The evolution of antimicrobial resistance in *Salmonella* Typhi

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- Antimicrobial resistance is a continuing clinical challenge in treating typhoid fever
- Resistance to first and second line antimicrobials in *Salmonella* Typhi is common and associated with treatment failure
- A specific genotype of Salmonella Typhi is associated with multi-drug resistance and resistance to fluoroquinolones and is spreading internationally
- Resistance to alternative antimicrobials such as azithromycin and ceftriaxone is rare but has been reported

Abstract

Purpose of review: Increasing antimicrobial resistance in *Salmonella* Typhi is a serious public health concern, especially in industrializing countries. Here we review recent clinical and laboratory data concerning the evolution of antimicrobial resistance, with particular reference to the emergence resistance against fluoroquinolones, third generation cephalosporins, and azithromycin.

Recent findings: The last 40 years have witnessed the sequential emergence of resistance to all first-line antimicrobials used in the treatment of *Salmonella* Typhi infections. Multi-drug resistance (MDR), defined by resistance to chloramphenicol, amoxicillin, and co-trimoxazole, emerged in the 1990's, followed rapidly by reduced susceptibility to fluoroquinolones. In the current decade, high level fluoroquinolone resistance has emerged in south Asia and threatens to spread worldwide. Increasing reliance is now being placed on the activity of third generation cephalosporins and azithromycin, but resistance against these agents is developing. Carbapenems and tigecycline may be alternatives, although clinical data are sparse, and in some settings reversion to chloramphenicol and co-trimoxazole susceptibility is occurring. Therefore, older drugs may yet have a role in the treatment of *Salmonella* Typhi infections.

Summary: Good surveillance, improved diagnostics, more prudent use of antimicrobials, and effective vaccines will all be critical to reducing the burden of disease caused by *Salmonella* Typhi.

Keywords

Salmonella Typhi, enteric fever, antimicrobial resistance, typhoid

Introduction

Bacteria belonging to the genus *Salmonella enterica* are a leading cause of community acquired bloodstream infection in low and middle-income countries (LMICs). *Salmonella enterica* serovar Typhi (*Salmonella* Typhi), a human restricted pathogen, causes a non-specific febrile illness called 'typhoid' or 'enteric' fever that is clinically difficult to distinguish from many other infectious diseases (1,2). The disease is common in many LMICs in Asia and parts of Africa and without effective antimicrobial treatment infection can lead to lead to serious, life-threatening complications, such as small bowel perforation and meningitis (3).

Several efforts have been made to estimate the global burden of typhoid fever (4,5). The most recent estimate, performed by Buckle *et al.* in 2010, suggested that between 13.9 and 26.9 million cases occur worldwide annually (6). However, these estimates provide only a broad measure of the typhoid burden and there are major regional gaps in these calculations (7). The lack of a reliable, rapid, and widely available diagnostic test for typhoid fever is a serious limitation for both for doctors caring for patients and for those attempting to define burden of disease (8). Diagnostic confirmation and antimicrobial susceptibility profiling is currently dependent upon the isolation of the bacteria from blood cultures, but the required microbiology laboratory capacity is limited in many typhoid endemic LMICs. This lack of diagnostic capacity has led to a particular reliance on serological testing and with the Widal test, which is associated with a high proportion of false positives. A consequence of a high rate of misdiagnosis is the likely overtreatment of patients, incomplete data regarding drug susceptibility, and potentially inaccurate estimates of disease incidence (9).

Text of the review

Clinical and epidemiological features

The clinical manifestations and the severity of typhoid fever can vary by patient population. The majority of patients presenting to hospitals in LMICs with typhoid fever are children or young adults between the ages of 5-25 years (10,11). In endemic areas with a high disease burden, community population based studies have indicated that many patients with typhoid have a non-specific febrile illness that is not recognized clinically as typhoid (12). Between 60 and 90 per cent of people with typhoid do not receive adequate medical attention or are treated as outpatients. For hospitalized patients, effective antimicrobials, good nursing care, adequate nutrition, careful attention to fluid electrolyte balance, and prompt recognition and treatment of complications are necessary to avert complications and the progression to severe and potentially fatal typhoid fever (13).

Antimicrobial therapy and resistance

Typhoid fever has a low mortality when it is recognized early and treated with effective antimicrobials. But if treatment is delayed or is rendered ineffective by resistance the complication and case-fatality rate increases substantially (13).

