	2019	
- Prioritising sepsis: Engagement of stakeholders in Gabon (5000 EUR)	2020	
- Sepsis Awareness in Gabon (5000 EUR)	2021	

CURRICULUM VITAE

Summary

I am a physician, epidemiologist and researcher working at the Centre de Recherches Médicales de Lambaréné, (CERMEL), Gabon. I conduct clinical trials, observational, epidemiology, and implementation studies. My research areas are infectious disease, epidemiology, and operational research.

Skill Highlights

- Project management
- Grant and proposal writing
- Stakeholder engagement
- Leadership
- Public health advocacy
- Innovative
- Team management
- Teaching

Education

➢ Discipline: **Infectious Disease-Tropical medicine and Epidemiology**

Institution: University of Amsterdam

Degree and Year: PhD 2023

➢ Discipline: **Public Health and Epidemiology**

Institution : Université de Bordeaux, France

Degree and Year: Master, 2020

➢ Discipline: **Medical statistic**

Institution : Université de Bordeaux, France

Degree and Year: Post Graduate Diploma, 2019

➢ Discipline: **Epidemiology**

Institution : Université de Bordeaux, France

Degree and Year: Post Graduate Diploma, 2018

➢ Discipline: **Medicine**

Institution : Université de Parakou, Benin

Degree and Year: Medical degree, 2013

▪ **Others Training**

✓ 2020 Infectious diseases clinical trials: Institut Pasteur (France)

✓ 2019 Clinical Immuno-microbiology: Bircham International University (USA)

✓ 2019 Design and Interpretation of Clinical Trials: University of Johns- Hopkins (USA)

- ✓ 2018 Tropical Parasitology: Protozoans, Worms, Vectors and Human Diseases: Duke University (USA)
- ✓ 2018 Implementation Research with a focus on Infectious Diseases of Poverty: The University of Ghana, School of Public Health

Experience

CERMEL Gabon,

Medical researcher, clinical trials, observational, implementation, and epidemiology studies: 2017- up to date

- Co-principal investigator
- Co-investigator
- Proposal and protocol writing
- Patients' and participants' follow-up
- Community engagement activities

Consultant, Minister of Heath /Global fund Benin

- Cooperate with health policymakers
- Develop project concepts and maintain optimal workflow
- Project management
- Community health and advocacy

Review activities and editorial board

I review for several journals, (number of manuscripts reviewed) :

- Review activity for Infection (31)
- Review activity for international journal of environmental research and public health. (23)
- Review activity for Tropical medicine and infectious disease. (10)
- Review activity for Journal of clinical medicine. (7)
- Review activity for Diagnostics. (7)
- Review activity for Antibiotics. (5)
- Review activity for BMC medicine. (5)
- Review activity for healthcare. (5)
- Review activity for Cochrane database of systematic reviews. (5)
- Review activity for Infection and drug resistance (4)

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