Enteric (typhoid or paratyphoid) fever is a systemic infection caused by Salmonella enterica, including S. enterica serotype Typhi (S. typhi) and serotypes Paratyphi A, B, and C (S. paratyphi). Humans are the only host for these pathogens, which are transmitted by fecal contamination of food and water. Salmonella typhi caused an estimated 22 million illnesses and 200,000 deaths, and S. paratyphi caused 5.4 million illnesses worldwide during the year 2000.\(^1\) The actual global burden of enteric fever is difficult to determine because many cases are unrecognized, particularly in young children who may have a nonspecific illness,\(^2,3\) and it is not a notifiable disease in endemic countries. In addition, there are no specific clinical diagnostic criteria, and the laboratory techniques for diagnosis lack sensitivity and specificity.\(^5\) According to the recently estimated global incidence, the highest concentration of typhoid fever is in Asia, especially in the Indian subcontinent (Table 1).\(^1\) Southern Africa and Latin America also have a high disease burden (Table 1).

Previously, S. paratyphi was thought to have caused 10% of cases of enteric fever and a milder form of disease than S. typhi.\(^6,7\) However, recent reports suggest that these two pathogens cause similar diseases\(^8-10\) and that there has been a disproportionate increase in the incidence of enteric fever caused by S. paratyphi, with up to 50% of enteric fever cases caused by S. paratyphi in some highly endemic areas of the world.\(^11-15\) Enteric fever also affects short-term and long-term travelers bound to highly endemic areas.\(^16\) Among the travel-related cases, most occur in foreign-born residents who visited friends or family in their country of origin.\(^17\) Travel to the Indian subcontinent is associated with the highest risk of contracting enteric fever.\(^16,18-20\) In addition, enteric fever in travelers from the UK due to S. paratyphi A surpassed disease due to S. typhi.\(^21\)

Given the significant burden of enteric fever and the threat of increasing antimicrobial resistance,\(^22-29\) the role of preventive vaccines is critical. Currently, there are two available vaccines against S. typhi (Table 2): the live attenuated oral vaccine containing the S. typhi strain Ty21a (Ty21a vaccine) and the parenteral capsular polysaccharide vaccine based on the S. typhi Vi antigen (Vi vaccine). The live attenuated vaccine is formulated in enteric capsules. It is licensed for children ≥6 years of age in the United States and, in other parts of the world, for children ≥2 to 5 years of age depending on the country. The parenteral capsular polysaccharide vaccine based on the S. typhi Vi antigen (Vi vaccine) is licensed for children ≥2 years of age. There are currently no licensed vaccines against S. paratyphi.\(^30\)

The live attenuated Ty21a vaccine was developed by Germanier and Füer\(^41\) by treatment of the wild-type strain of Ty2 with the mutagenic agent nitrosoguanidine. A mutant was selected that lacked the Vi antigen and the enzyme uridine diphosphate-galactose-4-epimerase.\(^32\) There have been no documented cases of the Ty21a vaccine reverting to virulence in any of the multiple large field trials conducted, which is likely due to the fact that this strain contains multiple mutations as a result of chemical mutagenesis. Ty21a induces protection against S. typhi by inducing mucosal [immunoglobulin (Ig) A] and serum (IgG) antibodies against the lipopolysaccharide O antigen, H antigen, and others. The Ty21a vaccine has also been shown to induce some cell-mediated immunity.\(^33\) Serum IgG antibodies and gut-derived O antigen–specific IgA antibody–secreting cells are the best surrogate markers of protection.\(^34\)

The Ty21a vaccine requires cold chain maintenance and is available in a lyophilized form in enteric-coated capsules. In the United States and Canada, four doses of Ty21a enteric capsules are administered based on data from field studies among Chilean children, showing higher efficacy with four doses,\(^35\) whereas three doses are given in the rest of the world. Indeed, one of the drawbacks of the Ty21a vaccine is the requirement for multiple doses for optimal immunogenicity. Herd immunity