Chloramphenicol was the first widely used antimicrobial treatment for typhoid fever. Discovered in 1947, chloramphenicol was introduced into clinical practice throughout the 1950s and quickly recognized as highly effective in typhoid fever treatment. By the 1980s, chloramphenicol, ampicillin, and co-trimoxazole were the first line treatments for typhoid fever globally, until resistance to these three drugs emerged in the late 1980s. These bacteria were defined as multidrug resistant (MDR) and their spread led to the increasingly common use of fluoroquinolones, such as ciprofloxacin and ofloxacin (14–16). By the late 1990s, widespread use of these fluoroquinolones led to the emergence of decreased ciprofloxacin susceptibility [MICs ≥2 μg/ml]. These bacteria, which were (are) generally defined by *in vitro* resistance to nalidixic

acid, were observed non-endemic countries and usually associated with international travel to South and Southeast Asia (7,17–19).

More recently, decreased ciprofloxacin susceptibility in south Asia has been followed by the emergence high level fluoroquinolone resistance, which is associated with sequential mutations in the chromosomal quinolone-resistance-determining regions (QRDR) of the genes encoding DNA gyrase (*gyrA*), and the topoisomerase IV (*parC*) (20). By 2011, there were reports from South Asia of highly fluoroquinolone resistant *Salmonella* Typhi (MIC ≥256 μg/ml) with a novel *gyrA* mutation (21–24). In work conducted during a randomized controlled trial in Nepal researchers found a new variant of *Salmonella* Typhi that was significantly associated with prolonged fever clearance times and treatment failure (25). Phylogeographic analysis has defined an on-going intercontinental epidemic of a specific antimicrobial resistant *Salmonella* Typhi lineage. This lineage, which is known as H58 (now defined as genotype 4.3.1) began to emerge in South Asia in the early 1990s, is associated with incH1 plasmids carrying the genes encoding an MDR phenotype. This very successful lineage, which may have been driven and selected by its ability to maintain and traffic MDR plasmids, is also associated with reduced susceptibility and resistance to fluoroquinolones through the common *gyrA*/*parC* mutations. The on-going dissemination of H58 *Salmonella* Typhi from Asia and into Africa suggests that the regional and global dispersal of a lineage exhibiting high level resistance to fluoroquinolones is now a real possibility (26–28).

Third generation cephalosporin resistance

Increasing resistance to fluoroquinolones in *Salmonella* Typhi has led to an increased use of azithromycin and third generation cephalosporins in the treatment of typhoid in South Asia. These agents have subsequently become the first line therapy for uncomplicated infection in many endemic countries, including India.

Ceftriaxone has been the principal third generation cephalosporin evaluated in recent clinical trials, although cefixime, cefotaxime, and cefoperazone have also been investigated with variable clinical success (29). Cefixime is the only third generation cephalosporin that can be given orally and has thus achieved widespread popularity amongst physicians looking to avoid the in-patient complication associated intravenous antimicrobial therapy. However, data from a randomized controlled trial conducted in Nepal, before the emergence of high-level fluoroquinolone resistance, indicated that cefixime was substantially less efficacious than gatifloxacin (29).

Resistance to third generation cephalosporins in has not yet emerged as widely as resistance against the fluoroquinolones. However, Extended Spectrum Beta Lactamase (ESBL) producing *Salmonella* Typhi organisms are being increasingly reported, particularly among patients in Asia and in travellers returning from South Asia (Table 1) (30–33). Reports have shown that in some isolates the MIC for ceftriaxone has gradually increased from <1μg/ml to isolates exhibiting an MIC of >20μg/ml (34). *Salmonella* Typhi has been reported to be associated with a variety of ESBL genes including those encoding the TEM, SHV, PER, and CTX-M enzymes and also Amp-C (35,36). The emergence of ESBL producing organisms is extremely concerning, particularly if they have already acquired MDR and/or fluoroquinolone resistance associated determinants and mutations.

Azithromycin resistance

Initial clinical studies of azithromycin for typhoid treatment suggested uncertain efficacy (37). However, more recent investigations have demonstrated that it is associated with prompt resolution of clinical symptoms, and low rates of relapse and convalescent faecal carriage (16,38–42). However, the doses of azithromycin in these studies varied between 10 and 20 mg/kg/day for

between 5 to 7 days and the optimum azithromycin treatment regimen for typhoid remains uncertain.

