Attenuated Strains of *Salmonella enterica* Serovars Typhi and Paratyphi as Live Oral Vaccines Against Enteric Fever

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TARGET POPULATIONS

Typhoid fever caused by *Salmonella enterica* serovar Typhi (*S.* Typhi) and paratyphoid fever caused by *Salmonella enterica* serovar Paratyphi (*S.* Paratyphi) A or B are exceedingly uncommon in modern industrialized countries where populations are served by treated, bacteriologically monitored water supplies and by sanitation that removes human fecal waste. In contrast, in many less developed countries where segments of the population commonly lack such amenities, typhoid and paratyphoid fevers (referred to as enteric fevers) are often endemic. From the public health perspective, enteric fevers typically constitute the most important enteric disease problem of school-age children (1). Systematic clinical, epidemiologic, and bacteriologic surveillance for typhoid fever carried out in relation to field trials of efficacy of candidate vaccines and as assessments of disease burden has provided more precise data on the incidence of typhoid and paratyphoid fever in many populations. Many of these studies relied on passive surveillance that detected cases severe enough for the patient (or the patient's caretaker) to seek health care (2–8); other studies used forms of active surveillance (9–12). The incidence rates recorded were much higher than predicted on the basis of nonsystematic surveillance. In urban slum environments in South Asia, systematic household and health center–based active surveillance demonstrated a high incidence of bacteremic typhoid infection among febrile toddlers and preschool children (13,14).

Besides children and young adults in less developed countries, travelers (15–17) and clinical microbiologists (18,19) represent other groups at increased risk of developing typhoid and paratyphoid fever. Among U.S. travelers, the risk is highest in the Indian subcontinent (16,17). Because of increased exposure to *S.* Typhi and *S.* Paratyphi A and B, clinical microbiologists, even in industrialized countries, constitute an identifiable group at increased risk of developing enteric fever (18,19).

MULTIRESISTANT *SALMONELLA* TYPHI AND *SALMONELLA* PARATYPHI STRAINS

Since the 1990s, strains of *S.* Typhi and *S.* Paratyphi A resistant to most of the antimicrobials that were previously clinically effective have spread aggressively throughout the Middle East, the Indian subcontinent, and Southeast Asia (20–24). The few antibiotics that remain effective against these multiply resistant strains, such as ciprofloxacin, ceftriaxone, and azithromycin, are relatively expensive and not readily available in rural areas of less developed countries. The dissemination of these multiply resistant *S.* Typhi and *S.* Paratyphi A strains in many less developed countries has rekindled interest in the development of improved oral typhoid vaccines.

LICENSED LIVE ORAL TYPHOID VACCINE Ty21a: ATTRIBUTES AND LIMITATIONS

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 *S.* Typhi strain Ty2 (25). This pioneering vaccine strain has many attributes but also has several notable deficiencies. The characteristic mutations in Ty21a include an inactivation of *galE* (which encodes uridine diphosphate-galactose-4-epimerase, an enzyme involved in lipopolysaccharide [LPS] synthesis) and an inability to express Vi capsular polysaccharide. However, Ty21a also harbors more than two dozen additional mutations compared with its wild-type parent. Whereas Ty21a was remarkably well tolerated in placebo-controlled prelicensure clinical trials and in extensive postlicensure surveillance (26,27), it is not clear exactly which mutations are collectively responsible for the stable attenuated phenotype of this vaccine. On the other hand, it is known that mutations in *galE* and loss of Vi expression alone cannot account for the attenuation because a recombinant vaccine candidate (EX 462) made from the same wild-type parent (Ty2) with precise mutations in *galE* and *via* was not attenuated when fed to healthy adult volunteers (28).

Ty21a provides significant protection without causing adverse reactions. Results of three double-blind, placebo-controlled studies that utilized active surveillance to assess the reactogenicity of Ty21a in adults and children show that adverse reactions were not observed significantly more often in vaccinees than placebo recipients for any symptom or sign (5,29,30). In large-scale efficacy field trials with Ty21a, involving approximately 514,150 schoolchildren in Chile (2–4), 32,388 in Egypt (31), and approximately 20,543 subjects from three years of age to adults in Indonesia (5), passive surveillance failed to identify vaccine-attributable adverse reactions (2–5,32).

Results of controlled field trials of Ty21a revealed that the formulation of the vaccine, the number of doses administered,