Typhoid fever

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Control of typhoid fever relies on clinical information, diagnosis, and an understanding for the epidemiology of the disease. Despite the breadth of work done so far, much is not known about the biology of this human-adapted bacterial pathogen and the complexity of the disease in endemic areas, especially those in Africa. The main barriers to control are vaccines that are not immunogenic in very young children and the development of multidrug resistance, which threatens efficacy of antimicrobial chemotherapy. Clinicians, microbiologists, and epidemiologists worldwide need to be familiar with shifting trends in enteric fever. This knowledge is crucial, both to control the disease and to manage cases. Additionally, salmonella serovars that cause human infection can change over time and location. In areas of Asia, multidrug-resistant *Salmonella enterica* serovar Typhi (*S* Typhi) has been the main cause of enteric fever, but now *S* Typhi is being displaced by infections with drug-resistant *S enterica* serovar Paratyphi A. New conjugate vaccines are imminent and new treatments have been promised, but the engagement of local medical and public health institutions in endemic areas is needed to allow surveillance and to implement control measures.

Introduction

Estimates of disease burden

Knowledge of the burden of disease is crucial for several reasons—first, data for effects of the disease on human health and the local economy are essential to inform decision-makers in public health; second, information about local trends is necessary to allocate resources; and third, understanding of local and regional disease trends is needed to provide informed guidance to travellers. Global estimates for the burden of typhoid fever (defined as symptomatic infection with *S* Typhi) are published regularly (26·9 million cases of typhoid fever were reported in 2010[1]) and general mortality data are available from global and regional mortality studies (figure 1).[2] However, detailed local surveillance data from endemic regions remain poor. In this article, we provide an update on the previous Seminar by providing an update on information on typhoid fever in endemic regions of the world.

Diagnosis and treatment of typhoid fever

Recent reviews of diagnosis and treatment of typhoid fever[3,4] make it clear that the laboratory diagnosis of typhoid fever is largely dependent on the detection of organisms in blood by PCR (best suited to epidemiological surveys) or culture (although sensitivity remains a limitation).[4–6] The Widal test for antibody production is unreliable and new-generation serology tests such as typhidot and tubex have not proved reliable in Africa[7–9] or Asia.[10,11] One new test format that shows promise is the typhoid–paratyphoid diagnostic assay,[12] which detects IgA. This method has specificity of detection of circulating IgA for the diagnosis of typhoid fever with use of ELISA[11] and improves the sensitivity (to 100%) through amplification of the signal by isolation and incubation of peripheral blood lymphocytes.[13] Treatment with fluoroquinolones, azithromycin, and third-generation cephalosporin drugs is the main treatment, with chloramphenicol used in regions in which susceptible strains are present (panel 1).[8]

Search strategy and selection criteria

We searched PubMed and Web of Knowledge for articles published in English from Jan 1, 2008, to Dec 31, 2013, using the terms "typhoid" or "Typhi". We did searches for highly cited articles in Web of Knowledge and Google Scholar that were tracked for citations since Jan 1, 2008. We also used the contacts and experience of the authors who live and work across the typhoid endemic regions of Asia and Africa.

Genomics of *S* Typhi

Despite the genetic similarity of *S* Typhi and *S enterica* serovar Typhimurium (90% of genes are shared), understanding is poor for the genetic differences that underlie the ability of *S* Typhi, but not *S* Typhimurium, to cause enteric fever.[15] Large-scale transposon knockout libraries[16] allow researchers to assess function at the genome level and show differences between *S* Typhi and *S* Typhimurium.[17] The same genes in *S* Typhi and *S* Typhimurium might have different regulatory pathways and possibly different functions.[18] This exciting new technology might provide targets for vaccine development and new antibacterial drugs for *S* Typhi in endemic regions. The investigation of why *S* Typhi infects human beings, but not mice, has led to the development of two mouse-studies for typhoid fever: one is based on mice grafted with human haemopoietic stem cells[19] and the other is based on mice grafted with bacterial flagella recognition cells with Toll-like receptor-11 knockouts.[20] Research has also led to the description of *gtgE*, a virulence gene present in *S* Typhimurium but not in *S* Typhi that allows *S* Typhi to infect mouse macrophages. Although still to be verified, these models could allow the previously impossible investigation of pathogenesis and immunity for this human-restricted pathogen. The importance of these new models is shown by the use of the humanised mouse model to describe receptor-binding specificity and delivery mechanisms for the typhoid toxin encoded by *ctdB* and *pltA*[21] and so to define a potential new vaccine target.