In the last decade there have been sporadic reports, predominantly again from South Asia, of *Salmonella* Typhi with azithromycin MIC of ≥32 μg/ml, although there are limited published data on the clinical response to azithromycin in such infections (Table 1)(43–45). In addition, there is lack of agreement as to how to define azithromycin susceptibility *in vitro*. The CLSI only provided azithromycin disc diffusion and MIC interpretive criteria for *Salmonella* Typhi in 2015 (46). Resistance to azithromycin may be more problematic in *Salmonella enterica* Paratyphi A, with reports from various parts of South Asia (Table 1).

To date there is only a single case report of clinical and microbiological failure using azithromycin in *Salmonella* Typhi (47). The mechanism for resistance was not defined in this specific report, despite the macrolide efflux pump genes, *macA* and *macB*, being reported in some *Salmonella* Typhi strains circulating in India (47).

Evolving resistance and treatment strategies

Increasing drug resistance has necessitated the investigation of other antimicrobials for typhoid, especially for severe disease. Carbapenems (meropenem, imipenem, and ertapenem) and the glycylcline antimicrobial, tigecycline, have become increasingly common empirical therapy for severe typhoid (48)(16). A recent study reported tigecycline was highly active at a concentration of 2 μg/ml against *Salmonella* Typhi *in vitro*, inhibiting growth of >97% of isolates (48). These data were comparable to data released by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and a further study performed on a large number of *Salmonella* isolates (48–50). Notably, tigecycline was found to have good *in vitro* activity against ceftriaxone resistant *Salmonella* isolates (48). Data from clinical trials are now required to assess the relative

merits of tigecycline in comparison to alternative antimicrobials for the treatment of typhoid fever.

Attention has also turned back to the use of older antimicrobials, such as chloramphenicol and co-trimoxazole, for the treatment of uncomplicated typhoid fever. The avoidance of these agents in treatment over the last two decades has led to the re-emergence of *Salmonella* Typhi susceptible to them and some recent reports from Asia have reported their successful use in typhoid fever treatment (51,52). Some studies have suggested that the MDR prevalence may now be as low as 10% in some settings that were previously dominated by MDR variants (35). A trial comparing azithromycin with co-trimoxazole for the treatment of undifferentiated fever in Nepal (around one third of which is caused by *Salmonella* Typhi) is currently underway and should provide valuable data as alternative treatment strategies are being considered (53).

Conclusion

The continuous evolution of resistance to commonly used antimicrobials in *Salmonella* Typhi is an important public health concern. With the emergence and circulation of the H58 *Salmonella* Typhi genotype in South Asia, fluoroquinolones should no longer be recommended as first line typhoid treatment. Ceftriaxone and azithromycin are being increasingly used, but *Salmonella* Typhi resistant to these agents is now being reported. Carbapenems and tigecycline may be effective in the treatment of more severe disease, but comparative clinical trials are required. The declining prevalence of MDR *Salmonella* Typhi mean that older drugs such as chloramphenicol and co-trimoxazole may offer renewed therapeutic options, but the rapid re-emergence of resistance seems likely if these drugs are widely used. Future reductions in the burden of *Salmonella* Typhi disease are likely to depend upon better surveillance systems and an effective vaccine. Routine vaccination for typhoid in LMIC will become a real possibility in coming years should Vi conjugate vaccines be prequalified by the World Health Organization. These new

generation vaccines have the potential to have a major impact in typhoid endemic areas. We should, however, remain vigilant and continue to evaluate the most effective antimicrobial treatments and monitor the ever-changing landscape of *Salmonella* Typhi antimicrobial resistance.

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Conflicts of interest

None

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Table 1. Reports of resistance to azithromycin and third generation cephalosporins in organisms causing enteric/typhoid fever

