

Typhoid Fever: Drug Resistance and Current Vaccine Recommendations

Sumitha Nayak

ABSTRACT

Typhoid fever continues to ravage across the globe. It affects young children and causes higher morbidity and mortality in them. The Diseases of the Most Impoverished (DOMI) study has added invaluable data regarding the disease incidence. The bacteria had developed resistance to the first generation of antimicrobials. Fluoroquinolones and recently third-generation cephalosporins have been found to be ineffective and extremely drug resistance typhoid had surfaced in certain regions. Vaccines are an important tool in the ongoing fight against typhoid fever.

Keywords: Cephalosporins, Disease burden, Drug resistance, H52 Clade, Incidence, Typhoid fever, Typhoid vaccines.

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INTRODUCTION

Typhoid fever continues to rage all across the globe, as it leads to morbidity and avoidable mortality. According to reports, there are at least 21 million reported cases of typhoid fever across the world, of which roughly 200,000 die annually.^{1,2} This is a public health problem that needs to be aggressively tackled.

DISEASE BURDEN

Typhoid fever affects young children and the marginalized populations of the poorer nations of the world, including much of Asia, sub-Saharan Africa, and parts of Latin America and the Middle East countries.³ While typhoid fever is a major problem in the school-going ages of 5–15 years, the children less than 5 years have shown incidence rates similar to or exceeding these levels.¹ As explained in Figure 1, there is reducing rates of distribution at all incidences, as the age progresses (Tables 1 and 2).

The high incidence of typhoid fever in South and Southeast Asia is highlighted from current available reports and data. Sub-Saharan Africa has strong data that give evidence regarding the disease burden.⁵ About 27% of the typhoid fever episodes occur in the 0–4 years of age, and of this, 29.7% occur ≤ 2 years, 9.9% ≤ 1 -year age group, and 2.9% in infants < 6 months.⁵ While the 0–4 years age group accounts for the severe disease, the 6 months to 2 years ages account for a large proportion of the disease.⁵ All the areas covered in this study were impoverished, hence the poor personal hygiene levels, with lack of access to safe drinking water, could possibly contribute to this incidence. An estimated 17.8 million typhoid fever illnesses occurred in the lower and middle income countries (LMIC) countries alone.⁵

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.⁶ This was called the Diseases of the Most Impoverished or DOMI program. At the same time, sporadic reports of organisms resistance to chloramphenicol also appeared.⁷

The DOMI study highlighted the varying incidence rates in the different countries of study, with an overall high prevalence rates ($> 100/100,000$ population) in the impoverished strata, especially the urban slums.⁸

The Children's Clinic, Bengaluru, Karnataka, India

Corresponding Author: Sumitha Nayak, The Children's Clinic, Bengaluru, Karnataka, India, Phone: +91 7975578064, e-mail: snayak1011@gmail.com

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The DOMI study was conducted using blood culture as the method of diagnosis and incidence was calculated in different areas. While the highest incidence of 451.7/100,000/year was detected in Karachi, Pakistan, Kolkata, India, was at the second position with an annual incidence of 214.2/100,000 cases and Hechi in China recorded the lowest incidence at 15.3/100,000 cases/year.⁸

The prevalence rates of culture-proven typhoid fever naturally followed a similar pattern as is noted in Table 3.

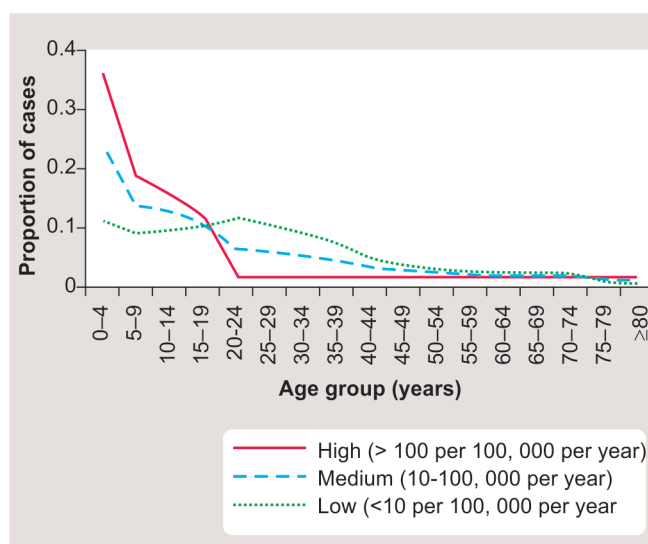


Fig. 1: Distribution of typhoid fever by age group. Ref: Crump et al. *BULL World Health Org*⁴