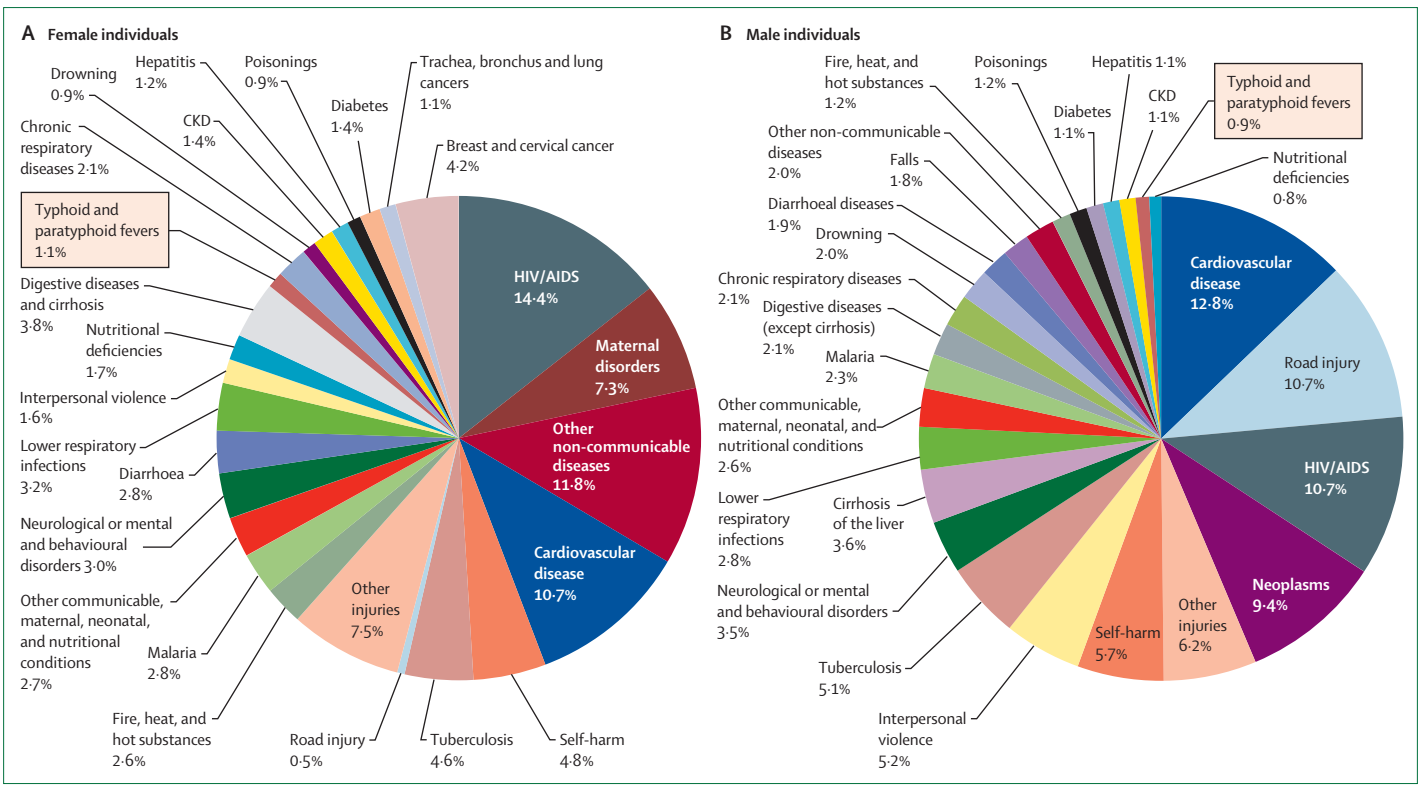

Figure 1: **Mortality from enteric fever worldwide**
Data from Jan 1, 2012, to Dec 31, 2012. 5 741 344 total deaths. CKD=chronic kidney disease. Used from Lozano and colleagues.[2]

Typhoid fever in Asia

Data from global burden of disease studies show most cases of typhoid fever to be reported on the Indian subcontinent;[1,22,23] however disease burden is not uniform within this region (table 1). In addition to variation by location and age group, differences are also noted in incidence of typhoid fever over time in one location. Retrospective analysis of data for *Salmonella* spp infection from an urban hospital in Kathmandu, Nepal, shows an increase in typhoid fever as cause of community acquired septicaemia. Among 82 467 blood cultures done, *Salmonella* spp accounted for 75%[28] of positive cultures, of which 71% (9124) tested positive for *S* Typhi. Between 1997–2000 and 2001–03, *Salmonella* spp septicaemia rates significantly increased from 6% to 14%. Conversely, decreases in typhoid fever incidence have been reported in the Mekong Delta region and in southern China.[29–35] Southern China is of particular interest because the once dominant *S* Typhi infection has now been replaced by infection with *S* Paratyphi A.[32] Although done with use of suitable surveillance systems, including diagnosis by blood culture, the studies that we describe above were not standardised, which might bias comparisons between regions—eg, incidence rate estimates are higher from studies with active,[24–26] as compared with passive, surveillance studies.[36] To address this comparability issue, the International Vaccine Institute in Korea did several