Investigation	Country/location	Year	Reference
Azithromycin resistance			
First report of resistance in *Salmonella* Paratyphi A leading to treatment failure	Pakistan	2010	(43)
Failure of oral antimicrobials (including azithromycin) in the treatment of a breast abscess caused by *Salmonella* Paratyphi A	Bangladesh	2012	(54)
Rationale for azithromycin prescribing practices for enteric fever in India	India	2012	(55)
Azithromycin and ciprofloxacin resistance in *Salmonella* bloodstream infections	Cambodia	2012	(56)
Antimicrobial susceptibility of *Salmonella enterica* serovars in a tertiary care hospital in	India	2013	(57)
Failure with azithromycin treatment in a case of *Salmonella* Paratyphi A	India	2014	(58)
Salmonella subtypes with increased MICs for azithromycin in travellers returning to the Netherlands	Predominantly South Asia	2014	(45)
Third generation cephalosporin resistance			
blaCTXM-1 ESBL producing *Salmonella* Typhi from hospitalised patients	Nigeria	2015	(59)
ESBL producing *Salmonella* serovar Typhi in a traveller returning from to Spain	South America	2016	(30)
Individual patient data analysis of 2092 participants enrolled in to 4 randomised controlled trials	Nepal	2017	(60)
Occurrence of extended spectrum and AmpC beta lactamases in *Salmonella* isolated from clinical samples	Nigeria	2017	(61)
Azithromycin and third generation cephalosporin resistance			
Drug resistance pattern in *Salmonella* Typhi with special reference to cephalosporins and azithromycin in the Gangetic plain	India	2017	(34)

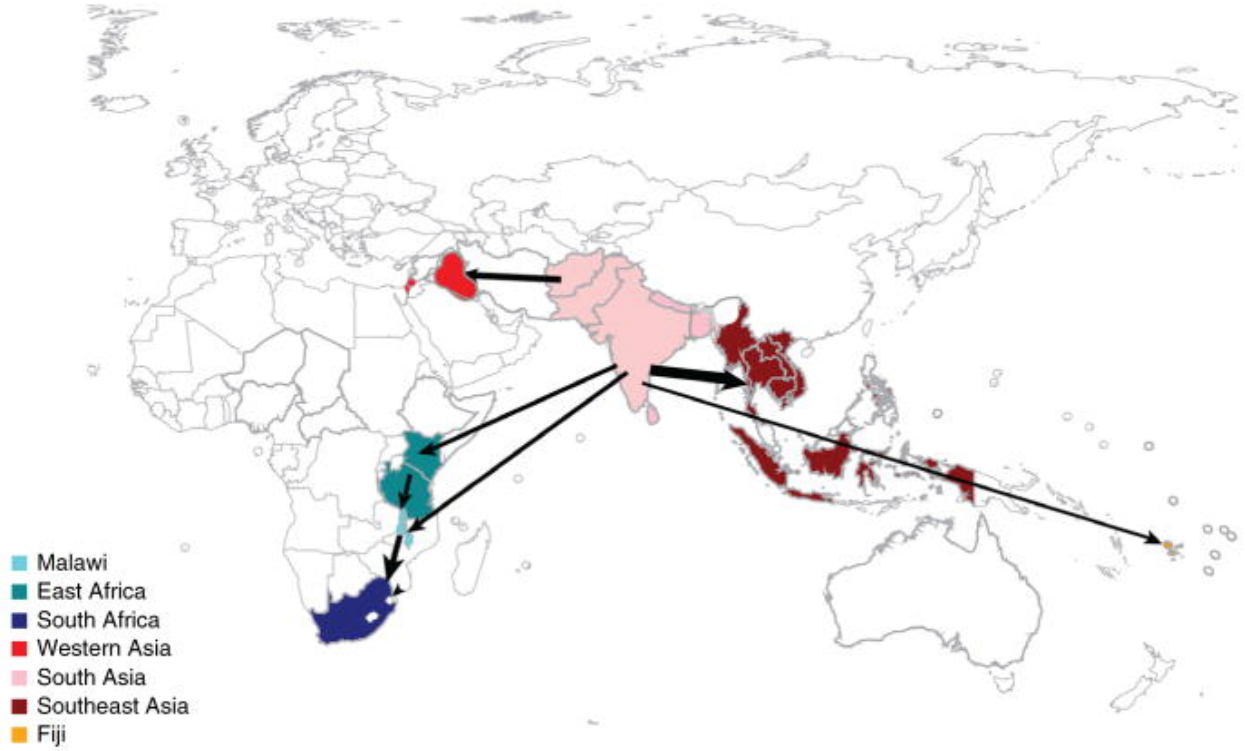

Figure 1. Major geographical transfers within the H58 lineage, inferred from a phylogenetic tree constructed through genome sequences. The size of each arrow indicates the relative number of likely transfers between regions or countries. Taken from Wong et al. 2015 (26).