Invasive *Salmonella* infections in Africa

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Although *Salmonella enterica* is a leading cause of community-acquired bloodstream infection in Africa,\(^1\) these infections are frequently neglected as a target for public health intervention. The typhoidal *Salmonella*, serovars Typhi and Paratyphi A, cause enteric fever. Areas with high levels of endemic\(^2\) and epidemic\(^3,4\) typhoid fever are increasingly reported in Africa, and paratyphoid fever is described in some locations.\(^5\) Furthermore, in many sub-Saharan African countries, non-typhoidal *Salmonella*, primarily serovars Typhimurium and Enteritidis, cause bloodstream infections with incidence levels rarely seen elsewhere in the world. Efforts to control other important invasive bacterial infections such as *Streptococcus pneumoniae*, *Haemophilus influenzae* type b and *Neisseria meningitidis* with conjugate vaccines are likely to leave *S. enterica* as a prominent next target for prevention. However, efforts to address invasive *Salmonella* infections in the region face a range of challenges.

Burden of disease data are an essential first step towards building a case for intervention yet data to underpin estimates for both typhoidal\(^6\) and invasive non-typhoidal *Salmonella* disease\(^7\) are particularly scant in Africa. Lack of investment in clinical microbiology services\(^8\) and in invasive bacterial disease surveillance in many parts of Africa contribute to this problem. Even at sentinel hospital sites where facilities for blood culture are available,\(^1\) ascertainment of cases, and the understanding of patterns of healthcare utilization and of the size and structure of the catchment population, are frequently insufficient to accurately estimate more than minimum disease incidence. Strengthening long-term routine surveillance, ensuring that existing datasets are made widely available and developing novel surveillance tools would all contribute to progress in refining disease burden estimates. Beyond incidence, measuring outcomes of greatest interest, such as severe or complicated disease and death, is challenging. Invasive *Salmonella* infections are difficult to distinguish clinically from other febrile illnesses, risking misattribution of deaths to other diseases.\(^9\) Disease complications and death may occur in the community and not reach the attention of facility based surveillance. Furthermore, outcomes may be modified by the early detection, and correct diagnosis, of cases inherent and appropriate in high quality disease surveillance systems.\(^10\) New approaches to improving these estimates are needed.

Managing patients with invasive *Salmonella* infections in low-resource areas continues to be problematic. In addition to challenges with clinical diagnosis,\(^11\) conventional diagnosis by blood culture is insensitive, slow and may not be available,\(^8\) and so can rarely inform acute management. Developing rapid diagnostic tests for invasive *Salmonella* infections has proved challenging. For invasive non-typhoidal *Salmonella*, comorbidities and late presentation contribute to high case fatality ratios.\(^12\) Multiple-drug resistant non-typhoidal and typhoidal *Salmonella* is established in Africa.\(^13\) The emergence of decreased fluoroquinolone susceptibility among typhoidal *Salmonella*\(^14\) and extended-spectrum cephalosporin resistance among non-typhoidal *Salmonella*\(^15\) threaten existing regimens for management of sepsis, leaving limited antimicrobial treatment options and, potentially, leading to worse outcomes. Therefore, the continuing emergence of antimicrobial resistance among invasive *Salmonella* should focus the attention of the research and public health community on strategies for control and prevention.

Despite many decades of research we have only a rudimentary understanding of sources, modes of transmission and risk factors for infection that, alongside disease burden estimates, are crucial to the design of non-vaccine prevention programs. Human feces are the ultimate source of typhoidal *Salmonella*, and the host risk factors for invasive non-typhoidal *Salmonella*, including malaria, malnutrition and HIV, are well appreciated.\(^12\) Research in industrialized nations indicate that non-human vertebrate animals are the major reservoir of non-typhoidal *Salmonella* and that transmission to humans is usually via the consumption of foods of animal origin, produce contaminated by animal feces, and occasionally via water or direct contact with animals and their environments.\(^16\) However, genomic studies suggest human–host adaptation of epidemic invasive non-typhoidal *Salmonella* in Africa raising the possibility of transmission cycles that do not involve animals.\(^17\) An understanding of the relative contribution of waterborne, foodborne and other routes of transmission of both typhoidal and non-typhoidal *Salmonella* remains elusive. Although the few risk factor studies that have been conducted in Africa have provided few clues, novel molecular epidemiological tools implemented together with high quality field epidemiology now provide an exciting opportunity to make real progress.
Therefore, renewed field epidemiologic efforts on invasive Salmonella in Africa are needed to inform and direct non-vaccine prevention and control efforts.

Typhoid fever vaccines have not been widely used in endemic countries, including in Africa. Newer conjugate typhoid vaccines offer protection earlier in life\(^1\) and for longer durations\(^2\) than established vaccines, but the lack of a commercial incentive has probably contributed to a long delay in their implementation.\(^3\) Furthermore, key questions remain unanswered about how to use them. What is the best timing of vaccination and how many doses will be needed? Will they provide herd protection? Should vaccines be used widely or targeted to high-risk segments of the population? If targeted, how would high-risk groups be identified? Vaccine development efforts for non-typhoidal Salmonella and Salmonella Paratyphi A have lagged far behind those for Salmonella Typhi. To identify an integrated vaccine solution to invasive Salmonella infections, progress needs to be made across a wider spectrum of responsible Salmonella serovars. Presently it is unclear whether an integrated solution to vaccine prevention of invasive Salmonella infections lies in conjugate vaccines stimulating antibodies to multiple surface antigens, including Vi and relevant O and H antigens, through strategies using new live-attenuated vaccines, targeting highly conserved proteins or using outer membrane fragments.\(^4\) Whatever the way forward in terms of antigen selection and vaccine design, vaccines implemented in Africa will have to overcome a number of challenges, particularly for invasive non-typhoidal Salmonella. These include the influence of host factors such as young age, HIV-related immunosuppression, malnutrition and malaria\(^5\) on vaccine efficacy.

Much remains to be done to address invasive Salmonella infections in Africa. Developing and refining estimates of the burden of illness and death will be vital for this group of infections to be more widely appreciated. A robust understanding of the disease burden envelopes will allow projection of the scale of potential impact of interventions. Fundamental epidemiologic research is needed to provide an evidence base for selection of both vaccine and non-vaccine interventions tailored to African countries. Progress with existing potentially highly effective vaccines for typhoid fever will require development of the investment case, a funding strategy, and progress on where and how they should be used. At the same time, vaccine development efforts that broaden the focus of non-typhoidal Salmonella and Salmonella serovar Paratyphi A will progress the field towards more integrated vaccine solutions. Invasive Salmonella infections remain an important but under-appreciated infectious diseases problem in Africa. The international research and public health community are only just beginning to appreciate that efforts across the spectrum from fundamental to implementation science are needed if we are to effectively tackle this major infectious diseases problem.

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References


