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General Article

TYPHOID VACCINE: PREVENTIVE STRATEGY FOR ENTERIC FEVER

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ABSTRACT
Typhoid fever is a serious systemic infection, caused by the enteric pathogen *Salmonella enterica* serovar *Typhi*, a highly virulent and invasive enteric bacterium. This disease occurs in all parts of world where water supplies and sanitation are substandard. Typhoid fever is now uncommon in the developed countries where most of the cases that occur are either acquired aboard or imported by immigrants but the disease still remains an important public health challenge in developing countries. The new-generation typhoid vaccines have the potential to produce large reductions in the burden of diseases among the poorest sub-populations worldwide. Typhoid vaccination programmes should be implemented in addition to other efforts to control the disease including health education, water quality and sanitation improvements, exclusion of disease carriers from food handling and training of health professionals in diagnosis and treatment. In the era of increasing antibiotic resistance, vaccination should be considered in the near-to-intermediate term in order to prevent the disease in developing countries.

Key Words: *Typhoid, Water Quality, Public Health, Sanitation, Vaccination*

INTRODUCTION
Typhoid fever is a serious systemic infection, caused by the enteric pathogen *Salmonella enterica* serovar *Typhi*, a highly virulent and invasive enteric bacterium. This disease occurs in all parts of world where water supplies and sanitation are substandard. Although typhoid is largely considered an endemic disease, the disease has epidemic potential. *S. typhi* spreads by typhoid patients and carriers in large quantities through feco-oral route. These pathogens then travel to food, drinks and water through house-flies and other vectors. When these contaminated food or drinks, are eaten by healthy person, bacteria enter in to the body and causes the disease. Person may contract typhoid fever by consuming food or drink that has been prepared or handled by typhoid patients or carriers, or if sewage contaminated with *S. typhi* moves into household water supply system (Park, 2011). A person infected with *S. typhi* may infect others for long time, as the bacteria remain in the body for months. Up to 10% of untreated patients with typhoid fever excrete *S. typhi* in the feces for up to 3 months, and 1–4% develop chronic asymptomatic carriage, shedding *S. typhi* in either urine or stool for >1 y and lead to further transmission in the community. A very low percent of typhoid patients remain chronic carriers regardless of treatment. Gastrointestinal bleeding (10– 20%) and intestinal perforation (1–3%) are most commonly occurring life-threatening complications (Pegues and Miller, 2008). Paratyphoid fever also has similar symptoms to typhoid fever but is generally a milder disease. Paratyphoid is caused by *Salmonella enteritidis paratyphi* A, B or C. *S. typhi* expresses a capsular "Vi" (for virulence) polysaccharide, whereas *S. paratyphi* A and B cannot synthesize Vi (Levine, 2009).

Prevalence
Typhoid fever is now uncommon in the developed countries where most of the cases that occur are either acquired aboard or imported by immigrants but the disease still remains an important public health challenge in developing countries. Globally, an estimated 12–33 million cases of enteric fever occur with 216,000–600,000 deaths per year, almost exclusively in the developing countries (Malisa and Nayaki, 2010). Before the use of antibiotics, typhoid fever had a case fatality rate of 10 to 20%. The incidence is highest (≥100 cases/100,000 population per year) in South-central and Southeast Asia, medium in the rest

of Asia, Africa and Latin America (these regions are characterized by rapid population growth, increased urbanization and limited safe water, infrastructure and health systems) and low in the rest of the world. It is more common not only in young children and adolescents (2–15 y) but also in preschool age group including infants and toddlers less than 2 y of age (Sinha *et al.,* 1999; Levine, 2003). The study of typhoid burden in five Asian countries found annual incidence rates of blood culture-confirmed typhoid fever of 180–494/100,000 among children in three urban slum areas (North Jakarta, Indonesia; Kolkata, India; and Karachi, Pakistan) (Ochiari *et al.,* 2008). While these studies confirm that school-aged children are at particularly high risk, pre-school children as young as 2 y old are also shown to be highly vulnerable. Health surveys conducted by the Health Ministry of India in the community development areas indicated a morbidity rate varying from 102–2,219/100,000 population in different parts of the country. A limited study in an urban slum showed 1% of children up to 17 y of age suffer from typhoid fever annually (Bhatta *et al.,* 2005).

Typhoid Vaccines

Early typhoid vaccines were developed in the 1890s and 6 decades later, the World Health Organization (WHO) sponsored large-scale, randomized, controlled field trials, in which investigators found that killed whole-cell vaccines conferred substantial protection against typhoid. However, because these vaccines commonly elicited debilitating adverse reactions, they were rarely used to control endemic typhoid fever (Ochiari *et al.,* 2008; Levine *et al.,* 1989). In 1970s epidemics of chloramphenicol-resistant typhoid occurred in Mexico and Vietnam. These outbreaks stimulated a search for alternative oral antibiotic therapies and accelerated efforts to develop a new generation of better-tolerated, efficacious typhoid vaccines (Levine, 2009). Vaccination is also a powerful tool for preserving the efficacy of existing pharmaceutical treatments in the face of growing microbial resistance to antibiotics. Because of the ready availability of over-the-counter antibiotics and subsequent resistance to these drugs in areas of endemicity, enteric fever is becoming harder to treat (Cook *et al.,* 2009; Maskey *et al.,* 2006).

