

## Epidemiology of typhoid and its vaccination therapy

N. K. Mishra

HOD, Dept. of Pharmacology, Mother Teresa Pharmacy College, Sankethika Nagar, Kothuru, Sathupally, India

**\*Corresponding Author:**

Email: montu.mph@gmail.com

### Abstract

Typhoid (enteric) fever caused by *Salmonella enterica* serovar Typhi (*S. Typhi*) is an important cause of morbidity and mortality globally. The burden of typhoid fever shows substantial variation within as well as between countries. Commonly identified risk-factors include a lack of clean drinking water, poor sanitation, inadequate hygiene practices and low socio-economic status. The incubation period is 1 to 14 days. Symptoms include: high fever, rash, weakness, constipation or diarrhoea, abdominal pain, vomiting, headaches, poor appetite. Antibiotic resistance is the major problem in order to treat effectively. The development of potent vaccine candidate for typhoid fever is a need of the hour. The prevention is made through Vi-polysaccharide conjugate typhoid vaccine and Ty21 (live typhoid) vaccination. Further supportive measures like appropriate food handling, washing hands with soap before preparing or eating food, proper sanitation contributes to reducing the risk of transmission.

**Keywords:** Conjugate typhoid vaccine, High fever, *S. Typhi*, Ty21.

### Introduction

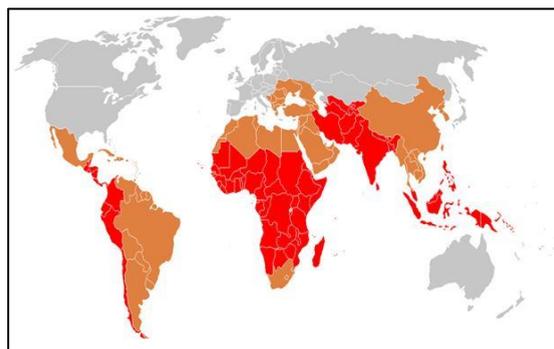
Typhoid (typhoid fever) is a serious disease. It is caused by bacteria called *Salmonella typhi* also known as *Salmonella enterica* serotype Typhi. It causes a high fever, fatigue, weakness, stomach pains, headache, loss of appetite, and sometimes a rash. It can kill up to 30% of people who get it, if it is not treated.

The bacterium that causes typhoid fever may be spread through poor hygiene habits and public sanitation conditions, and sometimes also by flying insects feeding on faeces. Public health education campaigns encouraging people to wash their hands after defecating and before handling food are an important component in controlling spread of the disease. The chlorination of drinking water has led to dramatic decreases in the transmission of typhoid fever in the United States. To help decrease rates of typhoid fever in developing nations, the World Health Organization (WHO) endorsed the use of a vaccination program starting in 1999. Antibiotic resistance is a challenge for effective treatment of typhoid and is likely to become increasingly problematic with the spread of multi-drug resistant strains.<sup>(1)</sup> Vaccinations have proven to be a great way at controlling outbreaks in high incidence areas.

### Epidemiology

From estimation 21.7 million illnesses and 217,000 deaths are found in 2000 occurred worldwide.<sup>(2)</sup> Most often children and young adults between 5 and 19 years old are affected. Infants, children, and adolescents in south-central and Southeast Asia experience the greatest burden of illness.

The developing nations, such as those found in parts of Asia and Africa, have the highest rates of typhoid fever (Fig.1). These areas have a lack of access to clean water, proper sanitation systems, and proper health care facilities. For these areas, such access to basic public health needs is not in the near future.<sup>(3)</sup>



**Fig. 1: Geographic range of typhoid fever**

◆ Strongly endemic, ◆ Endemic ◆ Sporadic cases.<sup>(4)</sup>

### Incidence and burden of disease in India

The annual mortality rate per 100,000 people from typhoid fever in India has decreased by 28.7% since 1990, an average of 1.2% a year. There have been two large-scale studies in India on the incidence of blood culture confirmed typhoid fever, one among individuals under 40 years old<sup>(5)</sup> and another among children 6 to 17 years old.<sup>(6)</sup>

### Transmission

The pathogenic transmissions in humans are broadly divided into two groups. The first, enteric fever, is transmitted by contaminated water or food, and is caused mainly by *Salmonella enterica* serovar Typhi (typhoid fever) or *Salmonella enterica* serovar Paratyphi A, B or C (paratyphoid fever). The second one, a range of clinical syndromes including diarrhoeal disease, is caused by a large number of nontyphoidal *Salmonella* serovars (NTS).

