Vaccines to Prevent Typhoid Fever

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Introduction

Typhoid and paratyphoid fever were highly endemic in many countries in Latin America in the 20th century. This chapter reviews the disease typhoid fever and the vaccines available to prevent it.

Etiologic Agents

Typhoid fever and paratyphoid fever, the "enteric fevers", are acute generalized infections of the reticuloendothelial system, intestinal lymphoid tissue, and gallbladder. *Salmonella enterica* serovar Typhi (*Salmonella* Typhi) is the etiologic agent of typhoid, while *Salmonella* Paratyphi A or *Salmonella* Paratyphi B (or rarely, *Salmonella* Paratyphi C) cause paratyphoid fever.

Epidemiology

Facile transmission of the agents that cause typhoid and paratyphoid fever ensues where populations have poor sanitation and lack access to potable water. Thus, these infections are endemic in many developing countries, while their transmission is rare in industrialized countries. High endemicity is observed in regions of South and Southeast Asia, the Middle East, Northeast Africa, sub-Saharan Africa and some Pacific Islands. In endemic areas typhoid generally comprises ~70–80% of enteric fever and paratyphoid the remainder,[1] but in some areas of South Asia, *S.* Paratyphi A is nearly as common as *S.* Typhi.[2,3] The burden of enteric fever has diminished markedly in Latin America since the early 1990s but endemic foci still persist in Central America, the Caribbean and some regions in South America. When enteric fever was highly endemic in South America, *S.* Paratyphi (mostly B) was responsible for ~one-third of cases.[4]

Endemic typhoid often exhibits seasonality. In Chile, Ecuador and Peru, where typhoid was highly endemic in the 1960s–1980s, there was a summer peak.[5]

Chronic gall bladder carriers constitute the long-term reservoir of *S.* Typhi and *S.* Paratyphi A and B.[6,7] In endemic areas, particularly during "typhoid season", persons with sub-clinical and clinical infection who

are short-term excretors constitute another important reservoir from which the infection is transmitted to susceptibles. Where urinary tract *Schistosoma haemotobium* or *Schistosoma mansoni* infections are co-endemic with typhoid, chronic urinary bladder carriers of *S*. Typhi serve as a reservoir.[8]

Typhoid and paratyphoid infection is almost always acquired by ingestion of food or water vehicles contaminated by human excreta that contain *S.* Typhi or *S*. Paratyphi A or B. In most large cities of North America and Europe in the late 19th and early 20th centuries, the treatment of water supplies by chlorination or sand filtration (or both) broke the cycle of endemicity and diminished the incidence of typhoid, even though the prevalence of chronic carriers in the populations remained high for decades thereafter.[9,10] A South American exception to this pattern was Santiago, Chile, where high endemicity persisted despite 96% of the population having access to potable water and 80% being connected to a sewerage system. In Santiago, sewage water was not treated and during summer (when there was no rain) it was used to irrigate crops (particularly salad vegetables) that were brought to the city's markets, sold and eaten uncooked.[11,12]

Enteric fever is transmitted by either a "short cycle" or a "long cycle" fecal-oral route. Short cycle involves an individual carrier who contaminates food vehicles consumed in proximity by family members or participants at a communal gathering (e.g., wedding), or by a food handler carrier in a restaurant.[13] Examples of short-cycle sporadic cases and outbreaks include families served by the notorious cook, "Typhoid Mary,"[14] and restaurant outbreaks in Texas,[15] Maryland,[13] and New York.[16] Examples of transmission by long-cycle include the contamination of water supplies by sewage,[17] irrigation of crops with untreated sewage,[11] contamination of widely distributed piped municipal water,[17,18] and dissemination of typhoid bacilli via contaminated processed foods transported over long distances.[19] Clinical microbiologists have increased potential exposure to *Salmonella* Typhi in the occupational setting and therefore also constitute a special high-risk group.[20,21]

The Disease

Clinical manifestations of acute typhoid fever vary somewhat depending on the host, the specific strain, inoculum size and vehicle of transmission. The older child or adult with severe clinical typhoid fever exhibits persisting high fever, malaise, abdominal discomfort, and frontal headache. In the pre-antibiotic era the clinical illness progressed over several weeks, culminating in a case fatality rate of ~10–20%.[22,23] The protracted, debilitating nature of this febrile illness in untreated (or improperly treated) cases is accompanied by mental cloudiness or stupor.

