Typhoid Fever Drug Resistance Outcomes and Current Vaccine Recommendations

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Abstract

The incidence of typhoid fever has not decreased since 1990, making it an important yet neglected contributor to health care costs. There has been an emergence of multi drug resistant typhoid fever, wherein there is no response to the first line of antimicrobials like ampicillin, chloramphenicol and cotrimoxazole. The fluoroquinolones and cephalosporins have been used in the treatment of cases, but there has been a recent epidemic of resistance to these drugs in some parts of the world. The H58 clade which is responsible for the development of resistance, has been found globally, indicating a geographical spread. Plasmid mediated transfer of resistance along with genetic mutations contribute to the extensive spread of antimicrobial resistance. To reduce the incidence of typhoid fever, the widespread use of protein conjugate typhoid vaccine is recommended in addition to improvements in awareness, general health and sanitation.

Keywords: Incidence; Plasmid mediated; Multidrug resistant; H58; Antimicrobial resistance; Conjugate vaccine; Vaccine recommendations; Global spread

Introduction

About the disease

Typhoid fever is an acute illness that can result in generalized symptoms [1]. It is caused by a highly virulent organism, *Salmonella enterica serovar Typhi*. This is referred to as *Salmonella typhi* (*S. Typhi*).

Humans are the only known reservoirs of *S. Typhi* and transmission of the organism occurs *via* the feco-oral route. The two main patterns of dissemination are–the short cycle, with food and water contamination, either by shedding from a temporary or chronic carrier, long cycle, where in pollution of the water supplies, untreated sewage or raw faeces used as crop fertilizer.

Children are disproportionately affected by Typhoid fever [1]. In ongoing surveillance from India, Pakistan and Bangladesh, it was found that school children between 6-10 years are commonly affected, along with children below the age of 5 years [2]. Thus, it poses a serious public health challenge [1,2].

Magnitude of the problem

On a global level, typhoid fever is responsible for an enormous amount of morbidity and mortality. According to reports, there are at least 11-21 million reported cases of the disease across the world, of which roughly 121,000-168,000 die annually **(Figure 1)** [1-3]. While typhoid fever is a major problem in the school going ages of 5-15 years, the children <5 years have shown incidence rates like or exceeding these levels [1]. The 0-4 year age group is very vulnerable, with almost 27% cases falling in this group, and of these, 10% are below 1 year of age [1]. Infact, serological data has shown that up to 80% of typhoid fever cases in the Pacific region remain undiagnosed [1]. Hence, typhoid fever continues to be a major global public health issue.

Age specific disease burden

As part of the DOMI (Diseases of the Most Impoverished) program, prospective population-based surveillance studies were conducted in various parts of Asia, including North Jakarta, Indonesia, Karachi, Pakistan, Kolkata, India, Hechi, China and Hue, Vietnam [3]. The results showed high incidence rates (>100/100,000 population) in the impoverished strata, especially the urban slums. The toddlers and pre-school young children, besides the school goers are at high risk of developing typhoid fever or bacteremia, in direct proportion to the overall incidence of the disease in the community [3]. Studies reported from some

countries in Asia and Africa have confirmed the high incidence of typhoid fever in children and adolescents, as well as a variation in incidence amongst different surveillance sites in the same region [3,4]. Systematic surveillance of hospital-based studies using blood culture in parts of Africa, revealed *S. Typhi*, *Para typhi* and NTS (Non Typhoidal Salmonellosis) as common invaders amongst the pre-school and school aged children [4,5]. As there is less prominent intestinal pathology, they tend to have milder illness [5,6].

New data obtained from Sub-Saharan Africa has further helped to improve the understanding of the disease burden in children [5]. Among all ages, it is found that 29.7% of typhoid fever episodes are in the ≤ 2-year age group, 9.9% in the ≤ 1 year age group and 2.9% in the ≤ 6 months age group [5]. Ongoing studies since the past 2 decades has confirmed the continued high incidence of typhoid fever in South and South East Asia with inter and intra-country heterogeneity as noted with incidence rates ranging from as high as 496.5/100,000 persons in India and 24.2/100,000 persons in Vietnam [5].