Table 1: Characteristics and incidence of typhoid fever from the study sites

Site	Hechi, China	Kolkata, India	North Jakarta, Indonesia	Karachi, Pakistan	Hue, Vietnam	Total	<i>p</i> value ^b
Site setting	Urban/rural	Urban slums	Urban slums	Urban slums	Urban	–	–
Total population from the study (year of census)	112,889 (2001)	56,946 (2003)	160,261 (2002)	101,937 (2001, 2003) ^a	281,781	713,814	–
Surveillance period	Aug 1, 2001–Jul 31, 2002	Nov 1, 2003–Oct 30, 2004	Aug 1, 2002–Jul 31, 2003	Aug 1, 2002–Jul 31, 2004 ^c	Jun 1, 2002–Jun 30, 2003	–	–
Surveillance target population (age in years)	5–60	All ages	All ages	2–15	5–18	–	–

Ref: Ochiai RL et al. Bull World Health Org⁸

^aSurveillance conducted from Aug 1, 2002 to Jul 31, 2003, at Hijrat and Sultanabad, and from Aug 1, 2003 to Jul 31, 2004, at Bilal Colony

^b*p* value for the five sites comparison, estimated with 4 degrees of freedom

^cBaseline census was conducted in Hijrat and Sultanabad in 2001 and in Bilal Colony in 2003

Table 2: Annual incidence of typhoid cases (China, India, Indonesia, Pakistan, Vietnam, in order)

Site	Hechi, China	Kolkata, India	North Jakarta, Indonesia	Karachi, Pakistan	Hue, Vietnam	Total	<i>p</i> value ^a
Typhoid incidence (per 100,000/year) by age	15.3	21.42	81.7	451.7	21.3	107.6	<0.0001
0–1 years	NA	89.2	0.0	NA	NA	21.6	0.0777
2–4 years	NA	340.1	148.7	573.2	NA	384.8	<0.0001
5–15 years	29.3	493.5	180.3	412.9	24.2	170.8	<0.0001
≥16 years	12.4	119.7	51.2	NA	10.9	46.8	<0.0001

p value for the five sites comparison, estimated with four degrees of freedom

Ref: Ochiai RL et al. Bull World Health Org⁸

Table 3: Prevalence rates of typhoid fever in the DOMI study

Site	Hechi, China	Kolkata, India	North Jakarta, Indonesia	Karachi, Pakistan	Hue, Vietnam	Total	<i>p</i> value ^a
Typhoid prevalence (per 1,000 febrile episodes with blood cultures taken) by age	12.3	28.1	33.1	25.2	5.0	23.1	<0.0001
0–1 years	NA	6.9	0.0	NA	NA	1.8	0.0986
2–4 years	NA	29.1	35.3	25.3	NA	27.0	0.5432
5–15 years	12.8	52.5	61.4	25.6	4.7	24.7	<0.0001
≥16 years	12.1	18.1	26.7	NA	9.5	20.2	0.0243

NA, not available

p value for the five sites comparison, estimated with four degrees of freedom

Ref: Ochiai RL et al. Bull World Health Org⁸

The younger children are at high risk of developing typhoid fever or bacteremia, possibly due to the unhygienic habits. This is directly proportional to the overall incidence of the disease in the community.