In individual patients it is impossible to differentiate on clinical grounds whether the enteric fever is caused by *S*. Typhi or *S*. Paratyphi.[24,25] Full-blown cases begin with malaise, anorexia, fever (that increases stepwise to reach 39°–40°C), abdominal discomfort, and headaches.[23,26,27] Without appropriate antimicrobials, fever persists for at least 10–14 days (and sometimes for weeks, if the patient survives). Appropriate antibiotics cause the fever to diminish stepwise over several days. During the period of sustained fever, ~20% of Caucasians manifest "rose spots", an exanthum seen on the chest, abdomen, and back consisting of subtle, salmon-colored macules, 2–4 mm in diameter, which blanch with pressure and from which *S*. Typhi can be cultured.[28] Constipation or diarrhea may be seen in older children and adults, whereas diarrhea may occur in ~20% of young children with typhoid fever. Although infants may manifest severe clinical forms of typhoid fever, bacteremic *S*. Typhi infection in children younger than 2 years of age can often be remarkably mild and not recognized clinically as enteric fever but rather as a non-descript febrile syndrome.[29,30] A bronchitic cough is common early in the illness in all ages. A particularly severe form of typhoid fever is occasionally encountered in which cerebral dysfunction, including obtundation, delirium or coma, and shock ensue, requiring adjunct corticosteroids plus appropriate antimicrobial therapy to avoid a case-fatality rate that can exceed 20%.[31]

In the preantibiotic era relapses were observed in about 8% of typhoid fever patients. The relapse rate in patients treated with the first (chloramphenicol) and second (ampicillin, amoxicillin and trimethoprim/sulfamethoxazole) generation of antibiotics used for typhoid therapy ranged from 10–25%. Typhoid bacilli can be recovered from bile and bone marrow many weeks after the patient has fully recovered from symptoms. Relapses typically occur ~3 weeks after the last febrile day or 2 weeks after cessation of antibiotics and are clinically milder and shorter than the initial illness and promptly respond to appropriate antibiotics. Following treatment of dug-sensitive acute typhoid with oral fluoroquinolones or azithromycin or after parenteral ceftriaxone, relapse is uncommon.

Two feared complications of typhoid fever, intestinal perforation and hemorrhage, occur in ~ 0.5–1.0% of cases, particularly those who have been ill for several weeks without appropriate antibiotic therapy.[32] These complications are consequent to the prominent lesions in the gut-associated lymphoid tissue. Typhoid can cause complications involving any organ system.[23] Uncommon complications include hepatitis, empyema, osteomyelitis, psychosis, septic arthritis, meningitis, myocarditis, and empyema of the gallbladder.[22,23]

Approximately 1%–5% of patients with enteric fever, depending on age and sex, become chronic gallbladder carriers of the organism (defined as excretion of the pathogen for >12 months following acute infection).[33,34]

Pathogenesis and Immunity

S. Typhi and *S*. Paratyphi A and B are invasive bacteria that efficiently pass from the intestinal lumen across the mucosa, to reach eventually the reticuloendothelial system, where, after an 8–14 day incubation, they initiate a systemic illness. *S*. Typhi and *S*. Paratyphi A and B are highly host-adapted pathogens, as humans comprise the only natural host and reservoir of infection.

In the fasting normochlorhydric stomach gastric acid kills many typhoid bacilli that are ingested, but some foods effectively buffer this acid barrier. After passing through the pylorus and reaching the small intestine, typhoid bacilli rapidly penetrate the mucosa to reach the lamina propria. *S.* Typhi targets M (microfold) cells overlying Peyer's patches and other gut-associated lymphoid tissue,[35] and are then ingested by dendritic cells and macrophages underlying the M cells. The bacilli may also invade enterocytes (absorptive cells) of the small intestine and enter endocytic vacuoles that transit the bacteria to be released into the lamina propria without destroying the enterocyte;[36] *Salmonella* may also pass paracellularly between enterocytes.[37]

Upon reaching the lamina propria in the nonimmune host, typhoid bacilli elicit an influx of macrophages and dendritic cells that ingest the organisms but are generally unable to kill them. Some bacilli apparently remain within macrophages of the small-intestinal lymphoid tissue, while others are drained into mesenteric lymph nodes where further multiplication and ingestion by macrophages take place.