Despite being an endemic disease, epidemics of typhoid fever are reported as large outbreaks from parts of Central Asia, posing a continued public health burden [3,5]. There is no definite data regarding the true burden imposed by these outbreaks, although well documented confirmed reports of outbreaks in several sub Saharan countries like Malawi, Mozambique, Uganda, Zambia and Zimbabwe have been noted [5]. These outbreaks are associated with a higher incidence of disastrous neurological complications like ataxia, tremors, altered mental status, dysarthria, upper motor neuron syndromes etc. has been reported from the Malawi- Mozambique region [5].

Case fatality rates range from 1%-4% in cases where adequate treatment with appropriate antibiotics are initiated early, but some studies have shown almost 10 times higher fatality in children aged <4 years, compared with older children (4% *vs* 0.4%) [1].

Drug resistance

Studies available have shown that since as early as 1980, there have been reports of drug resistance to antibiotics used to treat *S. Typhi* infections [5]. This phenomenon moved aggressively to spread throughout the Indian subcontinent, across Southeast Asia and the Middle East with persistence of multiply resistant strains. Multidrug resistance to *S. Typhi* has been increasing and almost 75%-82% are multidrug resistant in Kenya [3,5].

Noted as a sporadic phenomenon as early as 1970, cases of typhoid were found to be resistant to chloramphenicol the drug of choice for treatment at that time [5]. This was transient as it was limited to a geographical region and did not last for an extended length of time. The multi drug resistant typhoid fever, made its appearance in the 1980's with widespread resistance to the first line antibiotics used in the management, like ampicillin, chloramphenicol, ampicillin with trimethoprim-sulfamethoxazole, and was noted in South East Asia and Middle East countries [3,5,7]. **(Figure 2).**

While the multi centric DOMI study has shown the occurrence of Multi Drug Resistant Typhoid Fever (MDRTF) with a prevalence ranging from 7%-65%, it has also been reported from African countries [8]. This prospective study has provided a better understanding of the disease burden as well as the drug response pattern in the various regions of Asia and may be considered representative of the antibiotic susceptibility in this region [8].

As the fluoroquinolones became the drugs of choice in the management of typhoid fever, resistance to these second line drugs is also being frequently reported [5,9].

While multidrug resistance to chloramphenicol, ampicillin and Trimethoprim-Sulfamethoxazole (TMP-SMX) combination was noted at variable rates ranging from 65% in Pakistan, to 22% in
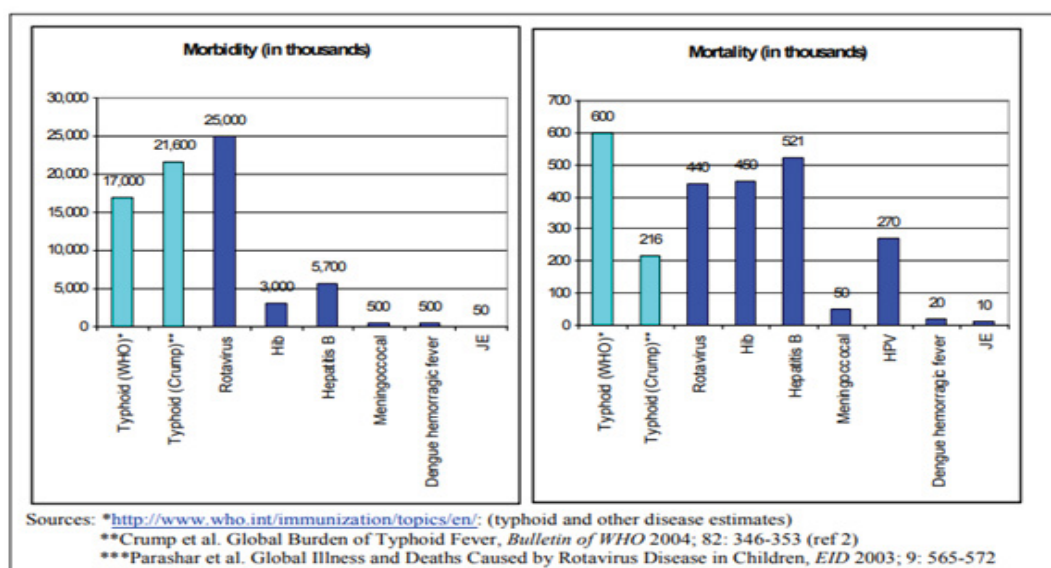