Panel 1: Key issues in diagnosis and treatment of typhoid in developing countries

- Emphasis should be placed on disease prevention; short-term measures include vaccination of high-risk populations in endemic areas, and rational and judicious antibiotic drug prescribing practices by health professionals
- In endemic regions, diagnostics do not meet the daily challenge of differentiation of the causes of fever and the disease burden for enteric fever cannot be defined
- Development of new diagnostic tests is a challenge because of low numbers of bacteria in the blood and antigenic cross-reactivity with other Gram-negative bacteria
- New technologies to exploit the in-vivo induction of antigens, immunoaffinity proteomics, and detection of metabolic products could identify new diagnostic targets
- Outbreaks of multidrug-resistant typhoid fever need costly and widely unavailable drugs for effective treatment
- There are no guidelines for the treatment of patients with quinolone-resistant S Typhi strains
- The lack of an adequate gold standard is a major hindrance in the development of new diagnostics for enteric fever and increases the size and cost of trials

Adapted from Parry and colleagues[4] and Zaki and colleagues.[14]

	Study design	Incidence of typhoid fever
Urban slums of Delhi[24]	Population based (1820 people)	9·8 per 1000 per year (3 times higher in children younger than 5 years)
Urban slums in Bangladesh[25,26]	Household based (roughly 11 400 people)	18·7 per 1000 per year in preschool-aged children; 2·1 per 1000 per year in older patients
Coastal community in Pakistan[27]	Household based (5700 people)	4·1 per 1000 per year in children younger than 5 years; 4·4 per 1000 per year in children younger than 2 years

Preschool age usually indicates children aged 1–5 years.

Table 1: **Estimations for burden of typhoid fever for regions within the Indian subcontinent**

	Site	Incidence of typhoid fever
China	Urban and rural	15·3 cases per 100 000 per year in people aged 5–60 years old
Vietnam	Urban	24·2 cases per 100 000 per year in people aged 6–18 years old
Indonesia	Urban slum	81·7 cases per 100 000 per year (all ages)
Pakistan	Urban slum	451·7 cases per 100 000 per year in children aged 2–15 years
India	Urban slum	493·5 cases per 100 000 per year (all ages)

441 435 people in the targeted age groups were under surveillance for 1 year at each site (the 12 month period was between August 2002 and July 2004). 463 culture-confirmed cases of typhoid fever were described.[36]

Table 2: **Surveillance data from sites in five Asian countries**

large studies that collected prospective population-based surveillance data in five Asian countries with use of standardised surveillance, clinical, and microbiological methods (table 2).[36] The results confirm variation in distribution of typhoid fever. Overall incidence was 170·8 cases per 100 000 people per year, but this rate varied substantially from location to location. Even when broken down by age group, variation in the annual typhoid fever incidence was still apparent—for children aged 24–60 months: 573·2 per 100 000 in Pakistan, 340·1 per 100 000 in India, and 148·7 per 100 000 in Indonesia. These differences are also shown in risk factors across all sites. Consumption of water at work site,[37] non-boiled untreated spring water,[38–40] water from a non-municipal source,[41] and contaminated tap water[42] all relate to waterborne transmission; whereas consumption of ice cream[37] and consumption of food from outdoor vendors[37,43,44] suggest foodborne infection. There are also general risk factors—ie, high population density,[38,42] unsanitary living conditions,[42] poor hygiene and hygiene practices,[41,43] low socioeconomic status,[45] and recent contact with a patient with typhoid fever.[45] Control measures should be tailored to local data, which are not available.

Typhoid fever in Africa

Typhoid fever is even less well understood in Africa than it is in Asia; largely due to poor resources for laboratory diagnostics and insufficient infrastructure to support epidemiological and clinical studies. These problems are manifestations of the challenges faced by a large, largely impoverished, continent with a high burden of HIV and unstable governments and with health-care priorities that overwhelm a country's ability to provide safe food and potable water. In Africa, access to safe water should not be confused with access to piped water because water treatment plants age and resources are diminished.[46] Attempts to define the burden of typhoid fever in Africa show very clearly a need for well designed studies. Crump and colleagues[23] attempted to calculate burden using published studies and concluded that information was too scarce to estimate anything better than a crude incidence rate—50 cases per 100 000 for a population of about 820 million. The 2010 Global Burden of Disease study[2] estimated similar rates, but Buckle and colleagues[1] increased these estimates—724·6 cases per 100 000—with the addition of rates from one publication from Kenya.[47] The difference in estimates is driven by data from an area in which no interventions to control typhoid fever had been introduced. Earlier studies, as used by Crump and colleagues,[23] assessed typhoid fever incidence rates after two large placebo-controlled trials for the typhoid vaccine. These trials involved more than 11 000 people in South Africa[48] and more than 32 000 people in Egypt[49] and so herd immunity (and hence decreasing incidence of typhoid fever in the controls) might have lowered disease rates. The shortcomings in use of these data for a continent of 1045 million people that covers 30·3 million km² were acknowledged in Kenya in 2009, where investigators identified the need to establish better estimates of the disease burden.[50] One method to address this issue could be to use local resources; several facilities in the least developed regions of Africa are capable of laboratory-based studies and have contributed to data for the disease, again results show large regional variation.