Postmortem studies have documented the inflammatory responses that occur in distal ileum Peyer's patches and other organized lymphoid aggregations. Later in the disease course hemorrhage can occur from these lesions. Gross bleeding comes from eroded vessels in or near the Peyer's patches. When perforations of the bowel wall occur, it is in the same sections of the gut as the hemorrhages.

Shortly after invasion of the intestinal mucosa, a primary bacteremia ensues in which *S.* Typhi is filtered from the circulation by fixed phagocytes of the reticuloendothelial system. Having gained its intracellular haven

throughout the organs of the reticuloendothelial system, the pathogen resides therein during the incubation period (usually 8–14 days) until the onset of clinical enteric fever. Clinical illness is accompanied by a fairly sustained, albeit low level (1–10 organisms/ml), "secondary" bacteremia. During bacteremia, the Vi capsular polysaccharide protects the bacteria from the lytic effects of O antibody (if present) and complement.[38] *S.* Typhi strains lacking Vi are rare[39] and somewhat less virulent than Vi-expressing strains.[40] Typhoid fever bacteremia can persist for several weeks if antibiotic therapy is not given. Symptoms and signs of typhoid fever are not due to circulating endotoxin.

During the primary bacteremia, typhoid bacilli also reach the gallbladder, an organ for which *S.* Typhi has a remarkable predilection,[41,42] and *S.* Typhi can be readily cultured from bile or from bile-stained duodenal fluid in patients with acute typhoid fever.[43-45] In ~2–5% of patients, the gallbladder infection becomes chronic. The propensity to become a chronic carrier is greater in females and increases with age at the time of acute *S.* Typhi infection, thereby resembling the epidemiology of gallbladder disease. The infection becomes chronic in individuals who have pre-existent gallbladder pathology at the time of acute *S.* Typhi infection. Carriers shed as many as 10^9 organisms/g feces but these organisms travel the length of their gastrointestinal tract without penetrating or causing disease.[46]

Following acute *S*. Typhi infection, serum antibodies to somatic O (lipopolysaccharide) and flagellar H antigens appear but, curiously, most patients with acute typhoid fever do not manifest rises in serum anti-Vi antibody.[47,48] In contrast, serum Vi antibody is highly elevated in chronic gall bladder carriers.[47,48] Intestinal secretory IgA antibodies responses to *S*. Typhi can also be detected.

Measurements of cell-mediated immunity (CMI) in patients with wild type infection has been limited in the modern era but CMI responses have been extensively studied in subjects vaccinated with attenuated strains administered as oral vaccines, demonstrating the appearance of classical MHC I-restricted cytotoxic T cells and T cells that secrete cytokines upon exposure to *S*. Typhi antigens.[49]

Diagnosis

Confirming the diagnosis of enteric fever currently requires recovery of *S.* Typhi or *S*. Paratyphi from a suitable clinical specimen. Multiple blood cultures should be obtained from patients in whom the diagnosis is suspected clinically. The isolation rate of *S.* Typhi or *S*. Paratyphi from blood cultures depends on many factors, including the volume of blood cultured, the ratio of volume of blood to volume of culture broth (ideally, the ratio should be > 1:8), inclusion of anti-complementary substances in the broth (e.g., sodium polyanethol sulfonate or bile), and whether the patient has already received antibiotics to which the *S.* Typhi is sensitive. If three 5-ml blood cultures are obtained, *S.* Typhi can be recovered from the blood in approximately 65–70% of untreated suspect cases.

The "gold standard" of bacteriological confirmation of typhoid fever is bone marrow culture, which is positive in 85–95% of cases, even when the patient has received antibiotics.[28,43,44,50] Use of duodenal string devices to obtain bile-stained duodenal fluid for culture is also quite useful.[43] The combination of a duodenal string and two blood cultures generally provides a sensitivity of bacteriological confirmation equal to that achieved with bone marrow cultures, but without the invasiveness of the latter.[43] Culture of skin snips from rose spots also provides a high yield.[28] Stool cultures are generally positive in only 45–65% of cases (somewhat higher in children). Bacteriologic confirmation of *S*. Typhi, *S*. Paratyphi A and *S*. Paratyphi B isolates can be made by agglutination of the isolate with typing sera or by testing its DNA by multiplex polymerse chain reaction (PCR).[51]

Over the years many attempts have been made to develop tests that detect *S.* Typhi antigens in blood, urine, or body fluids, thereby providing a rapid diagnostic test for typhoid fever. With few exceptions, these tests have been disappointing and have failed to warrant the enthusiasm of initial reports. PCR methods have attempted to ampify *S*. Typhi genes from blood.[52-56] However, even these sensitive assays are limited by the fact that the level of bacteremia in typhoid is low (~1–10 organisms per ml of blood). Heretofore, these methods have been amenable only to research laboratories and are not presently available for routine use in clinical laboratories in developing or transitional countries. Significant hurdles will have to be overcome to adapt them to become practical tests for clinical care even in industrialized country settings to diagnose enteric fever in travelers.