Sources: *http://www.who.int/immunization/topics/en/: (typhoid and other disease estimates)
**Crump et al. Global Burden of Typhoid Fever, *Bulletin of WHO* 2004; 82: 346-353 (ref 2)
***Parashar et al. Global Illness and Deaths Caused by Rotavirus Disease in Children, *EID* 2003; 9: 565-572

Figure 1 Global disease burden of typhoid and other vaccine preventable diseases.

Vietnam and 7% in India, Nalidixic acid resistance was noted in 57% of cases in India and 59% of cases in Pakistan, while a small percentage 1.6% showed resistance to Ciprofloxacin from India [8]. Overall, there are reports of more antibiotic resistance from Pakistan, India and Vietnam, as compared to China and Indonesia [8,10]. However, even developed nations like United Kingdom and America have reported the MDRTF ranging from 13%-22% [5,10]. This points to a geographical spread of the MDRTF strains from countries where there were outbreaks of disease or endemicity with these strains.

The outbreaks of nalidixic acid resistant strains was noticed first in Vietnam and Tajikistan as early as 1990's from where it spread to Pakistan and India and it was thought that they would respond less well to ciprofloxacin. However, current reports indicate that is not the case [3,10]. These cases usually tend to have more prolonged duration of fever, higher rates of treatment failure and possibly higher stool carriage of the bacteria post recovery [3,10,11]. Ciprofloxacin resistance has been reported among both *S. typhi* as well as *Para typhi* A infections [11] **(Figure3).** The emergence of MDRTF poses as serious threat to the treatment options making them more expensive with fewer drug options and a higher case fatality rate [3]. The recent outbreak of typhoid fever cases in the Sindh province of Pakistan has demonstrated a large-scale resistance to fluoroquinolones and the third generation cephalosporins, making it an extensively Drug Resistant (XDR) infection [1,9].
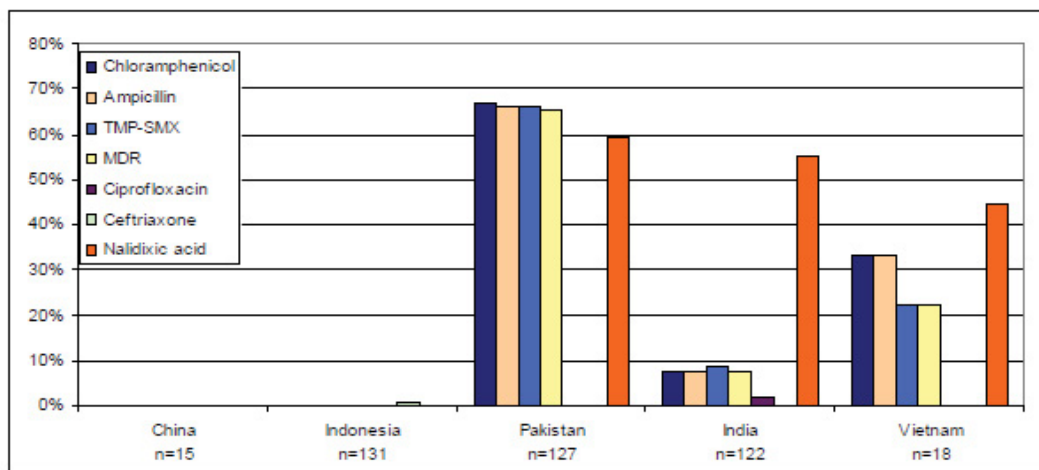
MDR – resistant to chloramphenicol, ampicillin and co-trimoxazole (TMP-SMX)