Comparison between surveillance data for Malawi and South Africa shows variance in demographics of patients with typhoid fever. Typhoid fever in Malawi and South Africa remains a disease mainly in children aged 5–15 years,[51] whereas in urban areas of Kenya (where crude incidence rates for typhoid fever can be as high as 247 cases per 100 000), disease is recorded predominantly in children younger than 10 years.[52] Incidence in urban areas is 15 times that reported for rural Kenya.[47] By contrast, in Ghana the disease seems to be more common in children younger than 5 years,[53] and in Moshi, Tanzania, typhoid fever is commonly diagnosed in both adults and children.[54,55] These data, as with the early data from Asia, are not comparable, but clearly there are huge demographic and geographic differences in individuals who are susceptible to typhoid fever. The situation in Zimbabwe is of particular concern—the official cumulative figures for 2013 to the end of April report more than 6800 suspected disease cases and 142 patients confirmed to have typhoid fever.[56]

A confounding factor in estimation of burden for typhoid fever is the rise of non-typhoidal salmonellosis as an invasive and often fatal disease in Africa (table 3);[57]

this issue has not been reported in Asia.[58] A lack of appropriate technology for *Salmonella* spp serotyping in low-resource settings prevents discrimination between enteric fever caused by *S* Typhi or *S* Paratyphi A and infection with non-typhoidal salmonellosis, therefore rates might obscure the true incidence of typhoid fever. Control measures, such as prevention with vaccination, treatment with antibacterial drugs, and control of transmission with public health interventions, are different for invasive non-typhoidal salmonellosis, typhoid fever, and paratyphoid fever; therefore, it is important that all of these diseases are recognised.

A further threat to control of typhoid fever in Africa, as it is elsewhere, is that of multidrug resistance. Culture remains the preferred method to confirm cases of typhoid fever and to capture information about emerging antimicrobial resistance in *S* Typhi in Africa. However, in outbreaks, the newer rapid diagnostic tests, although not ideal, might be more useful than culture to define the extent of the outbreak.[7–10] These tests cannot replace culture and recommendations for locations with poor resources are to continue culture of certain patients so that data for antimicrobial susceptibility are recorded.

Although it is rare to find a documented travel history for African patients, most multidrug-resistant cases of typhoid fever in Africa seem to be mainly from outside the continent.[60] Investigators have reported endemic outbreaks in Africa[61] and sporadic cases associated with travel to an African country,[61–64] although these reports are less frequent than are reports of typhoid fever associated with travel to Asia.[62,65,66] The threat of invasive, multidrug-resistant organisms circulating in a region with little capacity for epidemiology and laboratory study show the need for international collaboration and standardised methods to identify and subtype these pathogens. We are aware of some initiatives—eg, WHO supports an external quality assessment programme through its Regional Office for Africa, and the WHO Global Foodborne Infections Network offers training and simplified biochemical procedures for identification of *Salmonella* spp (including *S* Typhi) and *Shigella* spp (panel 2). International collaboration between participants of PulseNet have tracked isolates (and patients) across continents;[61] investigations that were enhanced by laboratories in Africa.

In summary, much is not known about typhoid fever in Africa; and appropriate technology to assess the actual burden of disease is not available.[8] Very little is known about the apparent protective effect of HIV against typhoid fever,[54,55] the role of vertical transmission, and the potential effect of inclusion of typhoid fever in a differential diagnosis in neonatal sepsis in endemic areas;[67] the role of outbreaks of circulating endemic strains in the generation of population immunity in all people apart from very young children;[60] the role of strain variation in outbreaks with high mortality rates that are complicated by intestinal perforation[68] (or neurological manifestations[69]); and the role of contaminated water supplies.[70] Diagnosis and management of typhoid fever in Africa is affected by several challenges, including poor access to epidemiological and diagnostic resources, inadequate supply of safe water and sanitation, and rapidly emerging resistance to antimicrobial drugs. Concerted efforts through provision of safe food and water and targeted vaccination campaigns[71–73] could help to control typhoid fever in Africa.

