Introduction

Typhoid fever is a clinical syndrome caused by a systemic infection with *Salmonella enterica* subspecies called *enterica* serovar Typhi (*S. Typhi*). Paratyphoid fever, caused by infection with *S. enterica* serovar Paratyphi A or B, is similar to, and often indistinguishable from, typhoid fever. The two infections are collectively known as 'enteric fever'. These pathogens only infect humans. There is no vaccine against paratyphoid fever.

Typhoid fever is spread by the faeco-oral route and closely associated with poor hygiene, lack of pure drinking water and inadequate sanitation. The disease is almost exclusively transmitted by food and water contaminated by faeces and urine of patients and carriers.

The fatality rate is approximately 16% for untreated cases and 1% for those given appropriate antibiotic therapy. Between 2% and 5% of typhoid cases become chronic carriers, sometimes shedding bacteria in stool for years. The risk of severe illness is increased in people with depressed immunity (e.g., due to HIV) or decreased gastric acid levels.

Increasing multidrug resistance of *S. Typhi* reduces the effective treatment options, increases treatment costs and results in higher rates of serious complications and deaths.

Bacteriology

Salmonella is a genus of the family *Enterobacteriaceae*. *Salmonellae* are rod-shaped, Gram-negative, facultative anaerobic bacteria, most of which motile by peritrichious flagella (H antigen). In addition to the H antigen, 2 polysaccharide surface antigens aid in the further characterization of *S. enterica*, namely the somatic O antigen and the capsular Vi (virulence) antigen.

Mode of transmission

Typhoid and paratyphoid bacteria are passed in the faeces and urine of infected people. People become infected after eating food or drinking beverages that have been handled by a person who is infected or by drinking water that has been contaminated by sewage containing the bacteria. Once the bacteria enter the person's body they multiply and spread from the intestines, into the bloodstream.

Clinical Features

After 5 to 21 days of incubation (range 3 to 60 days), patients experience a low-grade fever, dull frontal headache, malaise, myalgia, anorexia, abdominal tenderness, relative bradycardia, splenomegaly, and dry cough. Constipation usually occurs in older children and adults, whereas younger children may suffer

from diarrhoea. The fever tends to increase as the disease progresses

Typhoid fever normally results in lifelong immunity. Reinfections are rare, at least in cases where the primary infection is not aborted by early antibiotic treatment.

Complications:
Complications following typhoid occur in 10 to 15% of patients and tend to occur in patients who have been ill for >2 weeks. The more important complications include gastrointestinal bleeding, intestinal perforation and typhoid encephalopathy.

Relapse occurs in 5 to 10% of patients, usually 2 to 3 weeks after the initial fever resolves. Chronic asymptomatic biliary carriage of *S. Typhi* occurs in up to 5% of patients with typhoid fever, even after treatment.

Epidemiology

Global Situation

Improved living conditions and the introduction of antibiotics in the late 1940s resulted in a drastic reduction of typhoid fever morbidity and mortality in industrialized countries. However in developing areas of Asia, Africa and Latin America, typhoid fever continues to be a public health problem.

In 2004, WHO estimated the global typhoid fever disease burden at 21 million cases annually, resulting in an estimated 216, 000–600, 000 deaths per year, predominantly in children of school age or younger.

The true burden of typoid fever in developing countries is difficult to estimate. Asia, with 274 cases per 100,000 persons has the highest incidence of typhoid fever cases worldwide, especially in Southeast Asian countries and in the Indian subcontinent, followed by sub-Saharan Africa and Latin America with 50 cases per 100,000 persons. In an urban slum in Dhaka, incidence of bacteremic typhoid fever was found to be 390/100,000 population, with a 9-fold higher risk for preschool children than for older persons.

Situation in Sri Lanka

Enteric fever is a notifiable disease in Sri Lanka, is endemic in the country within certain geographical areas. A total of 1823 clinically suspected enteric fever cases were notified to the Epidemiology Unit in the year 2010. In the recent past a significant proportion of the reported small scale enteric fever outbreaks were mainly due to para typhoid rather than typhoid fever.

Typhoid vaccine

In view of the continued high burden of typhoid fever and increasing antibiotic resistance, and given the safety, efficacy, feasibility and affordability of 2 licensed vaccines (Vi and Ty21a), countries should consider the programmatic use of typhoid vaccines for controlling the endemic disease. In most countries, control of the disease will require vaccination only of high-risk groups and populations.

Currently, 2 typhoid vaccines of demonstrated safety and efficacy are available in the international market, namely the parenteral Vi polysaccharide vaccine and the live, oral Ty21a vaccine. These vaccines should now replace the old and relatively reactogenic heat-phenol or acetone inactivated whole-cell vaccine.

Characteristics of the typhoid vaccines

- **The Vi polysaccharide vaccine**

This subunit vaccine was first licensed in the United States in 1994. It is a clear coulerless solution composed of purified Vi capsular polysaccharide from the Ty2 *S. Typhi* strain

Each 0.5 ml pre-filled syringe contains 25 micrograms Vi polysaccharide of *Samonella typhi* and inactive ingredients: sodium chloride, disodium phosphate dehydrate, sodium dihydrogen phosphate dehydrate, phenol and water for injection. This vaccine is available in packs of one and ten glass prefilled syringes.

- **Ty21a oral vaccine**

This vaccine, which was first licensed in Europe in 1983 and in the USA in 1989, is an orally administered, live attenuated Ty2 strain of *S. Typhi* in which multiple genes, including the genes responsible for the production of Vi, have been mutated chemically.