Source: Diseases of the Most Impoverished Programme
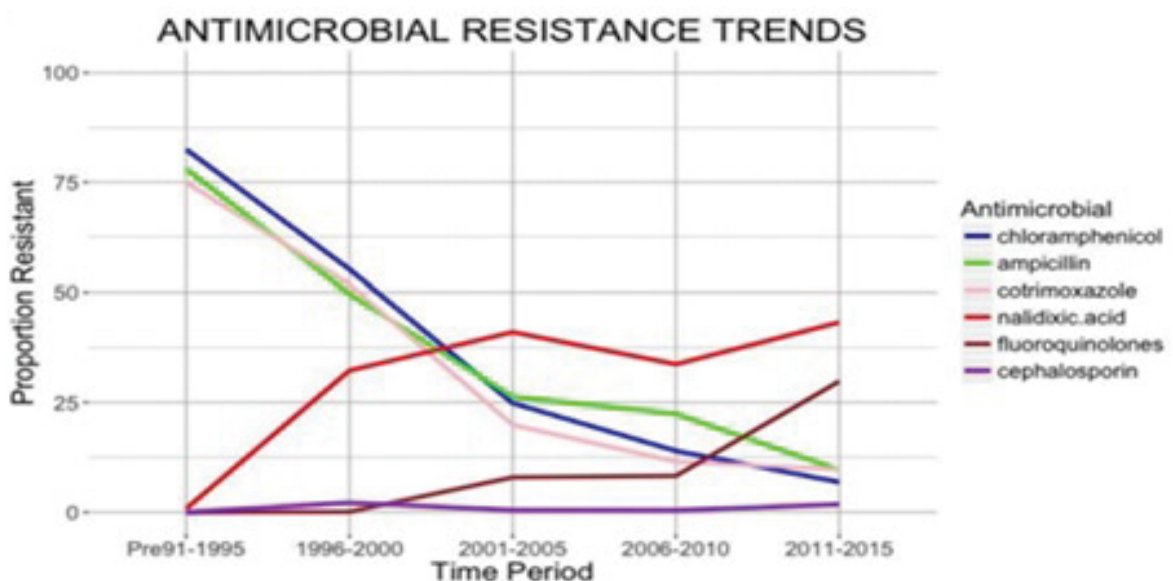
Figure 2 Pattern of drug resistance.

Figure 3 Trends of Antimicrobial resistance.

Genetic mutation in drug resistance

The initial outbreak of Multi Drug Resistant (MDR) Serovar was reported in 1993 from a province south of Vietnam against the first line drugs used in the treatment, ampicillin, chloramphenicol and cotrimoxazole, all of which were found to be ineffective [9,11,12]. With the advent and availability of other fluoroquinolones, notably ciprofloxacin and ofloxacin in 1998, these drugs were introduced to the treatment armamentarium, but led to high levels of resistance to nalidixic acid, resulting in severely restricted treatment options in several parts of the world [12]. Usage of other fluoroquinolones like ciprofloxacin became commoner in the developing countries. In recent years, along with MDR *S. Typhi*, a reduced susceptibility to ciprofloxacin has been reported from several regions in Africa, South and South East Asia, along with the emergence of ciprofloxacin resistant *S. Typhi* [9,13]. Asian countries like Nepal, India and Bangladesh have been reporting high levels of ciprofloxacin resistance in recent years, that could prelude a worsening drug resistance problem in the region [11].

The MDR *S. typhi* was responsible for large outbreaks of typhoid fever in East Asia and Africa. This phenotype was found to be encoded by resistance genes carried on transferable plasmids [5,13]. Studies have shown that these plasmids are closely related to those causing MDR in other enteric pathogens by sharing a recent common ancestor (approximately six decades old) which has evolved into several distinct lineages *via* accumulated point mutations [13].