	Findings
Moshi, Tanzania[54,55]	Typhoid fever is more common than is non-typhoidal salmonellosis in both children and adults
Malawi and South Africa[51]	Typhoid fever seen mainly in children aged 5–15 years with a case frequency lower than that for non-typhoidal salmonellosis
Kenya[52]	Typhoid fever more common than non-typhoidal salmonellosis in an urban area
Pemba Island, Tanzania[59]	*Salmonella enterica* serovar Typhi is the most prevalent isolate from blood cultures
Lagos, Nigeria[7]	*Salmonella enterica* serovar Typhi the most common *Salmonella* spp in blood cultures (1999–2008); estimated incidence 16 cases per 100 000

Table 3: **Comparison of typhoid fever with non-typhoidal salmonellosis**

Panel 2: Training courses from the WHO Global Foodborne Infections Network

The Global Foodborne Infections Network is a WHO network that among others builds capacity to detect, control, and prevent foodborne and other enteric infections. More than 80 training courses are coordinated through Technical University of Denmark, National Food Institute, Denmark, which is a WHO collaborating centre for antimicrobial resistance. Through this work, the institute is involved with surveillance of global antimicrobial resistance. Protocols that cover, among others, antimicrobial suscptibility testing, identification and isolation of foodborne pathogens, and pulsed-field gel electrophoresis, and complete sets of protocols for the different levels of training courses needed are on the website of the network.

For the WHO **Global Foodborne Infections Network website** see http://www.antimicrobialresistance.dk/232-169-215-protocols.htm

Antimicrobial drug resistance

The global distribution of drug resistance in *S* Typhi

Mortality rates in patients with typhoid fever who are not given specific chemotherapy can be as high as 26%,[74] although earlier work describes mortality rates of 10% or lower that were associated with careful management including strict adherence to a milk diet.[75] The introduction of chloramphenicol (in 1948), ampicillin (1961), co-trimoxazole (1970s), and third-generation cephalosporins and fluoroquinolones (1980s) reduced the mortality of typhoid fever considerably. However, multidrug-resistant strains[14] that were resistant to all three first-line antimicrobial drugs emerged in the 1980s, followed by stains resistant to fluoroquinolones in the 1990s.[76,77] Cephalosporin resistance has been slower to emerge, but extended-spectrum β-lactamase-producing organisms are increasingly noted.[78] If extended-spectrum β-lactamase-producing *S* Typhi become widespread, then treatment options could become severely scarce.[79]

For more on **PulseNet** see http://www.cdc.gov/pulsenet/

Azithromycin is increasingly given for enteric fever, but is mainly used to treat children and patients with multidrug-resistant enteric fever because of its cost.[80] *Salmonella* spp breakpoints for azithromycin are not formalised, complicating comparison with reported resistance; however the European Committee on Antibiotic Susceptibility Testing issued interpretative criteria that regard susceptible *S* Typhi isolates as those with minimum inhibitory concentrations of 16 mg/L or lower.

As long-distance travel becomes more accessible and residents in developed countries visit friends and relatives in typhoid-endemic areas, health-care providers in all countries need access to information about local and regional susceptibility to guide empirical treatment. This need will remain until the development of rapid diagnostics that can predict the susceptibility to an infecting organism. Peer-reviewed data for antibiotic resistance of *S* Typhi in the Americas are extremely scarce, but data available from regional laboratories[81] and from investigation of travellers returning to the USA[82] suggest little resistance in the region (figure 2).

In non-endemic Europe, 1417 confirmed cases of typhoid fever were reported to the European Centre for Disease Prevention and Control in 2012, of which most cases were either travel-related or in patients with an unknown travel history. In Russia and central Asia, data for antimicrobial resistance in *S* Typhi are available only from Russia, which reported no resistance to cephalosporin drugs in isolates, high rates of resistance to nalidixic acid (88% of isolates), and moderate rates of resistance to other antimicrobial drug classes, including ciprofloxacin (2%) and nalidixic acid from 2005 to 2011 (figure 2).[84]

Most countries in the Middle East have reported detection of *S* Typhi strains with decreased ciprofloxacin susceptibility. Several countries (Afghanistan, Jordan, Libya, Morocco, and the United Arab Emirates) have reported detection of isolates of *S* Typhi that were multidrug resistant. A few countries (Kuwait,[85] Saudi Arabia,[86] and Lebanon[87]) have reported detection of strains that were multidrug resistant and had decreased ciprofloxacin susceptibility. From Kuwait there have also been reports of extended-spectrum beta-lactamase-producing *S* Typhi.[88]