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has been demonstrated during field trials of this vaccine in Chile with an adequate safety profile. Each capsule should be given on alternate days for a total of three to four doses, and ideally, all doses should be completed at least 1 week prior to potential exposure. Depending on the country, reimmunization is recommended periodically. In North America, repeated immunization is recommended every 5 years. Ty21a is not recommended for immunosuppressed individuals. It is recommended to suspend the use of antimicrobials 1 to 3 days prior to the initiation of the first dose. It is acceptable to administer this vaccine while receiving antimalarial drugs including mefloquine, atovaquone/proguanil, chloroquine, and primaquine. Ty21a can be coadministered with Ig or other vaccines. It is recommended for human immunodeficiency virus–positive individuals with CD4+ counts ≥200/µL. The safety of this vaccine in pregnant women has not been determined (pregnancy class C).

The purified typhoid Vi polysaccharide vaccine was first licensed in the United States in 1994. It was created by an extraction method that resulted in a purified, non-denatured Vi antigen. The Vi (for virulence) antigen forms a capsule that protects the bacteria against complement-mediated lysis and phagocytosis. The parenteral Vi vaccine is available for children ≥2 years old and is administered as one dose intramuscularly. It is recommended that it be repeated as a booster every 2 to 3 years for those at risk. In a recent study of the safety of the Vi vaccine, the most common complaints were pain at the injection site and muscle aches. Protection begins 7 days after injection, but the maximum neutralizing antibody concentration has been demonstrated at 28 days after vaccination. This vaccine may be administered with concurrent vaccines. Like the Ty21a vaccine, it is a pregnancy class C medication. Immunization with the Vi antigen results in the induction of anti-Vi antibody titers. One drawback of the Vi polysaccharide vaccine is that it does not stimulate mucosal immunity or T-cell-dependent memory.

Cross-protection with the Vi and Ty21a vaccines against paratyphoid fever has been considered. No cross-protection is possible with the Vi vaccine because the Vi antigen is not present on S. paratyphi A and B. Pooled data from two randomized, controlled field trials of the Ty21a vaccine in Chile suggest that Ty21a vaccine provides moderate protection against paratyphoid B fever. Neither study was powered to detect a significant difference between vaccine and placebo in the prevention of paratyphoid B fever; therefore, the data were pooled retrospectively to enhance statistical power in examining protection against S. paratyphi B. Even with the pooled data, there were too few cases of S. paratyphi A disease to ascertain whether Ty21a protects against S. paratyphi A. The immunological explanation for cross-protection may be due to shared epitopes among O antigens of S. paratyphi B and S. typhi. So far, there have been no clinical trials to suggest protection against S. paratyphi A by Ty21a. However, there is one descriptive analysis of cases of enteric fever in Israeli travelers, showing that Ty21a vaccination may offer some protection against S. paratyphi A.

**Typhoid Fever Vaccine Efficacy**

There have been several trials that have examined the efficacy of the Vi and Ty21a vaccines (Table 3). The

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**Table 1**  Crude typhoid fever incidence rates by region, 2000

<table>
<thead>
<tr>
<th>Region</th>
<th>Crude incidence (per 100,000 persons per year)</th>
<th>Incidence classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>50</td>
<td>Medium</td>
</tr>
<tr>
<td>Eastern</td>
<td>39</td>
<td>Medium</td>
</tr>
<tr>
<td>Middle</td>
<td>39</td>
<td>Medium</td>
</tr>
<tr>
<td>Northern</td>
<td>33</td>
<td>Medium</td>
</tr>
<tr>
<td>Southern</td>
<td>233</td>
<td>High</td>
</tr>
<tr>
<td>Western</td>
<td>38</td>
<td>Medium</td>
</tr>
<tr>
<td>Asia</td>
<td>274</td>
<td>High</td>
</tr>
<tr>
<td>Eastern Asia</td>
<td>12</td>
<td>Medium</td>
</tr>
<tr>
<td>South central Asia</td>
<td>622</td>
<td>High</td>
</tr>
<tr>
<td>Southeastern Asia</td>
<td>110</td>
<td>High</td>
</tr>
<tr>
<td>Western Asia</td>
<td>33</td>
<td>Medium</td>
</tr>
<tr>
<td>Latin America/Caribbean</td>
<td>53</td>
<td>Medium</td>
</tr>
<tr>
<td>Oceania</td>
<td>15</td>
<td>Medium</td>
</tr>
<tr>
<td>Australia/New Zealand</td>
<td>&lt;1</td>
<td>Low</td>
</tr>
<tr>
<td>Europe</td>
<td>3</td>
<td>Low</td>
</tr>
<tr>
<td>Northern America</td>
<td>&lt;1</td>
<td>Low</td>
</tr>
</tbody>
</table>

Source: Data from Crump and colleagues.

