

# How to close the maternal and neonatal sepsis gap in sub-Saharan Africa

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## INTRODUCTION

Sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection.<sup>1</sup> The incidence of sepsis, as estimated by the Global Burden of Disease study, was 48.9 million cases with 11 million deaths in 2017.<sup>2</sup> In sub-Saharan Africa (SSA), the burden is highest, with an estimated 16.7 million cases and sepsis accounting for up to 45% of all deaths, in many SSA countries.<sup>2</sup>

Maternal sepsis is a sepsis that occurs during pregnancy, childbirth, postabortion or in the postpartum period and neonatal sepsis is a sepsis that occurs within the first 28 days of life. Reliable estimates of the incidence and mortality of maternal and neonatal sepsis in SSA are incomplete. Notwithstanding this limitation, the most recent estimate suggests that sepsis is responsible for 130 000 maternal deaths<sup>3</sup> and 300 000 neonatal deaths annually, though this may be an underestimate,<sup>4</sup> in view of the recent Global Burden of Disease study report.<sup>2</sup>

Sepsis-related deaths in SSA reflect underlying political, poverty, health inequity and health system challenges across Africa.<sup>5</sup> These challenges affect preventative and public health efforts to prevent sepsis and limit prompt and effective recognition and treatment of sepsis to prevent mortality. The challenges include access to clean water and sanitation, vaccination and provision of primary care in addition to access to antimicrobial agents and strategies for their stewardship.<sup>6-9</sup>

In 2017, the World Health Assembly (WHA) passed a resolution to improve the prevention, diagnosis and management of sepsis (WHA 70.7).<sup>10</sup> This resolution recommended key action areas for member states and future priorities.<sup>11</sup> Based on these recommendations, we outline nine key areas to accelerate progress in reducing death due to maternal and neonatal sepsis in SSA.

## HOW TO REDUCE MATERNAL AND NEONATAL SEPSIS IN SSA

### 1. Increase sepsis awareness in the community

Despite sepsis being a major cause of health loss globally, public awareness remains low,<sup>11</sup> with the delayed time from presentation to care in low-middle income countries (LMICs) contributing to adverse outcomes.<sup>12,13</sup> Increasing awareness among the public and health workers is vital for prevention. In high-income countries (HICs), strategies to increase public awareness include public service announcements of the early warning signs of sepsis, published in traditional print and electronic media.<sup>14</sup> With global mobile connections standing at 7.6 billion<sup>15</sup> and extremely high smartphone dissemination in SSA, there is potential for exploitation of this digital resource to increase sepsis awareness in LMICs. Rapid evaluation of public awareness can be measured using geospatial analysis of online information-seeking behaviours as a surrogate measure.<sup>16</sup>

Educational messages can be accessed remotely and in real-time on mobile phones by health workers in different geographic locations, unrestricted by time and space. Mobile applications (apps) are conceptualised as a set of tools designed to undertake specific tasks and jobs. A systematic review of 42 studies to assess the effectiveness of mobile health in LMICs supports their use.<sup>17</sup> The use of mobile phone apps in supporting, training, data collection and reporting, emergency referrals, work planning and communication between health workers was associated with improvements in adherence to treatment algorithms, more accurate data collection and a reduction in treatment errors.<sup>17</sup>

### 2. Improve sepsis surveillance networks

Sepsis surveillance systems are critical tools for comprehensively quantifying the burden of sepsis related morbidity and mortality over time. At facility level, surveillance systems alert clinicians to the early signs of sepsis, enabling initiation of timely treatment. The

ideal surveillance system should be available in real-time at the point-of-care with the need for early identification of patients with sepsis strengthened by the known linear increase in the risk of mortality with each hour of delay in appropriate antibiotic treatment.<sup>18 19</sup> The establishment of electronic health records systems to capture vital signs and laboratory values of patients have been shown to be very effective in alerting clinicians to possible clinical deterioration due to sepsis.<sup>20</sup> By harnessing these existing technologies, local and regional information system networks for sepsis could be established in Africa.

### 3. Invest in health workers

Existing data highlight a marked disparity in annual health expenditure per capita between LMICs and HICs; however, the economic cost of maternal and neonatal sepsis in Africa is not clearly defined.<sup>5 21</sup> The WHA sepsis resolution advocates for well-coordinated efforts by politicians, policymakers, healthcare administrators, clinicians and researchers to reduce the impacts of sepsis.<sup>10</sup> Understaffing and a higher workload is a common problem in health facilities across SSA<sup>9</sup> and is linked to higher infection rates as well as adverse outcomes.<sup>22 23</sup> Addressing this challenge will require accelerated progress in health worker recruitment and training.

Training and education of health workers, especially nurses and other frontline clinicians, is vital in improving the outcomes of critically ill patients.<sup>24 25</sup> Retention of skilled staff should be a key consideration as 'brain drain' disproportionately affects health workers in SSA. Strategies should include improved remuneration, better conditions of service, task shifting and increased collaboration between those working in community and hospital settings. In SSA, mobile devices have been successfully used to train health workers.<sup>26 27</sup> Aside from promoting contact with health workers in remote and hard-to-reach areas, electronic training has the added advantage of supporting provider-to-provider communication, feedback and professional networking. Programmes targeting education of health workers in prevention and early recognition and treatment of maternal and newborn sepsis should be prioritised.