ANTIMICROBIAL RESISTANCE

While sporadic reports of drug resistance appeared since the 1970s when chloramphenicol was the drug of choice for management, these reports continued until the 1980s.^{5,7} Subsequently, multidrug-resistant typhoid fever (MDRTF) appeared wherein widespread resistance to the first-line drugs like ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole was reported.⁷ The prospective DOMI study showed the drug response patterns and expanded the knowledge related to MDRTF.⁸ The reports pertaining to drug resistance from 1973 to 2015 were consolidated to arrive at the prevalent patterns of drug resistance (Fig. 2). The nalidixic acid

resistance pattern is utilized for understanding the response to fluoroquinolones, as an indirect indicator.

The increasing antimicrobial resistance noted in regions of high incidence poses a significant problem, as most of the isolates are multidrug-resistant (Fig. 3).⁸

The outbreaks of nalidixic acid-resistant strains were noticed as early as 1990s in Vietnam and Tajikistan from where it spread to Pakistan and India.^{6,8} It was surmised that these cases were responding less well to ciprofloxacin. However, current reports differ from this hypothesis.⁹ 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.^{6,9,10} These MDRTF strains pose a serious threat making the treatment options much more expensive with fewer drug options and a higher case fatality rate.⁶ Ciprofloxacin resistance has been reported among both *S. typhi* and *S. paratyphi A* infections.⁹

With the advent of other fluoroquinolones, notably ciprofloxacin and ofloxacin in 1998, they were introduced to the treatment armamentarium. But unfortunately around the same time very high levels of resistance to nalidixic acid were noted, resulting in severely restricted treatment options in several parts of the world.¹⁰ Ciprofloxacin usage 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 Asia, and South East Asia, notably India, Nepal, and Bangladesh with reports of the emergence of ciprofloxacin-resistant *S. typhi*.¹¹ This is an ominous sign that cannot be ignored, and that could be a prelude to a worsening drug resistance problem in the region.¹⁰ The search

for newer drugs has led to the use of azithromycin in the treatment of typhoid fever.¹¹ This drug has been used in combination with third-generation cephalosporins, in the face of growing resistance to fluoroquinolones.¹²

A recent systematic review of the current antimicrobial responses in India has shown that first-line drugs—ampicillin, co-trimoxazole, and chloramphenicol—are regaining their sensitivity to the *Salmonella* organisms (Fig. 4). This is attributed to the scant use of the first-line antimicrobials.¹² The recent outbreak of typhoid fever in the Sindh province of Pakistan has however revealed extensively resistant organisms causing severe disease.¹² These isolates had resistance to first-line antimicrobials, fluoroquinolones, as well as third-generation cephalosporins.¹²