**Table 2**  Currently available typhoid vaccines

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Manufacturer</th>
<th>Administration</th>
<th>Age</th>
<th>Booster</th>
<th>Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ty21a oral, live, attenuated</td>
<td>Berna Biotech Ltd.</td>
<td>1 oral capsule every 48 h × 4 doses</td>
<td>≥6 y (United States)</td>
<td>Every 5 y (United States)</td>
<td>Class C</td>
</tr>
<tr>
<td>Vi capsular polysaccharide Ty2 strain</td>
<td>Sanofi Pasteur</td>
<td>Intramuscular</td>
<td>≥2 y</td>
<td>Every 2–3 y</td>
<td>Class C</td>
</tr>
<tr>
<td>Typhim Vi</td>
<td>GlaxoSmithKline</td>
<td>Intramuscular</td>
<td>≥2 y</td>
<td>Every 2–3 y</td>
<td>Class C</td>
</tr>
<tr>
<td>Typherix</td>
<td>GlaxoSmithKline</td>
<td>Intramuscular</td>
<td>≥16 y</td>
<td>Must be followed by second booster of hepatitis A vaccine 6–12 mo later</td>
<td>Class C</td>
</tr>
<tr>
<td>Combined Vi and hepatitis A vaccines</td>
<td>Sanofi Pasteur</td>
<td>Intramuscular</td>
<td>≥15 y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(not available in United States)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vivaxim or VIATIM</td>
<td>GlaxoSmithKline</td>
<td>Intramuscular</td>
<td>≥15 y</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
efficacy ranged from 35% to 96%, depending on the formulation, dosing schedule, and duration of follow-up postvaccination (Table 3). This wide range is rather confusing and makes it difficult to assess whether the vaccines are beneficial for travelers or for control of disease in endemic countries. Two meta-analyses on the efficacy of the typhoid vaccines have been performed. The resulting cumulative 3-year efficacies reported in the meta-analysis by Engels and colleagues were 51% (95% CI: 35%–63%) for three doses of Ty21a, 55% (95% CI: 30%–71%) for Vi (only using data from one study), and 73% (95% CI: 65%–80%) for two doses of the heat-inactivated whole-cell vaccine. They concluded that whole-cell typhoid vaccines as a class, which are now no longer used due to increased adverse effects, were more effective than Ty21a and Vi vaccines. The conclusions from this meta-analysis have been highly criticized for several reasons. It may not be appropriate to compare the old field trials of the whole-cell vaccines performed between 1962 and 1975 to the more recently conducted trials of Ty21a and Vi vaccines because the surveillance methods to detect the incidence of typhoid in the study populations were different. In addition, the meta-analysis included studies with different

<table>
<thead>
<tr>
<th>Table 3 Summary of typhoid vaccine efficacy trials</th>
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<tbody>
<tr>
<td>Ty21a vaccine study</td>
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<tr>
<td>----------------------</td>
</tr>
<tr>
<td>Wahdan and colleagues</td>
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<tr>
<td>Levine and colleagues</td>
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<td>Levine and colleagues</td>
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<table>
<thead>
<tr>
<th>Vi vaccine study</th>
<th>Number receiving vaccine</th>
<th>Site, year published</th>
<th>Randomization/ blinding</th>
<th>Number of doses</th>
<th>Follow-up</th>
<th>Control incidence</th>
<th>Vaccine efficacy (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acharya and colleagues</td>
<td>3,457 Nepal, 1987</td>
<td>Yes/no</td>
<td>1 injection</td>
<td>3</td>
<td>655</td>
<td>72 (41–87)</td>
<td></td>
</tr>
<tr>
<td>Klugman and colleagues</td>
<td>5,692 South Africa, 1996</td>
<td>Yes/yes</td>
<td>1 injection</td>
<td>3</td>
<td>387</td>
<td>55 (30–71)</td>
<td></td>
</tr>
</tbody>
</table>

CI = confidence interval.