### 4. Improve the early identification of sepsis in facilities

Several sepsis diagnostic scoring systems have been developed to identify changes in physiological parameters which precede patient deterioration<sup>28</sup> and alert clinicians to promptly initiate treatment. Examples of these tools for use in the general adult population include the Modified Early Warning Score, Universal Vital Assessment Score,<sup>29</sup> National Early Warning Score 2 and the quick Sepsis Organ Failure Assessment (qSOFA) score. Importantly, none of these scores have been validated in pregnant women or newborns. As such, they are unlikely to account for physiological differences in these population groups.<sup>30</sup>

The Sepsis in Obstetrics Score, developed to detect maternal sepsis, appeared promising in initial reports from the USA; however, it was not superior to general sepsis scoring systems when tested in other regions.<sup>31</sup>

The obstetric modified SOFA score is an interesting adaptation of qSOFA that requires only clinical data for assessment and thus can be performed quickly and independently of laboratory tests.<sup>32</sup> The UK Modified Early Obstetrics Warning Score (MEOWS) was developed for the obstetric population to aid the identification of clinical signs of deterioration in women developing critical illness. The MEOWS is easy to administer and has been shown to have a high sensitivity (89%) and reasonable specificity (79%) in predicting maternal morbidity, though it is not specific to sepsis.<sup>33</sup>

The shock index (SI), defined as ratio of heart rate to systolic blood pressure, has recently been identified as a consistent predictor of adverse outcomes.<sup>34 35</sup> Various thresholds have been proposed for use of SI as an early warning system. In a prospective study involving women with postpartum haemorrhage or sepsis, the SI was found to be a consistent predictor of adverse outcomes compared with conventional vital signs.<sup>36</sup>

The introduction of maternal and neonatal sepsis scoring systems may be the first step towards achieving a reliable surveillance system for sepsis in SSA. Electronic surveillance tools which monitor physiological parameters should be developed to facilitate automatic recognition of the early signs of sepsis in health facilities.

### 5. Ensure laboratory diagnostics for sepsis are affordable and available

Infection is usually indicated by a rise in peripheral inflammatory makers such as the white blood cell count and C reactive protein. Cultures of relevant samples such as blood, urine, sputum and tissues provide microbiological confirmation of infections that give rise to sepsis. Rapid identification of pathogens from blood cultures has been shown to positively influence patient survival, length of hospitalisation and rational antibiotic prescriptions.<sup>37</sup> The development of local antibiograms is desirable to help facilities understand their local bacterial pathogens and match them to antibiotic choices. The establishment and maintenance of reference laboratories to support more sophisticated testing is essential.

In many LMIC settings, basic diagnostic modalities are lacking. Building local clinical microbiology laboratory capacity is an urgent priority and should incorporate regular training for staff to ensure they stay abreast with modern diagnostic methods. Recent research has focused on identifying biomarkers and molecular detection tools to increase the speed and reliability of diagnosis.<sup>38</sup> However, to ensure accessibility and affordability of modern diagnostic and biomarker testing, global health researchers and funders must ensure innovation in diagnostics and in their accessibility and affordability in LMIC settings.

Direct pathogen detection platforms promote the simultaneous identification of multiple bacterial and fungal species.<sup>38 39</sup> While there are several rapid molecular diagnostic platforms to identify bacterial and viral pathogens commercially available, none are widely available or affordable for resource-poor settings. Although

rapid, innovative and low-cost testing devices will improve the identification of causal micro-organisms; to improve outcomes, this must be matched with availability of appropriate antimicrobial agents. This requires certainty of supply chains, committed funding, along with strategies at institutional level for antimicrobial stewardship to prevent the emergence of resistant organisms.

### 6. Improve quality of care through sepsis specific guidelines

While adherence to protocols and clinical guidelines can improve survival and outcomes in sepsis, in a survey of 185 hospitals across SSA, only 1.5% used clinical sepsis guidelines. Lack of basic facilities, equipment and medicines were identified as barriers to implementation.<sup>7</sup> Resource limitations profoundly impact the ability to implement internationally recommended sepsis guidelines in SSA.<sup>40</sup>

In high-income settings, significant reductions in maternal and neonatal sepsis have been achieved through quality improvement initiatives to promote adherence to evidenced-based management of sepsis.<sup>41 42</sup> Quality improvement initiatives include educational programmes to increase awareness of the signs of sepsis; use of triage-based algorithms and decision support tools to screen for sepsis,<sup>43 44</sup> use of treatment order-sets<sup>45</sup> and initiatives to reduce time to antibiotics.<sup>46</sup>

Prompt administration of antibiotics remains the cornerstone of sepsis management. In the face of a growing burden of antimicrobial resistance and antibiotic-associated infections such as *Clostridioides difficile* infection, a greater alignment between antimicrobial stewardship and sepsis prevention and treatment programmes is essential.<sup>47</sup> Complementary strategies such as de-escalation protocols and prompt discontinuation of antibiotics when no longer indicated should be incorporated into sepsis quality improvement initiatives. Little is known about antimicrobial resistance in maternity units globally<sup>48</sup> and this information is essential to guide policy on the safe administration of prophylactic antibiotics during childbirth.