Serodiagnosis of typhoid fever was described in 1896 by Widal and Sicard,[57] who reported that the serum from patients with typhoid fever agglutinated typhoid bacilli. Widal tests are still used today in many developing countries to measure agglutinins in serum from patient with suspected enteric fever. The test is more accurate when performed with antigen in tubes rather than on slides. By careful choice of antigen, both O and H antibodies can be selectively measured. Using *S.* Typhi strain O901 (which lacks flagellar and Vi antigens), *S.* Typhi O antibody can be selectively measured. A strain such as *Salmonella* Virginia, that possesses the identical Phase 1 flagellar antigen H:d as *S.* Typhi but shares no O somatic antigens with serovar Typhi, can be used to measure H agglutinins.[58] Most patients with typhoid fever have elevated levels of O and H antibody at the time of onset of clinical illness.[58] The prevalence of H antibodies in adults living in endemic areas is generally too elevated for the test to be useful in that age group but it can be useful as a diagnostic test in children <10 years of age in endemic areas and in persons of any age from non-endemic areas.[58,59] One study from Indonesia supported use of the slide test for O agglutinins of *S.* Typhi, even for adults in that endemic area.[60]

Treatment

The first antibiotic to treat typhoid fever, chloramphenicol, reported in 1948,[61] was successfully used for a quarter century thereafter and remains useful where strains of *S.* Typhi are routinely susceptible. However, large-scale epidemics of chloramphenicol-resistant typhoid fever abruptly occurred, first in Mexico (1972),[62,63] then in Southeast Asia (1974),[64] and then in Peru[65] (1979–1980). The antibiotic-resistance genes were encoded on plasmids of incompatibility group HI1.[62,65] After ~2 years the resistant strains in Mexico and Peru were replaced by chloramphenicol-sensitive *S.* Typhi. Beginning in the late 1980s, *S.* Typhi strains resistant to chloramphenicol, amoxicillin, and trimethoprim–sulfamethoxazole disseminated widely throughout Asia.[66-68] Initially, effective alternative antibiotics included oral ciprofloxacin and parenteral ceftriaxone but widespread use of ciprofloxacin and other fluoroquinolones, often in inadequate dosages and duration, encouraged the emergence of fluoroquinolone-resistant strains.

The management of typhoid and paratyphoid is challenging, particularly where the disease burden is high, there is a dearth of clinical microbiology facilities to confirm the diagnosis and provide antimicrobial susceptibility, and the prevalence of multi-drug resistant strains is high.[69-74] Antibiotic-susceptible, uncomplicated typhoid and paratyphoid can be managed in outpatient settings with chloramphenicol, amoxicillin, ciprofloxacin or ofloxacin. Ciprofloxacin has the advantage of more convenient dosing and lower clinical relapse rates.[70,75]

WHO recommends cefixime as an alternative [76] for treating multi-resistant typhoid but reports of high failure rates in Nepal and Vietnam are concerning.[77,78] Oral azithromycin is another increasingly used first-line therapy in areas of high multi-drug resistant typhoid.[79] Severe or complicated typhoid should, if possible, be treated in hospital with parenteral antibiotics (preferably intravenous ceftriaxone) and careful monitoring to ensure good

clinical outcomes. Switching to an oral agent to which the strain is (or is presumed) susceptible can occur once the patient is afebrile. Prompt administration of high-dose dexamethasone reduces case fatality in patients with severe typhoid fever without increasing the occurrence of complications, carriers, or relapse among survivors.[31,80]

Typhoid and Paratyphoid Vaccines

Ty21a live Oral Vaccine. Ty21a, an attenuated strain of *S.* typhi that is safe and protective as a live oral vaccine, was developed in the early 1970s by chemical mutagenesis of pathogenic strain Ty2.[81] Mutations in this strain include the inability to express Vi polysaccharide and inactivation of the *gal*E gene (encoding an enzyme involved in LPS synthesis), along with ~ two dozen additional mutations. In large-scale field trials with Ty21a involving approximately 465,000 schoolchildren in Chile and 32,000 in Egypt, and approximately 20,000 subjects from 3 years of age to adults in Indonesia, passive surveillance failed to identify vaccine-attributable adverse reactions or other safety issues.[82-87]