Each enteric-coated capsule contains not less than 2 x 109 viable organisms of attenuated *S. Typhi* strain Ty21a Berna.

Indications

Immunization of adults and children over 2 years of age against typhoid fever. Typhoid vaccination is recommended for:

- high risk groups and populations who are living in typhoid endemic areas e.g: Immunization of school age and/or preschool age children is recommended in areas where typhoid fever in these age groups is shown to be a significant public health problem, particularly where antibiotic-resistant *S. Typhi* is prevalent,

- travellers to destinations where the risk of typhoid fever is high, especially to those hope to stay in endemic areas for longer periods and/or in locations where antibiotic resistant strains of *S. Typhi* are prevalent,

- controlling typhoid fever outbreaks,

- laboratory workers who frequently handle cultures of *S. typhi*.

Efficacy

- **The Vi polysaccharide vaccine**

The parenteral vaccine stimulates a specific antibody response (i.e. > 4-fold rise in antibody titre) in about 93% of healthy adults. Controlled trials have demonstrated that the serologic response to vaccine is correlated with protective efficacy.

Although antibody titres fall with time after vaccination, immunity following parenteral vaccine is thought to last for 2 to 3 years.

- **Ty21a oral vaccine**

Live, attenuated Typh-oral vaccines stimulate a cell-mediated immune response, as well as inducing both secretary and humoral antibody. Healthy subjects do not shed vaccine-strain organisms in their stool. As a result, secondary transmission to contacts does not occur.

In studies delivering at least three doses of the enteric-coated capsular form of the vaccine in typhoid endemic regions, reported a protective efficacy of 51%.

Immunization Schedule

- **The Vi polysaccharide vaccine**

The vaccine is licensed for individuals aged >2 years. Only 1 dose is required, and the vaccine confers protection 7 days after injection. To maintain protection, revaccination is recommended every 3 years.

After scrutinizing of local and international reports, the Epidemiology Unit suggests to administer the Vi polysaccharide vaccine only for high risk groups in the high risk areas through the EPI programme.

High risk categories are as follows:

* food handlers: People involved in food processing, cooking at the hotels, common community kitchens in pilgrimage and IDP camp settings,

* people who do not use or do not have proper toilet facilities,
* close contacts of typhoid patients (e.g. family members),
* children getting frequent episodes of diarrhoea (e.g. more than 4 attacks in the preceding six month),
* communities inaccessible to safe water,
* health care workers who associate with typhoid patients.

♦ **Ty21a oral vaccine**

The oral vaccine capsules are licensed for use in individuals aged >5 years; the liquid oral vaccine can be administered from the age of 2 years.
Recommended to repeat this series every 3 years for people living in endemic areas and every year for individuals travelling from non-endemic to endemic countries.

Dosage & Administration

♦ **The Vi polysaccharide vaccine**

A single dose of 0.5 ml is recommended for both children and adults and should be administered by intramuscular injection into the upper arm.

The Vi polysaccharide vaccine can be co-administered with other vaccines relevant for international travellers (such as yellow fever and hepatitis A) and with vaccines of the routine childhood immunization programmes.

♦ **Ty21a oral vaccine**

Both versions of the oral vaccine are administered every other day (days 1, 3 and 5); a total of 3-doses taken 1 hour before food. The dose (a whole capsule) is the same for both adults and children.

The capsule must be swallowed whole with water and must not be chewed since the organisms can be killed by gastric acid. Do not give the vaccine concurrently with antibiotics, or other drugs that are active against *Salmonellae.* Antibacterial drugs should be stopped from 3 days before until 3 days after giving Ty21a. The oral vaccine is unlikely to be efficacious if administrated at the time of ongoing diarrhoea.

The Ty21a vaccine may be given simultaneously with other vaccines, including live vaccines against polio, cholera, and yellow fever, or the measles, mumps and rubella (MMR) combination.

Storage

The recommended storage temperature is +2°C to +8°C for both Vi polysaccharide vaccine and Ty21a oral vaccine.

Cautions and contraindications

The following conditions are considered as contraindications for the use of typhoid vaccines:

- presence of one of the general contraindications for any vaccine,
- having a history of an allergy to any vaccine components,
- anyone having experienced anaphylaxis to a previous dose of typhoid vaccine preparations.

Ty21a oral live attenuated typhoid vaccine

Other than the above conditions the oral live attenuated vaccine is not recommended to:

- individuals with impaired immunity,
- pregnant women.

Vi polysaccharide vaccine is safe for HIV-infected individuals, the induction of protective antibodies is directly correlated to the levels of CD4 positive T-cells.

Ty21a live oral vaccine can be administered to HIV positive, asymptomatic individuals as long as the T-cell count (CD4) is >200/mm³.

Pregnancy is not a contraindication to vaccination with a parenteral Vi polysaccharide vaccine.

Adverse Events

Typhoid vaccines, both oral and parenteral, are associated with very few adverse events and, when adverse events do occur, they tend to be mild and transient.

- **The Vi polysaccharide vaccine**

Vi polysaccharide typhoid vaccine is associated with local adverse events such as erythema, swelling and pain at the injection site. Systemic adverse events are rare and include fever, malaise and nausea.

- **Ty21a oral live attenuated typhoid vaccine**

The reported adverse events following oral immunization are also relatively rare and mild. Local reactions, such as vomiting, abdominal discomfort and diarrhoea seldom prevent completion of the course of immunization. Low-grade fever can be expected in approximately 2% of vaccinees.

Sources

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