Substantial rates of resistance to first-line antimicrobial drugs were detected in southeast Asia in the 1990s. This trend prompted authorities to change empirical treatment guidelines for enteric fever from recommendations for chloramphenicol to recommendations for fluoroquinolones. This change resulted in the progressive re-emergence of susceptibility to first-line drugs and a rapid increase in resistance to nalidixic acid. For example, in Karnataka, India, 58% of *S* Typhi isolates collected between 1996 and 1999 were multidrug resistant; whereas in 2004, no multidrug-resistant *S* Typhi isolates could be identified.[89] In Nepal in 2006, only 3% of isolates were classified as multidrug resistant.[90] Investigators for a similar study in 2012 in Nepal identified no ampicillin resistance in *S* Typhi.[91] However, the global spread and clonal expansion of multidrug resistance and decreased ciprofloxacin susceptibility in clones suggests that this trend might not last and that the reintroduction of previously used drugs will probably not be useful. The situation is similar in Cambodia, China, Hong Kong, Indonesia, Malaysia, South Korea, and Vietnam.[35,92–96] Researchers of two studies have described low rates of resistance in Lao; 16% of the *S* Typhi isolates were multidrug resistant, with no combined nalidixic acid resistance detected in these strains.[92,97] By contrast, two confirmed cases of extended-spectrum β-lactamase-producing *S* Typhi have been reported in the Philippines (figure 2).

In Africa, the emergence of *S* Typhi strains with multidrug resistance[7,47,98] and decreased ciprofloxacin susceptibility[7,64,99–102] is now an important issue. Rates of

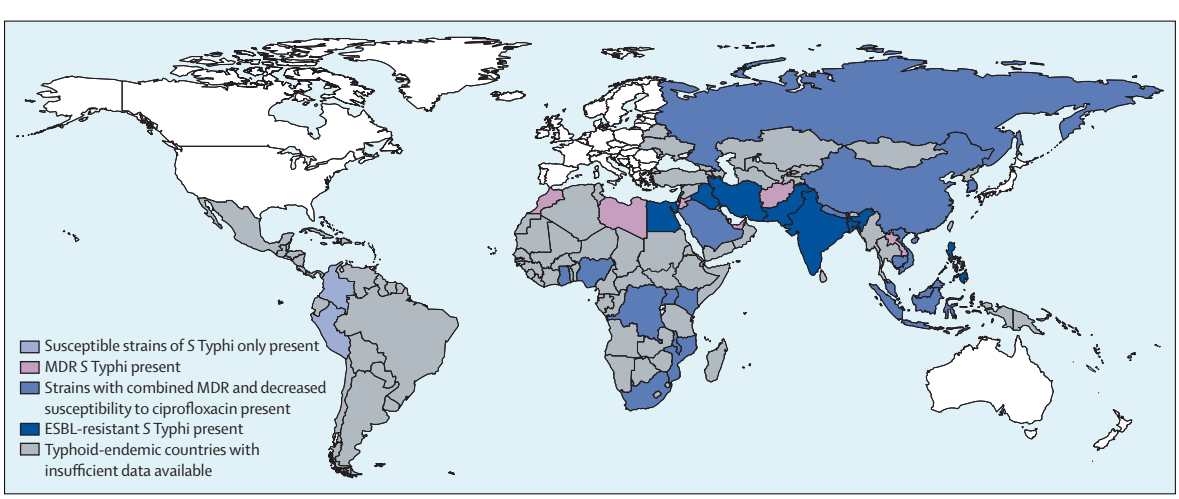

Figure 2: **Worldwide distribution of antimicrobial drug resistance in *Salmonella enterica* serovar Typhi**
MDR is defined as resistance to the first-line antimicrobial drugs ampicillin, co-trimoxazole, and chloramphenicol. MDR=multi-drug resistant. ESBL=extended-spectrum beta-lactamase-producer. Adapted from Bhan and colleagues,[83] with data up to April, 2013.

multidrug resistance vary—eg, 30% in the Democratic Republic of the Congo,[55] 63% in Ghana,[97] 70% in Kenya,[98] and 100% during an outbreak along the Malawi–Mozambique border.[59] During a prolonged outbreak in western Uganda, the percentage of multidrug-resistant strains of *S* Typhi rapidly increased from 5% in 2009 to 83% in 2011, and rates of resistance to nalidixic acid increased from 0% in 2009 to 6% in 2011, and reached 87·5% in 2012.[103] About 14% of isolates collected during 2011 in South Africa were nalidixic acid resistant, none of these isolates were resistant to ceftriaxone or imipenem. The global spread of a resistant strain, haplotype 58 (H58), described initially in southeast Asia[101] and now present in Africa,[60] is of particular major concern and highlights a need to improve epidemiological investigation to define the origin of multidrug-resistant clones.