Controlled efficacy field trials of Ty21a emphasize that the formulation of the vaccine, number of doses administered, and spacing of the doses markedly influence the level of protection that can be achieved.[83-86,88,89] Two formulations, including enteric-coated capsules and a "liquid" formulation (in which lyophilized vaccine is reconstituted along with buffer powder into a vaccine cocktail), are licensed; however, in recent years only the enteric coated capsule formulation has been manufactured. Based on a field trial in Chile that demonstrated that three doses of Ty21a in enteric-coated capsules given on an every other day schedule conferred 67% efficacy over three years of follow-up and 62% protection over seven years of follow-up,[83,90] this formulation and schedule are used throughout the world except for the USA and Canada where a four-dose regimen is used. The four-dose North American immunization schedule is based on results of a large-scale, randomized comparative trial carried out in Santiago, Chile where recipients of four doses of Ty21a in enteric-coated capsules (every other day schedule) experienced a significantly lower incidence of typhoid than those allocated to receive two or three doses.[89] Ty21a confers significant cross protection against *S*. Paratyphi B [86] but not against *S*. Paratyphi A.[86]

In the mid-1980s, a "liquid suspension" formulation of Ty21a that was amenable to large-scale manufacture was prepared consisting of two packets, one with the lyophilized vaccine and the other with buffer,[85] to be mixed together in a cup containing 100 ml of water for ingestion. Randomized, placebo-controlled field trials in Santiago, Chile[85] and Plaju, Indonesia[86] showed the liquid formulation of Ty21a to be more protective (significantly so in the Santiago trial) than the enteric coated capsule formulation,[85,86] and to protect young children as well as older children. In a randomized controlled field trial in Area Suroriente of Santiago, the liquid formulation of Ty21a conferred 78% vaccine efficacy over five years of follow-up.[91] Disappointingly, this efficient formulation of Ty21a, which is also amenable to immunizing toddlers and pre-school children,[92] is no longer being manufactured.

Vi Polysaccharide Parenteral Vaccine. In the 1970s and early 1980s, purified Vi capsular polysaccharide was manufactured that was 99.8% free of contaminating LPS and was not denatured.[38,93-96] This was an important breakthrough because as little as 5% impurity with LPS can cause systemic adverse reactions in a few percent of recipients.[94] In contrast, highly purified Vi vaccine is well-tolerated and febrile reactions are observed in only 1–2% of subjects. In clinical trials, well-tolerated 25 mcg and 50 mcg single parenteral doses of purified Vi stimulated rises of serum Vi antibodies in the vast majority of vaccinated adults and schoolage children.[94-96] Administration

of subsequent parenteral doses did not boost antibody titers.[97] This is because Vi polysaccharide, like other unconjugated polysaccharide vaccines (e.g., pneumococcal and meningococcal), does not stimulate immunologic memory and the ability to raise antibody titers further by administering booster doses. Passive surveillance carried out during field trials showed the Vi vaccine to be as well-tolerated as the licensed (meningococcal and pneumococcal) polysaccharide vaccines that served as the control preparations in these trials.[95,96]

Two randomized, controlled, double-blind field trials were carried out in Nepal and South Africa to assess the efficacy of a single 25-mcg dose of non-denatured purified Vi vaccine. Over 17 months of surveillance in Nepal, Vi vaccine conferred 72% vaccine efficacy.[96] In South Africa, Vi vaccine provided 64% protection over 21 months of follow-up [95] and 55% protection over 3 years.[98] The Nepal trial included participants from preschool age to adulthood, whereas the South African trial was performed in school-children. A third controlled field trial was carried out in subjects 3–50 years of age in Guangxi, China that evaluated the protective efficacy of a single 30 mcg dose of a Vi polysaccharide vaccine manufactured in China.[99] The vaccine conferred 69% efficacy (95% CI, 28%–87%) over 19 months of follow-up.