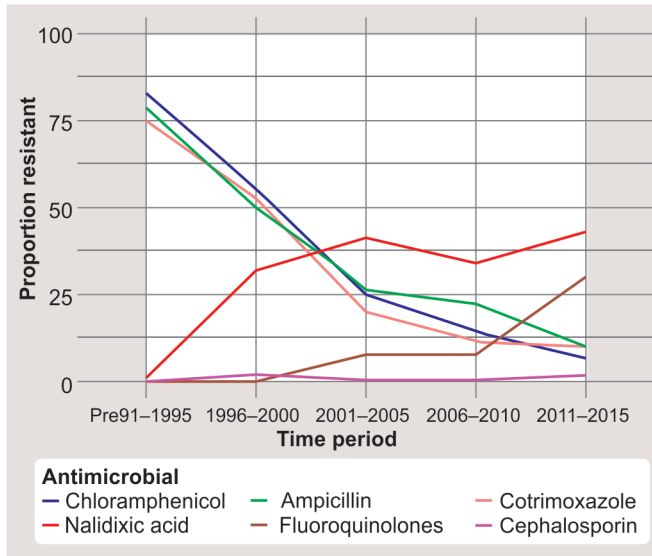
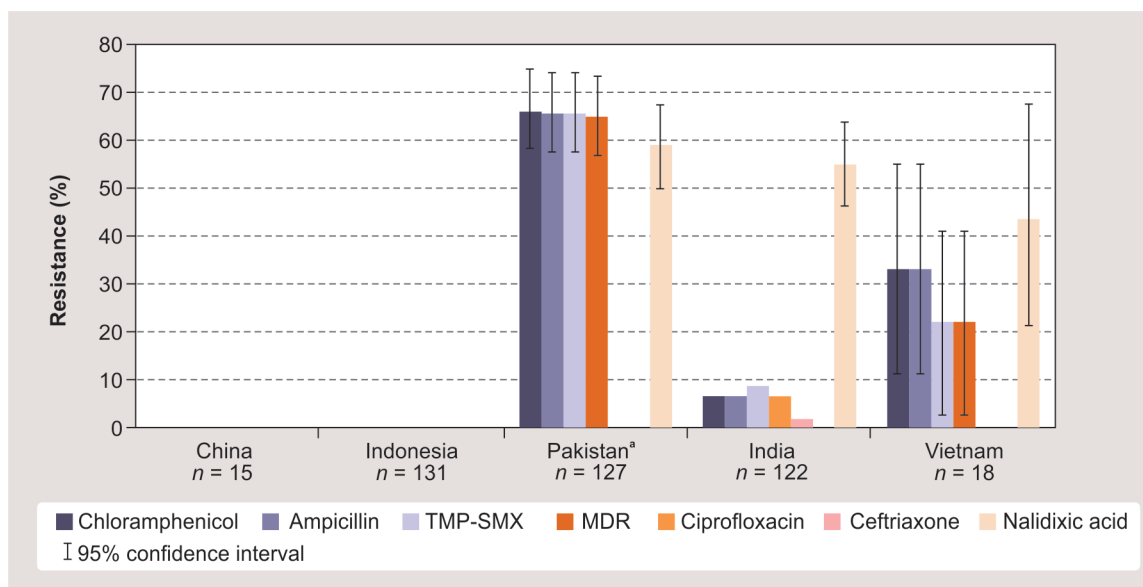


Fig. 2: Patterns of antibiotic resistance. Ref: Ochiai RL et al. Bull World Health Org⁸

GENETIC MUTATION IN DRUG RESISTANCE

The MDR *S. typhi* phenotype was found to be encoded by resistance genes that are carried on transferable plasmids.^{5,12,13} These 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 MDR *S. typhi* was driven by the acquisition of the IncHI1 plasmids, a self-transmissible plasmid of HI1 incompatibility type.^{13,14} Other plasmids are occasionally reported to be causative. By using single nucleotide polymorphism (SNP) typing schemes, it has been possible to stratify the *S. typhi* into haplotypes and map the emerging phylogeny.^{13,14} A single emerging, highly clonal MDR haplotype of *S. typhi*, H58, is endemic in many countries in Africa and Asia.¹⁴ Available data have suggested that the oldest confirmed H58 isolate was in the year 1991 from an Indian patient. The haplotype geoexpansion was associated with the acquisition of the PST6 plasmid, conferring a transposon that increased osmotolerance and ensured the survival and multiplication of the *S. typhi* in niche areas of the gut, gall bladder, urinary tract, or liver.¹³



MDR, multidrug resistant (i.e to chloramphenicol, ampicillin and trimethoprim-sulfamethoxazole); TMP-SMX, trimethoprim-sulfamethoxazole.

^a Isolates from Pakistan were not tested for susceptibility to ciprofloxacin with the disc method, but were tested for minimum inhibitory concentration with nalidixic acid-resistant strains and none were found resistant; out of 189 isolates detected during the surveillance period 127, isolates were subjected to all six susceptibility tests

Fig. 3: Antimicrobial resistance in countries with high incidence. Ref: Ochiai RL et al. Bull World Health Org⁸