Mobile genetic elements in *S* Typhi

The worldwide emergence of resistance to first-line antibiotic drugs has been associated with a well described group of plasmids, *inc*HI1.[104–108] Occasionally, investigators have reported other plasmids in extended-spectrum β-lactamase-producing *S* Typhi, but occurrence is rare.[104] Many of the resistance genes that cause the multidrug-resistance phenotype of *S* Typhi are contained in *inc*HI1 plasmids that contain several mobile elements (Tn*9*, Tn*10*, and Tn*21*), which, in turn, might contain class one integrons.[109] Some researchers have speculated that the presence of genes that encode resistance to antimicrobial drugs and to heavy metals are maintained in the bacterial population through selective advantage for plasmid carriage in *S* Typhi,[109] and that this carriage led to the emergence of one plasmid type associated with a haplotype of *S* Typhi (H58).[108] The next step in this rapid evolutionary pathway could be transfer of resistance genes to chromosomes.

Fluoroquinolone resistance in *S* Typhi

Fluoroquinolone resistance in *Salmonella* spp is usually mediated via chromosomal mutations, in the target proteins, DNA gyrase (encoded by *gyr*A and *gyr*B), and topoisomerase IV (*par*C and *par*E), or by plasmid-mediated resistance, typically encoded on *qnr* or *aac(6′)-Ib-cr*. In *S* Typhi, increase in minimum inhibitory concentration is associated with the accumulation of known chromosomal mutations[110–114] including a novel mutation at codon 64 in *gyr*B.[115]

Extended-spectrum β-lactamases in *S* Typhi

Despite emerging resistance to extended spectrum cephalosporins and carbapenems in non-typhoidal salmonella in human beings and animals, not many cases of extended-spectrum β-lactamases in *S* Typhi have been reported. extended-spectrum cephalosporinase-producing strains of *S* Typhi have so far been reported only in sporadic cases in Bangladesh,[116] Egypt,[117] India,[118] Kuwait and the UAE,[88] Iraq,[78] Pakistan,[119] and the Phillippines.[12] Of those, only the cases from India ($bla_{CTX\text{-}M\text{-}15}$)[88] Iraq, India ($bla_{CTX\text{-}M\text{-}15}$)[78,120] and the Phillippines ($bla_{SHV\text{-}12}$)[12] have been confirmed. The first case of an AmpC-producing *S* Typhi was reported in 2009 in which *S* Typhi isolates with the $bla_{CMY\text{-}2}$ gene were isolated from an Indian child.[118] This finding is not suprising since third-generation cephalosporins are now being given due to the wide distribution of multidrug-resistant *S* Typhi isolates with decreased cephalosporin susceptibility, and so selective pressure for resistance is increasing.

Emerging resistance

Increasing isolate resistance to fluoroquinolones and the emergence of cephalosporin resistance are of concern. Fourth-generation fluoroquinolones have good activity against *S* Typhi, but concerns about toxic effects (gatifloxacin was banned by the Indian Government in 2011), cross-resistance to other fluoroquinolones, and stewardship initiatives (potentially limiting moxifloxacin to treatment for tuberculosis[121]) could prevent the widespread use of these drugs for typhoid fever. Although not widely used, carbapenem drugs and tigecycline show good in-vitro activity and are potentially drugs of last resort.[122] The re-emergence of strains susceptible to chloramphenicol and co-trimoxazole has raised the possibility of re-introduction of these first-line antimicrobial drugs, but concerns remain that resistance would develop rapidly.[79,101,123]

Vaccination

Available vaccines

At present, typhoid fever can be effectively treated with antibiotic drugs, but the growing rates of antibiotic resistance make vital the consideration of a comprehensive approach to targeted vaccination of high-risk populations, combined with the longer-term solutions of provision of safe water and improved sanitation. Vaccination against *S* Typhi with heat-inactivated phenol-preserved, whole-cell typhoid is protective against typhoid fever; the vaccine has 51–88% efficacy in children and young adults, with protection for up to 7 years.[124] Toxic effects led to development of new-generation vaccines in the 1970s—one oral live attenuated vaccine (Ty21a) and one purified Vi polysaccharide vaccine. The Ty21a vaccine three-dose regimen has an overall protective efficacy of between 67% and 80%,[125,126] but is only licensed for use in individuals older than 2 years and availability is lower than needed. As of August 2012, WHO is reviewing the application for prequalification of Ty21a to allow procurement through UNICEF, the Pan American Health Organisation, and other organisations such as GAVI Alliance.

The Vi vaccine was developed from virulent *S* Typhi with use of non-denaturing purification and elicits anti-Vi serum IgG antibodies in 85–95% of people older than 2 years.[127] The Vi vaccine is well tolerated, safe, and shows evidence of herd protection when given to a large

proportion of a community.[128] The most common side-effect is localised pain. Similar to other polysaccharide vaccines, Vi is not immunogenic in children younger than 2 years, and is licensed for use from this age. There was no patent protection for the production technology of Vi vaccine so manufacturers in developing countries began producing the vaccine in the 1990s. At present, at least 3 manufacturers export the vaccine (Sanofi Pasteur, GlaxoSmithKline Biologicals, and Bharat Biotech) and many other companies produce it for local use (eg, Lanzhou Institute in China, Chengdu Institute in China, Finlay Institute in Cuba, and Dalat Vaccine Company in Vietnam). WHO prequalified one of these vaccines, from Sanofi Pasteur, and it is available to purchase for the UN agencies and the GAVI Alliance.