*Enteric-coated capsules are the currently available formulation for Ty21a (liquid formulation was available until a few years ago).
†The currently recommended and licensed immunization schedule is three capsules in many countries and four capsules in the United States and Canada. Capsules should be given with 2-day intervals and with an empty stomach.

preparations of Ty21a in doses and schedules that are no longer used. In the Vi vaccine group, only one trial was included with 5,692 subjects compared to more than 185,000 for Ty21a vaccine.

A more recent meta-analysis showed that the cumulative efficacy at 3 years for the Ty21a and the Vi vaccine was similar at 51% (95% CI: 36%–62%) and 55% (95% CI: 30%–70%), respectively. Additional data on cumulative 3-year efficacies for the oral formulations were also provided: liquid (including the formulation used in Egypt that is no longer available) 74% (95% CI: 38%–89%), enteric capsules 47% (95% CI: 33%–57%), and gelatin capsules 25% (95% CI: –10% to 49%) that are no longer available. Although there was a trend toward the superiority of the liquid formulation over the enteric capsules, the difference was not statistically significant. There have been no head-to-head comparison trials of the Ty21a and Vi vaccines. Interestingly, protective efficacy of natural immunity can be overcome by increasing the inoculum of the infecting organisms; therefore, it is not surprising that there are no vaccines that are 100% efficacious.

There are several promising typhoid vaccine candidates on the horizon. One such candidate is the conjugate...
Vi vaccine using *Pseudomonas aeruginosa* exotoxin A as a carrier. This vaccine has shown a 91.5% protection rate in a large-scale randomized, two-dose-controlled trial in 2- to 5-year-old children in Vietnam with 27-month follow-up.\(^{57}\) This vaccine has the potential to be immunogenic in children <2 years old and is currently being studied in infants in Vietnam. Single-dose oral vaccines are also being tested.\(^{60}\) MH1ZH09,\(^{48}\) CVD 908, CVD 908*-btrA*, CVD 909,\(^{49}\) and Ty800.\(^{50,61}\)

### Immunization for Travelers

Extrapolating these protective efficacy results to travelers from nonendemic areas may not be reliable. The protection induced by typhoid vaccination to persons living in endemic countries may involve a boosting of preexisting immunity due to previous exposure. Because typhoid vaccines are not 100% efficacious, it is crucial to stress safe food and water precautions for travelers. One might argue that these cautionary measures would be sufficient; however, one study found that 96% of travelers had ignored the “boil it, cook it, peel it, or forget it” guidelines within the first 3 days of travel.\(^{62}\) These precautionary measures are unlikely to be followed by travelers who are visiting friends and relatives.

Typhoid vaccines are recommended by the Centers for Disease Control and Prevention, World Health Organization (WHO), and the Health Protection Agency for Disease Control and Prevention, World Health Organization for travelers to endemic countries. However, vaccination for travelers remains controversial due to several reasons: the vaccines do not have optimal protective efficacy; they have never been formally shown to demonstrate protective efficacy in travelers because the overall incidence of infection in travelers who receive them is so low; they are expensive, and their cost-effectiveness remains in question.\(^{61,64}\) Low incidence of the disease among travelers, as well as low vaccination uptake, could be contributing to the sparse data on the effectiveness of typhoid vaccines in travelers. Based on travel-associated typhoid fever data from US travelers, there appeared to be a failure to vaccinate rather than a vaccine failure because only 4% of the travelers affected had received typhoid vaccines. In contrast, a nationwide Israeli review examined all cases of enteric fever among Israeli travelers and compared incidence to pretravel vaccination status and vaccine type. Sixty-two percent of the Israeli travelers who acquired typhoid fever had received typhoid vaccination within 3 years of their travel. Of note, prior immunization against *S. typhi* was not associated with a better clinical course compared with those who were not immunized.\(^{10}\) A study of travelers in four packages from the Netherlands to Indonesia noted six cases of typhoid fever of 110 participants. All six persons affected had been vaccinated with Ty21a.\(^{61}\)