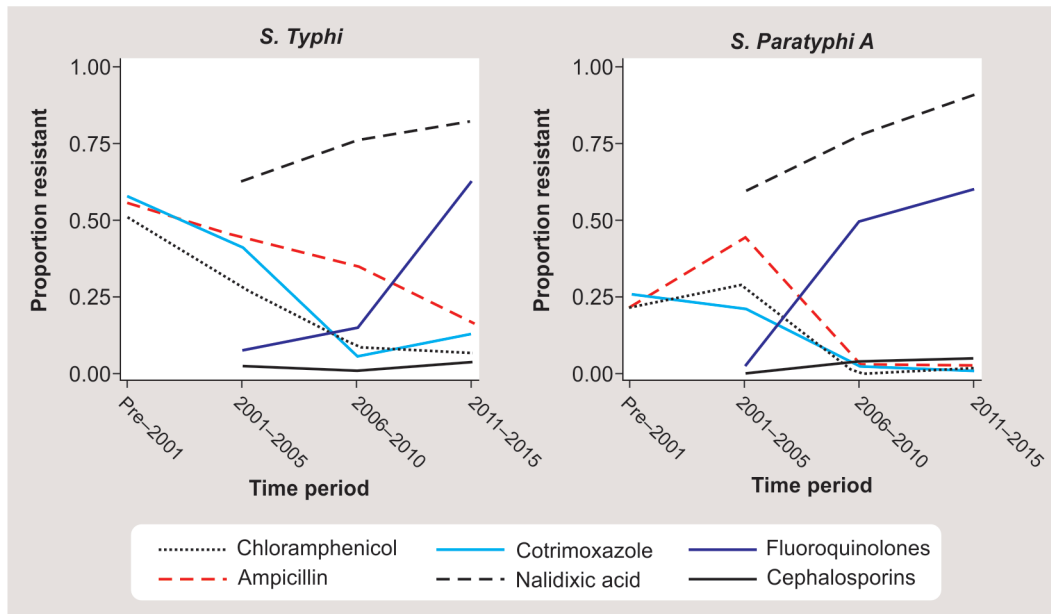


Fig. 4: Current drug resistance patterns to typhoid organisms. Ref: Britto CD et al. Indian J Med Res 2019¹²

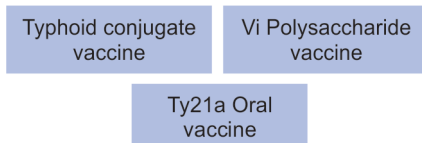


Fig. 5: Types of typhoid vaccines. Ref: WHO. Weekly Epidemiol Rep 2018¹⁸

The samples from Bangladesh, Vietnam, Indonesia, and Taiwan were genotyped and analyzed for antibiotic susceptibility.¹¹ Chiou et al. reported their study, wherein all isolates belonged to the H58 haplotype, with reduced susceptibility to fluoroquinolones. This trend was noted to be widespread to regions in the Indochina peninsula, Indian subcontinent, and Africa.¹¹ The resistance to the first-line treatment drugs was associated with resistance genes bla_{TEM-1} , $strA$ - $strB$, $sul1$, $sul2$, $tetA$, $tetA(B)$, and $dfrA7$, all of which are frequently carried on IncHI1 plasmids. While the majority of the isolates from Bangladesh and Vietnam showed MDR along with resistance to nalidixic acid, the isolates from Indonesia and Taiwan were found to be pan-susceptible, with five genotypes that are clonal and could point to the recent outbreak at the time of sampling.¹¹ Isolates from Bangladesh showed 82 and 40% resistance to nalidixic acid and ciprofloxacin, respectively. The widespread usage of fluoroquinolones has possibly driven up the clonal expansion of nalidixic acid-resistant serovar Typhi H58 in Southeast Asia.¹⁰

THREAT BY EXTREMELY DRUG RESISTANT ORGANISMS

The recent cluster of cases reported from the Sindh province of Pakistan was found to be resistant to chloramphenicol, ampicillin, trimethoprim-sulfamethoxazole, fluoroquinolones, and third-generation cephalosporins.¹⁵ Thus named extensively resistant, the genetic characterization of these bacteria revealed the acquisition by the endemic H58 clone of an extended spectrum β -lactamase (ESBL)-encoding antimicrobial resistant AMR plasmid, possibly from an *E. coli* donor strain.¹⁵