Future vaccines

Vaccines are poorly immunogenic in young children and immunity lasts only a few years. The most accessible vaccination route is to young children through the expanded programme for immunisation and, in developing countries, young children are those who probably have the highest burden of disease. There are therefore efforts to develop new vaccines that can be given to young children. The most advanced is a glycol-protein conjugated vaccine, the Vi-conjugate vaccine. There are several different protein carriers to the Vi-conjugate vaccine—recombinant exoprotein of *Pseudomonas aeruginosa* (rEPA), tetanus toxoid, and diphtheria toxoid or its derivative CRM_{197}. Vi-rEPA was first developed by the US National Institutes of Health and underwent clinical trials in the USA and Vietnam, but production was not brought forward to industrial scale.[129] Two Vi-conjugate vaccines are licensed in India, both conjugated to tetanus toxoid (PedaTyph and TypBar-TCV). Other candidate Vi conjugate vaccines are in clinical trials done by several manufacturers and developers,[130,131] and single-dose live attenuated oral vaccines, which could be given to infants, are in development.[132,133] Although research into novel vaccine candidates rightly continues,[21] implementation of existing vaccines is priority for global control of typhoid.

Programmatic use of vaccines

WHO recommended use of typhoid vaccines in high-risk populations in 1999; however, the public sectors of only three countries have complied.[71,134] Use as a preventive action has been reported—ie, after a tsunami in 2004, Pondicherry (India) local government used 17 000 doses of Vi polysaccharide vaccine; in 2010 after cyclone Tomas, the Vi polysaccharide vaccine was used as a response to an outbreak of typhoid in Fiji to control the outbreak and prevent further spread from the neighbouring villages; in 2009 the Government of Sri Lanka set up a guideline to vaccinate, with Vi polysaccharide vaccine, the internally displaced population after the civil war; and more recently school-based pilots to introduce vaccine programmes with Vi polysaccharide have been done in parts of Karachi, Pakistan, and Kathmandu, Nepal, vaccinating nearly 400 000 students. In China, technology transfer by the US National Institutes of Health allowed six state-run vaccine companies to produce the vaccine for the mass vaccination of school children and food handlers in the mid-1990s. The Chinese programmes have largely reduced incidence of typhoid in some areas of southwest China (eg, parts of Guangxi[32]). The Vietnam National Immunisation Programme also began annual campaigns in 1997 with use of imported and then locally-produced Vi polysaccharide vaccines for children aged 3–10 years in some high-incidence districts. Although there is no data to assess its effect, Delhi state, India, introduced use of Vi polysaccharide vaccines in children aged 2–5 years through community-based vaccination campaigns in 2004. Thus, available vaccines are effective methods for public health, but are still not being used widely enough to protect whole populations.

Conclusions

Typhoid fever remains the predominant enteric fever worldwide, but enteric fever caused by *S* Paratyphi *A* is increasingly reported.[35,135,136] Since the different *Salmonella* spp serovars that cause enteric fever have very different ancestries, clinical similarities must be the result of convergent evolution and it is therefore not appropriate to assume that all enteric fever can be managed in the same way; risk factors vary,[135] and vaccines are not cross-protective. However, there is scope for a concerted disease-prevention programme against all enteric fevers through use of improved surveillance to differentiate between the causes of enteric fever so that public health interventions can be targeted correctly and any further serovar replacement can be detected early. For the findings outlined in this Seminar to be used, support for laboratories within developing countries is essential.

Contributors

KHK did the searches for and wrote the section on typhoid fever in Africa. MLM and RSH did the searches for and wrote the section on antimicrobial resistance. RSH also created figure 2. JW drafted the outline for the original Seminar, recruited the authors, drafted the general introduction and conclusions, created the reference list, did the article coordination and final drafting, responded to the reviewers, and created figure 1 and the panels and tables. RLO did the searches for and wrote the sections on typhoid fever in Asia and vaccination. All authors had input into final Seminar, including for revisions.

Declaration of interests

KHK is a permanent employee of the National Institute for Communicable Diseases, South Africa. MLM is a permanent employee of the US Government (Department of Health and Human Services, Centers for Disease Control and Prevention). The findings and conclusions in this manuscript are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention. RSH is permanently employed by the Technical University of Denmark, National Food Institute. JW is the Chief Scientific Officer and Director for Discuva, an antibiotic discovery company. RLO is currently an employee of Sanofi Pasteur, which is a producer of typhoid vaccine. He was formerly an employee of the International Vaccine Institute, Seoul, Korea and independent at the time of writing

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