Another obvious gap is found in the Third International Consensus on Sepsis (Sepsis-3)<sup>1</sup> which does not provide criteria for diagnosis of sepsis in pregnant women. The ability of clinicians in SSA countries to adhere to sepsis guidelines is also limited by shortage of appropriately trained health workers, equipment and other supporting infrastructure.<sup>7</sup>

### 7. Increase access and use of vaccines to prevent the most common infections that lead to sepsis in pregnancy and the newborn period

Vaccinations are estimated to prevent 2–3 million infection-associated deaths every year among women and children.<sup>49</sup> Vaccines also have an indirect action on minimising antimicrobial resistance by reducing febrile illnesses and antibiotic use.<sup>50</sup> A vaccine for Group B Streptococcus is currently under evaluation and if effective, will have the potential to save 150 000 newborn lives every year and prevent up to 260 000 cases of maternal and

newborn sepsis.<sup>51</sup> Seasonal influenza caused by types A, B, C and D of influenza viruses is a public health problem which can be prevented by vaccination. Although the burden of seasonal influenza in Africa is yet to be fully described, the morbidity, mortality and economic losses from this infection are likely to be very high.<sup>52</sup>

Despite widespread availability of whole-cell pertussis (wP) vaccines, the burden of pertussis remains unacceptably high in the African continent.<sup>53</sup> This has been attributed to factors such as a lack of disease awareness and surveillance, diagnostic limitations and low prioritisation of this disease by policy makers. Intensified efforts to promote greater coverage with three primary doses of diphtheria-tetanus-pertussis vaccines and booster doses in older children and adolescents in Africa is also required.

Widespread protocols around immunisation for both adults and children is likely to decrease sepsis mortality in SSA. Current barriers to vaccination in this region include armed conflict, funding shortfalls, vaccine shortages and a lack of political will.<sup>54</sup> Measures to address these barriers include the establishment of lasting peace across the continent, improved funding for vaccination programmes and strengthening regional supply chains.

### 8. Strengthen infection prevention and control programmes and best practices during labour, childbirth and postnatal care

Water, sanitation and hygiene (WASH) is critical for the prevention of sepsis and provision of safe and quality care.<sup>55</sup> Less than 30% of delivery rooms in four East African countries reported access to a safe water supply<sup>56</sup> while a global review of health facilities in low-resource settings found that 40% had no water supply and 19% lacked adequate sanitation conditions.<sup>6</sup> Improvements in WASH could reduce the total burden of disease worldwide by as much as 10%.<sup>57</sup> Implementation of basic measures such as hand hygiene, reducing overcrowding in maternity and neonatal units, promoting hygienic care of the umbilical cord and kangaroo care for small and/or preterm babies have all been shown to mitigate the risk of infection.<sup>58 59</sup> Thus, the provision of safe water and promotion of effective hygiene practices should be emphasised and urgently prioritised in healthcare settings in SSA. This could be achieved by securing the commitment of policy makers to provide clean water in health facilities and by educating health workers and the wider population on the importance of adhering to standard hygiene practices.

### 9. Undertake high-quality research in pregnant and newborn African populations

There are imminent dangers in transferring effective solutions for sepsis management in HICs to LMICs. This is mirrored by recent well designed randomised controlled trials which have reflected worse outcomes for both children and adults with sepsis treated with

fluid boluses in Africa.<sup>13 60 61</sup> The two trials conducted in Zambia comparing an early goal directed therapy (EGDT) protocol (involving intravenous fluids among other measures) to usual care found increased in-hospital mortality in the EGDT arm compared with usual care.<sup>13 61</sup> High-quality research led by local investigators needs to be conducted to provide answers to conundrums associated with sepsis management among pregnant and newborn populations. These include determining the ideal type and volume of resuscitation fluid for sepsis, ascertaining the role of targeted/precision medicine approaches, rapid diagnostic tests and defining predictors of sepsis long-term morbidity and mortality.

## CONCLUSION

Maternal and neonatal sepsis is under-recognised in SSA with significant mortality and morbidity consequences. Although mostly preventable, a complex interplay of several factors is hampering a robust response to the threat posed by sepsis in SSA.

A multimodal approach is required to tackle maternal and neonatal sepsis within the fragile health systems of the SSA region. Pragmatic steps in alignment with the WHA sepsis resolution include increasing public and health worker awareness of sepsis, establishing surveillance networks, developing laboratory and human capacity, facilitating research and the development of clinical guidelines in addition to promoting routine vaccination and good infection prevention and control practices.

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