The extended spectrum cephalosporins along with azithromycin have been the most effective antimicrobials in recent times, for

management of typhoid fever.^{4,16} Data show that plasmids bearing qnr or $aac(6')-Ib-cr$ genes that are responsible for ciprofloxacin protection against DNA gyrase and aminoglycoside-modifying enzyme may also contain an extended spectrum cephalosporin gene.⁴ A mention of the isolation of non-Typhi *Salmonella* that confers resistance to meropenem and decreased ciprofloxacin sensitivity containing carbapenemase bla_{IMP-4} and $qnrB4$ must be made.^{4,17} The emergence of the spread of the H58 clade, together with extremely drug resistant organisms (XDR) and MDR typhoid, has resulted in more patients facing treatment failures and complications, more expensive treatment options, with the possibility of a chronic carrier state.¹⁸ This increased threat is the rationale for the implementation of an effective vaccine program in the high-risk population.¹⁸

The emergence of the XDR typhoid organisms in Pakistan, that was detected in a patient in the United Kingdom, enhances the threat of the global spread of XDR typhoid.

VACCINATION

As per the World Health Organization, 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.^{1,9,18}

There are currently three licensed vaccines that are available for protection against typhoid fever (Fig. 5).

Since 2008, the World Health Organization had recommended the use of two vaccines for protection against typhoid fever—the ViPS and the oral Ty21a vaccine for school age and preschool ages in affected areas—in an attempt to tackle the epidemic and endemic disease burden.^{5,18,19}

The ViPS Vaccine

This vaccine is prepared from the polysaccharide of the Ty2 *S. typhi* strain. It induces a T-cell-independent immune response and does not confer immunological memory.^{5,18} Various studies have shown varying levels of vaccine effectiveness ranging from 72% in Nepal at 17 months after administration to 69% in China after 19 months

of vaccine administration.⁵ Studies done in India after the licensure of the vaccine showed a higher protection rate at around 80% in younger children under 5 years of age, while the 5–16 years age group had a protection rate of 56%.⁵ This was attributed to the herd effect of immunizing the older children. Similar results were shown in another trial done in Karachi, Pakistan, in those between the ages of 5 years and 16 years, while no protection was noted in children below 5 years of age, with the ViPS vaccine.⁵ Klugman et al. have reported a vaccine effectiveness of around 55% during 3 years of follow-up.¹⁹ This ViPS vaccine is licensed for use in individuals above the age of 2 years as a single subcutaneous or intramuscular injection.⁵ In persons living in nonendemic areas, the antibody titers decline rapidly after the 2nd year of vaccination.¹⁸ Repeat doses may induce a hyporesponsiveness, but no robust data are available to support this.^{5,18} An outbreak of typhoid in ViPS-immunized French soldiers was reported from Ivory Coast, Africa, proving the poor immunogenicity of the vaccine in those who had received their vaccine over 3 years previously with a two times higher likelihood of developing disease compared to those who had their vaccine within the previous 3 years.^{18,19}

Ty21 a Vaccine

This vaccine has been licensed for use in individuals ≥ 5 years of age. It is an enteric-coated capsule that must be administered on alternate days orally as a three-capsule regimen.^{5,18} It is also available as a liquid formulation with one sachet and a buffer in another, which is generally recommended for use in children.¹ The Ty21 a vaccine is a live attenuated vaccine that harbors numerous attenuating mutations among which the inactivation of enzymes involved in lipopolysaccharide biosynthesis and the inability to synthesize Vi polysaccharide are important characteristics. This vaccine stimulates serum and mucosal antibodies to O, H and other surface antigens and elicits long-lasting cell-mediated immune responses, but no Vi antibodies, as it lacks the Vi antigen.^{5,17} Serum IgA antibody secretion and IgG anti-O seroconversion occur 7 days following oral immunization. Field trials of efficacy showed a 67% protection rate over 3 years and 62% protection rate over 7 years.¹⁸ A large-scale trial done in Santiago, Chile, in which 216,692 school children were administered the vaccine, revealed a reduction in the incidence of typhoid fever, as the number of administered doses increased from two to three and four. The disease incidence was found to reduce to about 30% of the initial value in a nonimmunized portion of Santiago, probably due to herd protection that developed following the mass immunization.¹⁸ This Ty21 a vaccine also provided a moderate 49% level of protection against paratyphi B disease.⁵ Protective efficacy is achieved 7 days after the last dose of the vaccine.¹⁸