The continued high burden of typhoid fever and the alarming spread of antibiotic resistant strains led the World Health Organization (WHO) to recommend immunization using the two new-generation vaccines in school aged children in areas where typhoid fever posed a significant problem and where antibiotic resistant strains were prevalent (Bulletin World Health Organization, 1999). New data from Asia on the disease and economic burden of typhoid fever, recent trends in antibiotic resistance and vaccine effectiveness and cost-effectiveness, along with the increased availability of typhoid vaccines and sharp reductions in their price, led WHO to review, update and reinforce its recommendations for the use of typhoid vaccines for populations at high risk, so that this disease can truly be controlled in developing countries (Typhoid vaccines Position Paper, 2008).

The World Health Organization (WHO) recommendations for the use of typhoid fever vaccines are described in the recent "Typhoid Vaccines Position Paper." These include recommendations that in view of the continued high incidence and increasing antibiotic resistance of typhoid fever, and given the safety, efficacy, feasibility and affordability of two licensed vaccines (Vi and Ty21a), affected countries should consider programmatic use of typhoid vaccines for controlling this endemic disease (Bulletin World Health Organization, 1999). The position paper indicates that the use of vaccine should be based on an understanding of the local epidemiology of typhoid fever to target vaccine to groups at high risk of disease, such as pre-school-or school-age children, and that vaccine should be implemented in the context of broad disease control efforts (Typhoid vaccines Position Paper, 2008). These new-generation vaccines have the potential to produce large reductions in the burden of diseases among the poorest sub-populations worldwide.

The single-dose injectable Vi vaccine provides about 70% protection against blood culture- confirmed typhoid fever, and protection lasts for at least 3 years. The live attenuated Ty21a vaccine is available as capsules and as a liquid suspension, both administered as one oral dose every other day. The liquid formulation is licensed for use in people aged >2 y; the capsules from 5 y of age. The recommended 3–4 dose schedule of the liquid Ty21a vaccine provides 53–78% protection against confirmed typhoid fever.

An advantage of parenteral Vi vaccine is its single-dose regimen; unconjugated Vi does not elicit immunologic memory, so serum Vi titers are not boosted by additional doses. A drawback of the Ty21a vaccine is that it requires a 3-dose regimen with an every other- day interval. Nevertheless, oral immunization is logistically very practical in school children (Sur *et al.,* 2009).

Recently in India, Bharat Biotech International Ltd on 26 August 2013 launched the typhoid vaccine called Typbar TCV, which is capable of providing higher efficacy and longer immunity against typhoid. The vaccine showed 98 percent sero-conversion (a measure of checking vaccine efficacy), in the infants between age 6 months to 12 months. It also showed 99 percent sero-conversion in the children between 2 years to 15 years age group and 92 percent in the age group 15 years to 45 years. The vaccine has the capability of providing immunity for a minimum of ten years and can be given to infants too (Bharat Biotech International Limited, 2013).

Despite extensive data documenting the safety, efficacy and practicality of the Vi and Ty21a vaccines, they have not been widely applied programmatically in developing countries (Typhoid vaccines Position Paper, 2008). In 2008, the WHO and the Global Alliance for Vaccines and Immunization took more active steps to encourage programmatic use of these vaccines where typhoid is a major public health problem. Sur et al. showed that the Vi vaccine conferred an adjusted vaccine effectiveness of 80% in preschool children, thereby providing a biologic basis for including preschoolers in mass typhoid immunization campaigns. Evidence from China suggests that the programmatic use of Vi vaccine in selected areas largely controlled the disease within a 4- to 5-y period, reducing outbreaks as well as incidence to very low levels (Typhoid vaccines Position Paper, 2008; Steele, 2008.)

The Vi vaccine does not protect against *S. Paratyphi* A or B, since these strains do not express the Vi polysaccharide. Thus, countries with high rates of paratyphoid fever cannot expect reduction of the disease by using the Vi vaccine. The Ty21a vaccine confers substantial cross-protection (vaccine effectiveness, 49%) against S. Paratyphi B (Levine *et al.,* 2007) but not against *S. Paratyphi* A (Simanjuntak *et al.,* 1991). Since India has very low rates of paratyphoid fever, Vi polysaccharide vaccine is suitable for preventing typhoid in India. Parenteral unconjugated Vi is available for use by public health practitioners. The time has come to implement use of this vaccine vigorously. Most developed countries recommend typhoid vaccine to travelers visiting high-risk areas.

Although many countries have expressed interest in introducing typhoid vaccines, progress on the use of these vaccines has been slow due to a lack of local surveillance of the burden of disease, commitment of resources to support countries introducing the vaccines, a simple and affordable diagnostic tool, and pre-qualifed vaccines. Typhoid vaccination programmes should be implemented in addition to other efforts to control the disease including health education, water quality and sanitation improvements, exclusion of disease carriers from food handling and training of health professionals in diagnosis and treatment. In the era of increasing antibiotic resistance, vaccination should be considered in the near-to-intermediate term in order to prevent the disease in developing countries, as improvements in sanitation and water systems are the ultimate but expensive solutions. Morbidity and mortality due to high incidence (World Health Organization, 2011) of typhoid fever favors the introduction of typhoid vaccine in routine immunization in India.

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