Although Vi vaccine provides protection after a single dose, the anti-Vi titers cannot be boosted and the efficacy does not appear to persist beyond three years. Concern over the relatively short-lived duration of protection of Vi was heightened following epidemiologic investigation of an outbreak of typhoid fever that occurred among Vi-vaccinated French soldiers deployed to Ivory Coast.[100] Prior to the outbreak, the standard operating procedure had been to immunize French soldiers with Vi vaccine every five years. The outbreak investigation revealed that receipt of Vi more than three years earlier was associated with a significantly increased risk of developing typhoid fever during the outbreak.[100]

The epidemiologic observations that Vi efficacy endures for only ~3 years fits with a report that monitored the duration of serum Vi antibodies for three years after a single inoculation of adults in a non-endemic area. The percentage of subjects with a putative protective level (1.0 mcg/ml) of Vi antibody fell from 87% at one-month post-immunization to 46% after 2 years and to only 35% at 3 years post-immunization.[101]

In a cluster-randomized effectiveness trial in Kolkata, Vi conferred indirect protection on non-vaccinated subjects,[102] but the same Vi vaccine tested in Karachi in a trial of similar design did not provide indirect protection. In the Kolkata trial the Vi vaccine significantly protected pre-school children, whereas in Karachi the same lot of vaccine conferred no measurable protection for pre-school children. Table 1 summarizes salient characteristics of Ty21a, unconjugated Vi and two licensed (in India) Vi conjugate vaccines.

Table 1. Salient Characteristics of Licensed Live Oral Ty21a and Parenteral Vi Polysaccharide and Conjugated Vi Polysaccharide Typhoid Vaccines

Parameter of Comparison	Ty21a	Vi Polysaccharide	Vi-Protein Conjugates
Route of Administration	oral	parenteral	parenteral
No. of Doses	3 (4 in USA & Canada)	1	1–2
Interval Between Doses	~ 48 hours	–	1–2 months
Well Tolerated	yes	yes	yes
Efficacy	~ 65%	~ 65%	89–100%
Duration of Efficacy	7 yrs	up to 3 years	4 years
Herd Immunity	yes	yes	unknown
Serum Igg Anti-Vi	no	yes	yes
Boostable Immune Responses	yes	no	yes
Cmi (Including Cytotoxic Lymphocytes)	yes	no	not reported
Amenable for Infant Immunization	no[a]	no[b]	yes
Protects Against Vi-Negative Strains	presumably	no	no
Protects Against S. Paratyphi	*S.* Paratyphi B only	no[c]	no[c]
Recommended for Pregnant Women	no	yes	likely to be
Large-Scale School-Based Vaccination	yes	yes	yes
Effective in Endemic Population	yes	yes	yes
Effective in Travelers	yes	yes	not tested

[a] Enteric coated capsules cannot be administered to infants

[b] Vi polysaccharide is a T-independent antigen that is poorly immunogenic in infants

[c] *S.* Paratyphi A and B do not express Vi.

New Generation Typhoid

Vi Conjugates. Vi polysaccharide has been conjugated to carrier proteins such as recombinant exotoxin A of *Pseudomonas aeruginosa* (rEPA),[103,104] diphtheria toxin protein CRM_{197},[105,106] and tetanus toxoid,[107-109] to increase the immunogenicity of these parenteral vaccines by conferring T-cell-dependent properties upon the antigen, including the induction of immunologic memory. Pre-licensure trials have shown differences in the patterns of anti-Vi responses of the different Vi conjugate vaccine candidates, suggesting that differences among the vaccines in the carrier protein and conjugation method used, amount of polysaccharide and other factors may impact immunogenicity. Widely-spaced booster parenteral doses of some Vi conjugate vaccines given to adults and children in endemic areas have increased the titers of antibody over those elicited by a priming dose, suggesting induction of immunologic memory.[104,110,111]

Efficacy data from field evaluations are available for two Vi conjugates. A pre-licensure randomized, controlled field trial of a 2-dose regimen (6 weeks apart) of Vi-rEPA in children at 2–4 years of age in Vietnam's Mekong Delta demonstrated 91.5% vaccine efficacy (95% CI, 77.1–96.6%) over 27 months of active surveillance[110] and 82% efficacy (95% CI 22.3–99.1%) during an additional 19 months of follow-up that utilized a passive surveillance system.[111] There

has also been a post-licensure effectiveness evaluation of the Vi-TT conjugate Pedatyph™.[112] The design of the latter trial was not rigorous and there are many details that are not described. Nevertheless, in this comparison there were no cases of confirmed typhoid fever during 12 months of surveillance among 765 recipients of 2 doses of vaccine (6 weeks apart), while 11 confirmed typhoid fever cases were recorded among 860 unvaccinated schoolchildren.

