Optimizing the management of children with Multi-Drug Resistant Sepsis in low-middle income countries setting

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Box. Key information gaps that remain a barrier to the optimal management of paediatric sepsis in low-middle-income countries (LMIC)

- What is the relative contribution of different infection syndromes to the overall burden of paediatric sepsis in the LMIC setting?
- What is the relative proportion of community-acquired, hospital-acquired and healthcare associated paediatric sepsis in the LMIC setting?
- Which are the key pathogens causing paediatric sepsis, and what are their current antimicrobial resistance patterns in LMIC setting?
- Which are the empirical and targeted antibiotic treatments currently used globally for the treatment of paediatric sepsis?
- What are the determinants of adverse clinical outcomes in multi-drug resistant paediatric sepsis?
- What does the global map of access to appropriate antimicrobials for sepsis in LMIC look like; and where gaps exist can these be addressed?

Sir,

Infectious diseases remain a leading cause of child mortality globally. Of the 6·3 million children who died in their first 5 years of life in 2013, 51·8% (3·257 million) died of infectious causes. High variability was observed between regions, with sub-Saharan African and southern Asia contributing to around 80% of mortality.[1] After pneumonia, paediatric

(older than 28 days) and neonatal (up to 28 days old) sepsis was the second leading cause of child mortality by infectious disease (7%).[1] In contrast to other infectious diseases, the annual rate of reduction of paediatric sepsis is low. [1] Average mortality rates of paediatric sepsis can reach 5% in previously healthy and 10% in chronically ill children. [2]

We strongly support the work of the World Health Organization (WHO) and the Global Sepsis Alliance and we particularly acknowledge the specific attention to neonatal sepsis during the World Sepsis Congress Spotlight this year (https://www.world-sepsis-day.org/). Experts highlighted that under reporting of sepsis and poor recognition of sepsis symptoms result in a significant underestimation of the burden of maternal and neonatal death from sepsis, with a clear need to improve diagnosis, management and prevention. The Global Antibiotic Research and Development Partnership (GARDP), a joint initiative of the WHO and the Drugs for Neglected Diseases initiative (DND*i*) is launching the NeoAMR Project, aiming to develop new, globally applicable, empiric antibiotic regimens and strategies for the treatment of neonatal sepsis (https://www.dndi.org/diseases-projects/gardp/).

However, we suggest that the impact of antimicrobial resistance on the optimal antibiotic treatment of paediatric sepsis have not been given adequate attention. As noted in the recent update of the hemodynamic support guidelines for paediatric and newborn septic shock, published by Davis et al., [2] initiation of appropriate antibiotic therapy is one of the most important components of effective management of these life-threatening responses to infection. Determining the appropriate empirical treatment is now increasingly challenging, and depends on several factors such as the different pathogens causing sepsis, and their relative prevalence and resistance within the community and hospital settings. It has been recommended that administration of IV empiric broad-spectrum therapy be initiated within

60 minutes. [2] The current WHO guideline for the empiric treatment of paediatric sepsis is amoxicillin plus gentamicin. [3]

Only very limited reliable data on the aetiology, epidemiology and antimicrobial susceptibility of the key pathogens are available in paediatric sepsis from low-middle-income countries (LMIC). To the best of our knowledge, apart from the Child Health and Mortality Prevention Surveillance (CHAMPS) program, which focuses primarily on mortality causes, no large multicentre global prospective observational cohort study is currently evaluating the clinical origin, management and outcomes of paediatric sepsis in LMIC. Clear, epidemiological differences exist between LMIC and high-income countries (HIC). In HIC, the epidemiology of paediatric sepsis has changed markedly in the conjugate vaccine area, and *Staphylococcus aureus*, *Escherichia coli* and coagulase-negative staphylococci have become increasingly predominant, [4] while in LMIC non-typhoidal *Salmonella*, *E. coli* and *Klebsiella sp.* appear to rank higher, while several non-bacterial infections are associated with severe sepsis, such as dengue and influenza viruses or malaria. [5–7] These findings suggest that the clinical infection sources causing sepsis may differ, with an increased prevalence of intra-abdominal and urinary sepsis in the LMIC settings. The increasing incidence of *E. coli* resistant to fluoroquinolones and third generation cephalosporins is a serious threat globally, with a wide variability noted between WHO regions. [8] Although paediatric data remain scarce, extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae* represent 7-10% of paediatric sepsis in HIC, [4] while rates of 60-90% in LMIC are reported, especially in Asia and Sub-Saharan Africa. [5,6] Similar findings were observed for the asymptomatic carriage of ESBL-producing *Enterobacteriaceae*, with a prevalence about 8% in Europe [9,10] and 25-60% in different LMIC. [11,12]

To define the optimal empiric broad-spectrum antibiotic regimen, particularly focussing on multi drug resistant infections in the LMIC setting, it is important that we obtain reliable clinical and microbiological surveillance data on the current epidemiology of paediatric sepsis and antimicrobial resistance patterns from all WHO regions, rather than extrapolating knowledge from HIC. To address this need, a prospective international cohort study on children with sepsis in LMIC would aim to describe the epidemiological and clinical features of these patients, identify the sources of their infection, and assess the current clinical management in terms of appropriateness of the antibiotic therapy, antimicrobial resistance patterns, and their impact on outcomes (see Box).

WHO has recently launched the Global Antimicrobial Resistance Surveillance System (GLASS), and the first report is expected by the end of 2017. Data should have been recorded stratified by age, as we have noted previously that AMR patterns of key pathogens vary between adults and children. [13] Finally, implementation of high quality clinical trials is required. We have noted that from January 1st 2012 to August 24th 2017, only 21 trials can be retrieved using the terms 'sepsis' AND 'antibiotic' for 'Child (birth-17)' on the ClinicalTrial.gov website, almost three times lower than in adults (n=59). Even more striking, ten were from the USA or Canada, seven from Europe, while only three were from Asia and one from Mexico.

In conclusion, there is an urgent need for global collaboration, to collect high quality data on the current epidemiological, clinical and microbiological features in paediatric sepsis in the LMIC settings so as to update and target empiric prescribing guidance of the most appropriate combination antibiotic regimen to optimise clinical outcomes.

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