Nevertheless, it seems safest to recommend vaccination for travelers to endemic countries, especially if they are traveling to the Indian subcontinent, if they are traveling to areas with compromised food and water supplies, and if they are visiting friends and relatives. As previously stated, even short-term travelers may be at risk. Both the Ty21a and the Vi vaccines have low rates of adverse effects. The main drawback is the cost of the vaccines. The practitioner should discuss the efficacy of the vaccines and reinforce the necessity of strict food and water precautions. Ultimately, the decision to be vaccinated or not is made by the traveler.

### Immunization in Endemic Countries

Enteric fever was prevalent worldwide until early in the 20th century. With the advent of industrialization, improvement of sanitation, and implementation of safe water supplies, the areas affected have changed. Enteric fever is a disease in which humans are the only host; it can be controlled by eradicating the disease in carriers, by efficient sanitation and sewage systems, and by safe water supplies. Because improvements in the public health infrastructure that lead to safe water supplies may take a long time, vaccination programs have been proposed as the best means to control the spread of typhoid in endemic areas. The WHO has recommended both Vi and Ty21a vaccines as tools for school-based programs to control disease in high-risk endemic areas. However, the vaccines are primarily used for travelers to endemic countries rather than for those most affected in the endemic countries.\(^{66}\)

During the 1970s and 1980s, mass vaccination of schoolchildren with whole-cell vaccines in Bangkok led to sharp decreases in the incidence of typhoid fever.\(^{65}\) But the whole-cell vaccines are no longer used due to their high rate of adverse effects. The current available vaccines have some limitations for widespread use. Ty21a requires strict cold chain maintenance and has multiple precise dosing requirements. The Vi vaccine has been deemed a better candidate for widespread immunization campaigns. It is affordable in nonindustrialized nations because the technology is in the public domain and has been transferred to local producers. One drawback is that reimmunization is recommended every 2 to 3 years. So far, only China and Vietnam have incorporated the newer vaccines into their routine immunization programs and only in a limited manner.\(^{68}\)

A series of demonstration trials on Vi vaccination have been performed, and vaccination was noted to be feasible in both school and community settings, acceptable to the population, and relatively inexpensive to deliver in China,\(^{69}\) Indonesia,\(^{70}\) Pakistan,\(^{71}\) India,\(^{72}\) and Vietnam.\(^{71}\) Results of vaccine effectiveness from these trials are not yet available. One of the foremost reasons that typhoid vaccines have not been more widely implemented in endemic countries is cost. Developing countries are faced with many competing demands for health care expenditures. The cost-effectiveness of typhoid vaccines for each country will depend on effectiveness of the vaccine, epidemiology of enteric fever, cost of available typhoid vaccines in each country, and disease
costs. Another potential role for vaccines in endemic countries is during epidemics.\cite{7,4,7} WHO recommends strong consideration of vaccination against typhoid fever during an outbreak.\cite{18}

Conclusions

There is a large global burden of disease associated with enteric fever; the proportion of disease due to \textit{S. paratyphi}, for which we have no licensed vaccines, is rising, and the antimicrobial resistance of \textit{S. typhi} and \textit{S. paratyphi} has greatly increased. As huge investments and infrastructures are needed for the development of sanitation and safe water systems in endemic countries and these infrastructures may take years to develop, vaccination programs of nursery school- and school-aged children in endemic areas are currently the best means to control disease in conjunction with sanitation and poverty alleviation programs. More effective vaccines in the form of conjugate vaccines or improved live oral vaccines that also protect young children against \textit{S. typhi} and \textit{S. paratyphi} are vital. These vaccines would benefit both travelers and inhabitants of endemic areas.

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Declaration of Interests

The authors state that they have no conflicts of interest.

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