Two Vi conjugates consisting of Vi linked to tetanus toxoid, Pedatyph™ and Typbar-TCV®, produced in India, have been licensed by the national regulatory authority. Immunogenicity data are available for both vaccines,[107-109] and some efficacy data are also available for Pedatyph™ and Typbar-TCV.[112] The Advisory Committee on Vaccines and Immunization Practices of the Indian Academy of Pediatrics has recommended use of the Typbar-TCV conjugate for children as young as six months of age.[113]

Extensive immunogenicity data from clinical trials with Typbar-TCV document this conjugate's immunogenicity in infants as young as six months of age, its' ability to elicit significantly higher, longer-lasting and higher avidity anti-Vi antibody titers than recorded among recipients of unconjugated Vi polysaccharide.[109] Typbar-TCV also conferred upon adult Oxford volunteers markedly higher protection (87.1% VE) against experimental challenge with virulent *S.* Typhi than protection conferred by unconjugated Vi polysaccharide (52.3% VE) in a randomly allocated, placebo-controlled trial when the readout was fever (38°C) followed by a positive blood culture.[114] An application for pre-qualification of Typbar-TCV was submitted to the World Health Organization (WHO) in 2017. Also in 2017, WHO's Scientific Advisory Group of Experts (SAGE) committee voted that Vi conjugate vaccine should be administered to infants as young as six months of age as a single dose and that accompanying community-wide "catch-up campaigns" in children > 6 months to school age should be encouraged where feasible. Table 2 summarizes target populations by age and the immunization strategies and regimens to vaccinate those sub-populations by harmonizing Vi conjugate administration with existing EPI visits or campaigns.

Table 2. Strategies for Vaccinating Sub-Populations with High Disease Burden with Vi Conjugate Vaccines and Immunization Regimens

Disease Burden and Target Population	Immunization Strategy for Delivering Vi Conjugate Vaccine	Immunization Schedule
High incidence in toddlers and pre-school children (12–59 months of age)	Expanded Program on Immunization (EPI)	**Option 1:** Two doses, the first given at age ~ 9 months in conjunction with measles containing vaccine 1 (MCV1) and the second at age 15–18 months in conjunction with MCV2 **Option 2:** Two or three doses to young infants in conjunction with pentavalent vaccine[a] **Option 3[b]:** Two doses, one given in conjunction with pentavalent-2 or pentavalent-3) and the second in conjunction with MCV1
High incidence in school age children	School-based immunization or combined with measles vaccination campaigns	Single-dose
High incidence in young adults	Mass immunization campaigns in conjunction with other vaccines[c]	Single-dose

[a]Pentavalent vaccine (or DPT where pentavalent is not used) is given at 6, 10 and 14 weeks in sub-Saharan Africa and at 2, 4 and 6 months of age in many countries in South Asia and in Latin America

[b]Although this option is plausible for certain pediatric populations where the disease incidence is high in toddlers and young pre-school children, there are no clinical trials that have been reported where this regimen has been tested

[c]For example, in conjunction with Japanese encephalitis virus vaccine campaigns in Asia or with MenAfrivac campaigns in Africa

Single-Dose Live Oral Vaccines. Engineered recombinant strains of *S.* Typhi that contain precise attenuating mutations have been shown to be well tolerated and immunogenic after ingestion of a single oral dose in Phase 1 and 2 clinical trials. Live oral vaccine candidates include strains M01ZH09,[115-117] Ty800,[118] CVD 908-*htrA*[119,120] and CVD 909.[121,122]

Prevention and Control

Safe water and food. Since enteric fever pathogens are typically acquired via the ingestion of contaminated water or food, enteric precautions should be taken when living or traveling in endemic areas. Only treated (boiled or chemically treated) water should be consumed and foods that may be fecally contaminated (e.g., uncooked salad vegetables) should be avoided.

Conclusion

Both for the prevention of disease in populations in typhoid-endemic countries and for travelers from industrialized countries to regions of the world where typhoid is endemic or epidemic, parenteral (including a new Vi conjugate vaccine) and oral vaccines currently exist to protect against typhoid fever. Widespread use of these vaccines can diminish the burden of typhoid worldwide. Additional Vi conjugates and new live oral vaccines to prevent typhoid are in clinical development. Moreover, parenteral conjugates and live oral vaccines to prevent paratyphoid fever are also in clinical development.

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