However, it was found that the vaccine uptake was very low, despite the WHO directions to implement these vaccines as school-based programs, due to various policy, financial, and implementation challenges.^{5,19} There have been no head-to-head comparative trials using the Ty21a and the ViPS vaccines.¹⁹

Typhoid Conjugate Vaccine

This vaccine provides protection to younger infants via a T-cell-dependent vaccine response. The Vi surface polysaccharide of *S. typhi* is conjugated to the protein, which allows the extension of the response in younger ages.⁵ There are two varieties of the Vi conjugate vaccine that are currently available.

Vi-r EPA vaccine where the Vi antigen is conjugated to the exoprotein of *Pseudomonas aeruginosa*.

Vi-TT Vaccine in which the Vi antigen is conjugated to the tetanus toxoid protein.

The Vi-r EPA vaccine was tested in large trials done in Vietnam and found to be safe and immunogenic.^{5,19} It was recommended in a 3+ dose schedule at 2, 4, and 6 months with a booster at 12 months of age. A single dose of vaccine showed excellent efficacy of 89% over the 46-month period of the trial. In case of disease occurrence in these vaccines, the extent and severity of illness, hospitalization, and complications were found to be greatly decreased. This vaccine was recommended as a primary vaccine at 2, 4, and 6 months of age, concomitantly with other immunizations, and one booster at 12 months of age.⁷ The antibody titers were found to persist for 8 years after immunization in a small cohort that was immunized after the trial was over. This vaccine has not been commercially produced, despite being recognized as safe and immunogenic and is the only vaccine to have efficacy data.^{5,17,20}

The Vi TT conjugate vaccine contains 25 μg of the Vi antigen conjugated to the tetanus toxoid protein, in saline, and is licensed for use from 6 months of age until 45 years of age.⁵ The WHO position paper mentions two brands of the Vi-TT conjugate vaccine: the Typbar TCV and the Pedatyph.¹⁷ It also mentions that as the evidence available for the latter vaccine is minimal, and the position paper refers to the Typbar TCV vaccine.¹⁷ This vaccine has undergone several trials before certification.^{5,17} The controlled trial showed a 97.3% seroconversion by day 42 and the antibody geometric mean titers geometric mean titres (GMT) of this vaccine was higher at day 42 compared to the unconjugated Vi-PS vaccine, Typbar, produced earlier by the same company.²¹ The open-label trial conducted on infants between 6–23 months and 12–23 months of age showed excellent antibody titers at day 42 after immunization in 98% and the elevated levels persisted more than fivefold above baseline at Day 720 in 84% of the cohort.^{17,22} The human challenge trial was a bridging study that enabled the collection and analysis of data in a faster manner.²³ This unique trial used immunologically naïve adult volunteers who were administered either the Vi-TT vaccine, Vi-PS vaccine or the control, meningococcal vaccine, and subsequently challenged with a heavy oral inoculum of *S. typhi*.²³ They were followed up for 1 month for development of symptoms of typhoid fever. This trial showed a seroconversion rate of 100% with the Vi-TT and 88.6% with the Vi-PS vaccine with significantly higher GMTs at 1 month postimmunization with Vi-TT.^{17,23} The estimated vaccine efficacy is 87.1%, which is similar to that provided by the Vi-r EPA vaccine at 89%.²³ This proved the immunogenicity of the vaccine to provide protection against a large inoculum of the microorganisms.^{17,22} The conjugate vaccine activates the T helper cells, which in turn enhance the magnitude, avidity, and subclass of the IgG Vi antibody particularly the increased levels of the IgG3 subclass, which have the higher capacity to facilitate bacterial uptake by the phagocytic cells.²¹

