Vaccine 33 (2015) S21–S29

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Review

Antimicrobial resistance and management of invasive *Salmonella* disease

Samuel Kariuki[a,b,*], Melita A. Gordon[c,d], Nicholas Feasey[d,e], Christopher M. Parry[f,g]

[a] *Centre for Microbiology Research, Kenya Medical Research Institute, PO Box 43640-00100, Nairobi, Kenya*
[b] *The Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge CB10 1SA, United Kingdom*
[c] *Institute for Infection and Global Health, University of Liverpool, United Kingdom*
[d] *Malawi Liverpool Wellcome Trust Clinical Research Programme, United Kingdom*
[e] *Liverpool School of Tropical Medicine, United Kingdom*
[f] *Department of Clinical Research, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 5HT, United Kingdom*
[g] *School of Tropical Medicine and Global Health, Nagasaki University, Nagasaki, Japan*

ARTICLE INFO

Article history:
Available online 23 April 2015

Keywords:
Invasive Salmonella
Non-typhoidal salmonella
Typhoid
Epidemiology
Antimicrobial resistant

ABSTRACT

Invasive Salmonella infections (typhoidal and non-typhoidal) cause a huge burden of illness estimated at nearly 3.4 million cases and over 600,000 deaths annually especially in resource-limited settings. Invasive non-typhoidal Salmonella (iNTS) infections are particularly important in immunosuppressed populations especially in sub-Saharan Africa, causing a mortality of 20–30% in vulnerable children below 5 years of age. In these settings, where routine surveillance for antimicrobial resistance is rare or non-existent, reports of 50–75% multidrug resistance (MDR) in NTS are common, including strains of NTS also resistant to flouroquinolones and 3rd generation cephalosporins. Typhoid (enteric) fever caused by *Salmonella* Typhi and *Salmonella* Paratyphi A remains a major public health problem in many parts of Asia and Africa. Currently over a third of isolates in many endemic areas are MDR, and diminished susceptibility or resistance to fluoroquinolones, the drugs of choice for MDR cases over the last decade is an increasing problem. The situation is particularly worrying in resource-limited settings where the few remaining effective antimicrobials are either unavailable or altogether too expensive to be afforded by either the general public or by public health services. Although the prudent use of effective antimicrobials, improved hygiene and sanitation and the discovery of new antimicrobial agents may offer hope for the management of invasive salmonella infections, it is essential to consider other interventions including the wider use of WHO recommended typhoid vaccines and the acceleration of trials for novel iNTS vaccines. The main objective of this review is to describe existing data on the prevalence and epidemiology of antimicrobial resistant invasive Salmonella infections and how this affects the management of these infections, especially in endemic developing countries.

1. Introduction

Invasive Salmonella infections (typhoid and non-typhoidal) are a leading cause of morbidity, with high rates of mortality, in resource-limited settings especially in sub-Saharan Africa (SSA) and parts of the Indian and Asian sub-continents. Specifically, invasive non-typhoidal *Salmonella enterica* (iNTS) are a major cause of bloodstream infections in SSA, especially among children and HIV-infected adults who have low CD4 T-lymphocyte counts with mortality rates of nearly 10–30% [1,2]. Most paediatric cases of iNTS occur between ages 6 months and 3 years, an observation which supports the importance of passive and acquired humoral immunity in prevention of invasive disease [3–5]. Multidrug resistant iNTS disease poses a major challenge to the clinical management of infections in resource-limited settings especially as alternative more effective antibiotics are either unaffordable or simply unavailable for majority of patients. Furthermore, there are no published clinical trials to support treatment decisions in iNTS disease especially in endemic settings in SSA although a number of clinical handbooks give treatment recommendations. *Salmonella enterica* serovar Typhi (*Salmonella* Typhi), remains an important global public health problem, causing 22 million outbreak-associated and sporadic cases of typhoid and approximately 200,000 deaths

* Corresponding author at: Centre for Microbiology Research, KEMRI, Off Ngong Road, PO Box 43640-00100, Nairobi, Kenya. Tel.: +254 722 232467.
E-mail address: samkariuki2@gmail.com (S. Kariuki).

http://dx.doi.org/10.1016/j.vaccine.2015.03.102
0264-410X/

annually worldwide [6]. It is primarily a rare imported disease in industrialized countries, since improved sanitation and water supply has eradicated endemic disease, but is endemic in South/South East/Central Asia and parts of SSA and still causes large outbreaks [7–10]. The true burden of typhoid fever is largely unknown in SSA because credible measures of disease incidence require a confirmed diagnosis based on blood or bone marrow culture. Laboratory facilities to make such a diagnosis are limited or non-existent in many potentially endemic SSA countries. This review looks at the current situation on epidemiology and burden of illness caused by invasive Salmonella infections (including iNTS and Typhoid fever), especially in endemic areas and further explores the problem of AMR in these infections, their clinical impact and management issues.

2. Invasive non-typhoidal Salmonella (iNTS) disease

2.1. Global epidemiology

In industrialized countries, NTS predominantly cause non-invasive enteric diarrhoeal disease. The bacteria are transmitted by either infected animal products or by industrially produced food contaminated with infected animal faeces. NTS usually cause a self-limited enterocolitis with diarrhoea in immunocompetent humans, although individuals with immunocompromising conditions are susceptible to invasive bloodstream infection. Bloodstream infections (iNTS) occur in approximately 6% of laboratory confirmed patients with diarrheal enterocolitis, although his may be an underestimate as blood cultures are not always taken. Infants, young children, the elderly, and immunocompromised individuals are at particular risk for bacteremia, and multidrug resistant strains are also more likely to cause invasive disease [5,11,12].