The IncHI1 plasmids, which is a self-transmissible plasmid of HI1 incompatibility type is mostly responsible for MDR *S. Typhi* [13,14]. However, other plasmids are occasionally reported to be causative of MDR *S. Typhi*. By using Single Nucleotide Polymorphism (SNP) typing, it has been possible to stratify the *S. Typhi* into haplotypes and map the emerging phylogeny [13,14]. By this, it has been possible to identify a single emerging, highly clonal MDR haplotype of *S. Typhi*, namely H58. This is found to be endemic in many countries in Africa and Asia and was responsible for the emergence of MDR *S. typhi* between 1970-1980s [9,13,14].

The PST 6 plasmid was observed in H58 haplotype in virtually all MDR *S. Typhi* reported after 1995 with the same PST6-H58 clone, indicating a global spread *via* clonal expansion [13]. Since humans are the only reservoir of disease, the transcontinental spread is attributed to migration and international travel, producing symptomatic carriers globally [13]. Data is currently available to show that H58 is now widely disseminated across distinct geographical areas, with very closely related isolates from different countries. South Asia was the early hub for H58, from where it was propagated to many global locations, including South east Asia, western Asia, East Africa and Fiji [14]. Chiou et al. [12] reported the results of their study covering Bangladesh, Vietnam, Indonesia and Taiwan, where the samples were genotyped and analyzed for antibiotic susceptibility. The isolates all belonged to the H58 haplotype, with reduced susceptibility to fluoroquinolones and is wide spread in the Indochina peninsula, Indian subcontinent and Africa [11]. The resistance to the first line treatment drugs were among associated with resistance genes blaTEM-1, strA-strB, sul1, sul2, tetA, tet A(B), and dfr A7,

all of which are frequently carried on IncHI1 plasmids. Most of the isolates from Bangladesh and Vietnam showed MDR with resistance to nalidixic acid. However, the isolates from Indonesia and Taiwan were found to be pan-susceptible, with 5 genotypes that are clonal and could suggest the recent outbreak at the time of sampling [12]. Bangladesh showed 82% and 40% resistance to nalidixic acid and ciprofloxacin respectively. The widespread usage of fluoroquinolones has driven up the clonal expansion of nalidixic acid resistant serovar Typhi H58 in South east Asia [11]. In the US, the isolation of MDR *S. Typhi* with decreased ciprofloxacin susceptibility are associated with travel to the Indian subcontinent [4]. This H58 clade is believed to be acquiring new phenotypes that increase the bile resistance, which may be noted in the Indian subcontinent. Other newer clades have also been noted in the Democratic Republic of Congo and Nigeria [5].

Threat by XDR

The recent cluster of cases reported from Sindh province of Pakistan was found to be resistant to chloramphenicol, ampicillin, trimethoprim-sulfamethoxazole, fluoroquinolones and third generation cephalosporins [9]. The genetic characterization revealed the endemic H58 clone had acquired extended spectrum β- lactamase ESBL encoding anti-microbial resistance AMR plasmid, possibly from an *E. coli* donor strain and is considered extensively resistant (XDR) [9].

The extended spectrum cephalosporins have been the most effective antimicrobials in recent times, along with azithromycin for management of typhoid fever [4,15]. The plasmids bearing *qnr* or *aac (6')-lb-cr* genes that are responsible for ciprofloxacin protection against DNA gyrase and aminoglycoside modifying enzyme, may also contain an extended spectrum cephalosporin gene [4]. The isolation of non-Typhi *Salmonella* containing carbapenemase *blaIMP-4* and *qnr B4*, which confers resistance to meropenem and decreases ciprofloxacin sensitivity must not be ignored [4,16].

With the emergence of the XDR typhoid organisms in Pakistan, which was also transferred and detected in a patient in the United Kingdom, the threat of the global spread of XDR typhoid looms ahead.

Prevention

The risk of transmission of *S. typhi* is higher in populations that do not have access to safe drinking water [1,8,10]. Adequate sanitation and poor hygiene amongst food handlers are high risk factors for transmission [1,8,10]. Improved sanitation hygiene and safe drinking water are the cornerstones in breaking the short and long cycle of disease transmission. The carrier state acts as a huge undetected reservoir of infection in the community and being asymptomatic, it is extremely difficult to diagnose these cases and break the reservoir of infection.