### Clinical signs and symptoms

The symptoms of typhoid become noticeable generally in 6-30 days, after the bacteria are exposed. Usually the incubation period is 1 to 14 days. High fever and rash are generally the prime symptoms. Fever at some occasions can go as high as 104 degrees Fahrenheit. The rashes are rose-colored and mainly appear on the abdomen and neck. The other symptoms include weakness, constipation or diarrhoea, abdominal pain, vomiting, headaches, poor appetite, general aches and pains in the body, fatigue, intestinal bleeding or perforation (after 2 to 3 weeks), chest congestion (in some patients).<sup>(7)</sup>

### Pathophysiology

*Salmonella* possess cellular mechanisms enabling bacterial proteins to be transferred to enterocytes and M cells (specialized epithelial cells of the mucosa-associated lymphoid tissues) with subsequent growth within endosomes. Subsequent events include an inflammatory response with neutrophil recruitment and mucosal damage. The host immune response typically controls non-typhoidal infection; however, the very young, elderly, debilitated and immunosuppressed may lack the response necessary to control infection. *S. typhi* more commonly invades M cells bacteria are phagocytosed by histiocytes in underlying lymphoid tissue. The bacteria proliferate and widely disseminate through blood vessels and lymphatic channels.

### Diagnosis

Diagnosis is made by any blood, bone marrow or stool cultures and with the Widal test (demonstration of antibodies against *Salmonella* antigen). Typhidot is a medical test consisting of a dot ELISA kit that detects IgM and IgG antibodies against the outer membrane protein (OMP) of the *S. typhi*. The Typhidot test becomes positive within 2–3 days of infection and separately identifies IgM and IgG antibodies. The test is based on the presence of specific IgM and IgG antibodies.

### Prevention

Typhoid disease (enteric fever) was found to be resistant to treatment with most of the commonly used antibiotics such as chloramphenicol, ampicillin, streptomycin fluoroquinolones and tetracycline.<sup>(8)</sup> Protection against enteric fever might be best achieved by a vaccine that stimulates IgG antibodies. There are two internationally licensed vaccines against typhoid:

**1. Vi-polysaccharide conjugate typhoid vaccine (Inactivated typhoid vaccine):** It is a Vi-capsular polysaccharide conjugate typhoid vaccine conjugated with tetanus toxoid. The dose of Vi polysaccharide is 25 µg/0.5 mL. The vaccine has been licensed by the Drug Controller General of India (DCGI) in August, 2013 for clinical use in India. This vaccine has been approved for use in children below 1 years of age. Though sero conversion rates of 98.05% have been reported with this

vaccine, the antibody titres fall significantly after 18 months suggesting that a booster dose may be required. However when the booster dose should be given can only be established on long term follow up. The Indian Academy of Paediatrics recommends that the TCV can be given below one year of age, preferably between 9-12 months (minimum age 6 months).

**2. Ty21 (Live typhoid vaccine):** Due to the side effects and low effectiveness of the killed whole cell vaccine a need for a more competent vaccine candidate emerged. Live attenuated, formulated as a capsule for oral administration. It contains the Ty21a strain of *S. typhi*, which is a mutant strain lacking UDP galactose epimerase enzyme.<sup>(9)</sup> It induces local gut immunity without any systemic immunity. Live attenuated vaccine (Ty21a) is not able to elicit anti Vi antibodies may be because Vi expression is highly regulated. Also unexpected symptoms like dizziness and pruritis, fatigue and myalgia and occasional cases of reactive arthritis has also been reported with this vaccine. Oral Ty21a vaccine is a course of 4 capsules given orally on alternate days. Four doses: one capsule every other day for a week (day 1, day 3, day 5, and day 7). The capsules should be swallowed intact and not opened or chewed. The capsule is recommended for children aged ≥ 5 years of age, but the liquid formulation can be administered even to younger children (aged ≥ 2 years).

**Storage temperature and shelf life:** The vaccine is recommended to be stored at + 2<sup>o</sup> C to + 8<sup>o</sup> C, and freezing should be avoided.

**Risks from typhoid vaccine:** Serious problems from either typhoid vaccine are very rare.

**Inactivated typhoid vaccine:** Fever (up to about 1 person in 100), Headache (up to about 1 person in 30), Redness or swelling at the site of the injection (up to about 1 person in 15).

**Live typhoid vaccine (oral):** Fever or headache (up to about 1 person in 20), Stomach pain, nausea, vomiting, rash (rare).

### Conclusion

Worldwide spread of *S. typhi* strains which induces typhoid disease (enteric fever) that are resistant to most previously useful antibiotic. Public health authorities should now devise ways of using the two currently available improved typhoid vaccines i.e. parenteral Vi polysaccharide and oral Ty21a, in large-scale nursery-based and school-based immunization programmes, and should monitor their public health impact. Preventive measures like appropriate food handling, washing hands with soap before preparing or eating food, proper sanitation contributes to reducing the risk of transmission.

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### Conflict of interest

Author declares no conflict of interest.

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