Enteric NTS syndromes were globally estimated to cause 93.8 million illnesses and 155,000 deaths [13]. In further estimates, enteric NTS infections accounted for 4.8 million disability-adjusted life years [14] and 81,300 deaths [15]. In contrast to the picture in industrialized settings, in Africa NTS are associated with invasive disease without gastroenteritis as a prominent feature. The clinical features of iNTS disease are either nonspecific and similar to those of other common diseases such as malaria or may be focal or cause pneumonia or meningitis. This not only presents a diagnostic dilemma to health workers in a resource-limited setting but also makes burden of disease estimates uncertain in the absence of laboratory confirmation. The global burden of disease for iNTS disease has recently been estimated for the first time, and suggests that there is a huge and unrecognized burden of illness and mortality [101]. There are an estimated 3.4 million cases globally, and assuming a case fatality of 20%, 681,316 deaths annually. Approximately two-thirds of this burden falls on children, and 55% in Africa. It is, however, important to note that it is still unknown to what extent the NTS strains that cause invasive disease are genomically or phenotypically different from NTS strains that cause enteric disease, so the term "iNTS" should be used with caution with reference to the micro-organisms. This is an important area of current research, as described below.

Salmonella Typhimurium and *Salmonella* Enteritidis are the most widely reported invasive serovars across SSA. Smaller more localized contributions or outbreaks in SSA are reported for *Salmonella* Concorde in Ethiopia [16], *Salmonella* Bovismorbificans [17], *Salmonella* Stanleyville and *Salmonella* Dublin in Mali [18] and *Salmonella* Isangi in South Africa [19]. Case fatality rates for iNTS vary according to the infecting serovar. Some serovars, *Salmonella* Newport for example, are associated with a lower case fatality ratio (0.3%) when compared with *Salmonella* Typhimurium [12,20].

2.2. Genomic adaptation of invasive Salmonella

Host restriction among *Salmonella* spp. appears to be associated with a more specialized lifestyle involving an invasive pathogenesis and the loss of the ability to colonize and infect the gastrointestinal tract of multiple vertebrates. The genomic changes associated with host restriction and invasive disease in *Salmonella* spp. are increasingly understood, having been first described in *Salmonella* Typhi strains [21,22]. They are typified by the loss or degradation of genes, including those associated with an enteric lifestyle [23], such as metabolic genes required for anaerobic survival in the inflamed intestinal lumen [23,24].

A novel *Salmonella* Typhimurium multi-locus sequence type, ST313, has been described that accounts for a significant proportion of the invasive disease in sub-Saharan Africa. This sequence type has a unique prophage repertoire, and a degraded genome that shows some convergence with *Salmonella* Typhi, consistent with increased host specialization or invasiveness [25]. One putative virulence gene, *ST313td*, has been described in *Salmonella* Typhimurium ST313 that is also present in *Salmonella* Dublin, another pathovar which is invasive in humans [26]. Current genomic, transcriptomic and phenotypic investigations of *Salmonella* Typhimurium ST313 and other iNTS pathovars from Africa, such as *Salmonella*. Enteritidis, promise further new insights.

2.3. Sources and modes of transmission

Epidemiologic studies of iNTS in endemic areas of sub-Saharan Africa are very limited. Although transmission by food contaminated with animal faeces must be considered, a greater role than in industrialized countries has been suggested for waterborne transmission, or transmission between people, independent of a non-human animal reservoir. Sub-genomic studies of iNTS strains from humans and those carried by animals found in the households of children with invasive disease in Africa have not suggested any domestic animal sources for transmission, whereas family members of cases have been found to have more closely related isolates [4]. Although it was hypothesized that the degraded genome of *Salmonella* Typhimurium ST313 might reflect a reduced host range and human-restriction of the ST313 pathovar, recent studies have shown that ST313 strains also display a severe invasive phenotype in chickens with a reduced potential for cecal colonization [27]. In a study of the epidemiology of invasive *Salmonella*. Typhimurium strains using whole-genome sequence-based phylogenetic methods to define the population structure of these strains in SSA compared to global *Salmonella*. Typhimurium populations it was shown that the vast majority of SSA invasive *Salmonella*. Typhimurium ST313 pathovars fell within two closely related, highly clustered phylogenetic lineages that were estimated to have emerged independently ~52 and ~35 years ago in close temporal association with the current HIV pandemic. The emergence of the two distinct clades of *Salmonella* Typhimurium ST313 pathovars across SSA also show important temporal relationships to acquired antimicrobial resistance determinants, particularly to the first-line antimicrobial chloramphenicol [28]. This suggests that transmission among humans may have exerted a significant genomic selection pressure.

Little is known about the spectrum of prevalent enteric NTS strains in Africa. NTS were not a common cause of moderate–severe diarrheal disease in the recent GEMS study in multiple African sites [29]. In contrast, asymptomatic carriage of NTS appears to be relatively common [4,29]. The contribution in Africa of *Salmonella* Typhimurium ST313 or other invasive pathovars of NTS, to diarrhoeal illness or asymptomatic carriage is also still unclear, although there appears to be considerable diversity among NTS strains from enteric samples in Africa [30]. Taken together, these