Vaccination

Vaccines remain the mainstay of prevention of *S. typhi* serovar infections [10]. As per the WHO, the increasing problem posed by antibiotic resistant strains of *S. Typhi* is the key rationale for the introduction of typhoid vaccines into the susceptible and endemic community [1].

There are currently three licensed vaccines that are available for protection:

1. Typhoid Conjugate Vaccine (TCV)

2. Vi Polysaccharide Vaccine- ViPS (unconjugated)

3. Live attenuated Ty 21a vaccine

Typhoid Conjugate Vaccine (Typbar–TCV) was licensed for use in India in 2013 for children of 6 months and older up to 45 years. It comprises 25 μg of purified Vi-capsular polysaccharide conjugated to tetanus toxoid. The Phase III immunogenicity and safety trials in typhoid endemic areas showed higher serum anti-Vi antibody response with GMT of 1293 compared to 411 with the Vi-polysaccharide vaccine (Vi-PS) and 97.3% sero-conversion by 6 weeks [1,17]. After two years of immunization, the anti-Vi titers remained higher with GMT of 82 in the Vi-TT group compared with the GMT of 46 in the Vi-PS group [17]. The human Phase II b trial, wherein a controlled human infection model was used, showed the immunogenicity, safety and efficacy of the Vi-conjugate (Vi-TT) vaccine [1,18]. The vaccine efficacy was 54.6% with 100% sero-conversion in the Vi-TT group compared with 52% efficacy and 88.6% sero-conversion in the Vi-PS group of participants [18]. A recently published field estimate of the sero efficacy trial of Vi-TT vaccine showed a lower sero incidence with a relative risk of 0.372 with Vi-TT vaccine compared with an RR of 0.424 with the Vi-PS vaccine , with a vaccine sero efficacy of 85% [19]. This trial showed that the Vi-TT vaccine substantially reduced the number of serologically defined clinical or sub clinical infections in infants, children and adults [1,19].

Vi Polysaccharide vaccine elicits high levels of serum IgG anti-Vi antibodies, which decline rapidly in the second year. The vaccine effectiveness was found to be 56% amongst children aged between 5-14 years and 80% in those between 2-4 years. The higher protective levels in younger children could be attributed to the mass vaccination that induced herd immunity in the non-vaccines [20]. However, the vaccine does not stimulate mucosal immunity or a T-cell dependent memory, and hence a dose must be repeated every 2-3 years to provide a booster effect [20,21].

The Ty 21a vaccine given orally had an efficacy of 51% for three doses in the meta analyses conducted by Engels et al. [21]. However, the efficacy has been shown to be almost 80% in challenge tests using Ty21a vaccine [1]. This vaccine cannot be administered in immune-suppressed persons, as well as in case of antimicrobial administration, which needs to be suspended at least three days earlier [21]. This vaccine stimulates serum and mucosal antibodies to O, H and other surface antigens but no anti-Vi antibodies, as it lacks this antigen [1]. Trials done in Santiago showed some herd protection as the incidence of typhoid fever decreased in the non-vaccinated community [1]. The vaccine must be repeated every three years for those residing in endemic areas and every year for those travelling from non -endemic to endemic areas [1].

The updated recommendation

The WHO position paper 2018 suggests that protection from the Typbar TCV vaccine may persist up to 5 years after primary immunization, with natural boosting in the endemic areas [1]. The WHO recommends the usage of typhoid fever vaccine in the control of typhoid fever, alongside other measures for disease control namely health education, water, sanitation and hygiene (WASH). It also recommends TCV as the preferred vaccine at all ages, given as a single dose in public health campaigns, especially as it can be used in younger children and produce a longer duration of protection [1]. It has recommended the prioritization of this vaccine in regions with the highest burden of typhoid fever, which are also regions with high anti -microbial resistance.

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