CURRENT VACCINE RECOMMENDATIONS

In its updated report, the WHO has recommended the administration of the Typbar TCV vaccine as a single dose of 0.5 mL given intramuscularly to children above the age of 6 months, until 45 years of age.¹⁸ The ViPS vaccine is recommended above the age of 2 years, as a single dose of 0.5 mL given subcutaneous or intramuscular.¹⁸ The Ty21 vaccine is available only as enteric-coated capsules for oral administration on alternate days in a

three-dose regimen.¹⁸ Among all the available vaccines, the WHO takes the position of recommending the TCV vaccine as preferred for programmatic implementation as its improved immunological properties and longer duration of protection, together with the suitability for younger children, make it the preferred choice.¹⁸ Catch up vaccination until 15 years is recommended whenever feasible programmatically. In case of immunocompromised including HIV infection, the WHO recommends the use of TCV or ViPS vaccines, while the Ty21 can be given to stable individuals with a CD4 count greater than 25% in children less than 5 years of age or CD4 count more than 200 cells/cm³ if aged more than 5 years. The WHO mentions that the current need for revaccination with TCV is unclear as it refers to the programmatic implementation of this vaccine. However, the ViPS vaccine needs to be repeated every 3 years, while the Ty21 a must be readministered every 3–7 years.¹⁸

The IAP recommendations are in line with the WHO recommendations. Currently, the vaccine is recommended above the age of 6 months as a single dose of 0.5 mL intramuscularly above the age of 6 months.²⁴ The need for revaccination is unclear, as natural boosting is thought to occur in endemic regions, and protection with TCV may last up to 5 years. In case the polysaccharide vaccine has been administered, a single dose of TCV can be given after an interval of at least 4 weeks. The TCV can be co administered along with measles containing vaccines at 9 months. At present, the routine boosters at 2 years is not recommended.²⁴

CONCLUSION

Typhoid fever continues to be responsible for the high morbidity and mortality rates globally. Studies from various countries have shown the high disease incidence in countries with poor socioeconomics, urban slums, and poor hygiene. Younger ages have the highest susceptibility, especially in the under-5 age group making it a significant contributor to the under-5 mortality. Despite being an endemic disease, epidemic outbreaks of typhoid fever are reported from various parts of the world.

The MDR typhoid fever appeared in Southeast Asia and Middle East countries in the 1980s when there was widespread resistance to the first-line antibiotics used in the management, like ampicillin, chloramphenicol, and ampicillin with trimethoprim-sulfamethoxazole. This varied from 65% in Pakistan, 22% in Vietnam, and 7% in India. Nalidixic acid resistance was noted in 57% of cases from India and 59% of cases from Pakistan. The emergence of MDRTF poses as serious threat as it makes the treatment options much more expensive with fewer drug options and a higher-case fatality rate. Currently, there is a reemergence of susceptibility to the first-line drugs due to their nonusage.

Studies have identified a single emerging, highly clonal MDR haplotype of *S. typhi*, H58, to be endemic in many countries in Africa and Asia. This H58 clade is believed to be acquiring new phenotypes that increase the bile resistance, making the traditionally used drugs chloramphenicol, ampicillin, and trimethoprim-sulphamethoxazole no longer effective in treatment. At the same time, the quinolone group is also rapidly developing resistance as noted from the isolation of specimens with double mutation of *gyr A*. Against this background of rising antimicrobial resistance and the potential of the organism to expand and thrive across geophysical destinations globally, it is pertinent to seek out methods of disease prevention, which could go a long way in decreasing the morbidity and disease fatalities.

Immunization against typhoid is recommended as the most important tool in preventing typhoid infection. The WHO currently recommends the programmatic administration of a single dose of Tybbar TCV conjugate vaccine above the age of 6 months. The IAP ACVIP has also issued similar guidelines for the administration of a single dose of Tybbar TCV above the ages of 6 months. The need for repeat doses has not been elucidated as yet.

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