4.21 TYPHOID

4.21.1 Bacteriology

Typhoid fever is a clinical syndrome caused by a systemic infection with *Salmonella enterica* subspecies *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, have largely overlapping geographic distributions, and, although there is no vaccine specifically targeted against paratyphoid fever, there is evidence to suggest some cross-protection from the oral live attenuated typhoid vaccine against Paratyphi B.1-4

4.21.2 Clinical features

Typhoid fever has a usual incubation period of 7 to 14 days (range 3 to 60 days).5 Although clinical presentations of typhoid fever can be quite variable, a typical case presents with a low-grade fever, dull frontal headache, malaise, myalgia, anorexia and a dry cough.5 The fever tends to increase as the disease progresses; constipation (more typically diarrhoea in young children), abdominal tenderness, relative bradycardia and splenomegaly are common. Complications occur in 10 to 15% of patients and tend to occur in patients who have been ill for more than 2 weeks. The more important complications include gastrointestinal bleeding, intestinal perforation and typhoid encephalopathy.5 Relapse occurs in up 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. Chronic carriage is defined by the continued shedding of the organism for longer than 1 year. Carriers serve as an important reservoir in endemic areas and are of public health significance (e.g. if a carrier works in the food industry).5

4.21.3 Epidemiology

Humans are the sole reservoir of *S. Typhi*. It is shed in the faeces of those who are acutely ill and those who are chronic asymptomatic carriers of the organism; transmission usually occurs via the ingestion of faecally contaminated food or water.

The vast majority of typhoid fever cases occur in less developed countries, where poor sanitation, poor food hygiene and untreated drinking water all contribute to endemic disease, with moderate to high incidence and considerable mortality.6 Geographic regions with high incidence (>100 cases per 100 000 population per year) include the Indian subcontinent, most Southeast Asian countries and several South Pacific nations, including Papua New Guinea. Estimates of incidence from African countries are more limited. In many regions, particularly the Indian subcontinent, strains partially or completely resistant to many antibiotics (including ciprofloxacin) are detected with increasing frequency.7

In developed countries, typhoid fever is predominantly a travel-related disease, with a considerably greater risk following travel to the Indian subcontinent than to other regions.8-10 Those who travel to endemic regions to visit friends and relatives (e.g. immigrants who travel to their former homelands) appear to be at considerably greater risk of acquiring typhoid fever than other travellers.8-10 There are typically fewer than 150 cases of typhoid fever reported in Australia each year, with most following travel to regions with endemic disease.11

4.21.4 Vaccines

### Monovalent typhoid vaccines

- **Vivotif Oral** – Seqirus Pty Ltd (oral live attenuated typhoid vaccine). Each enteric-coated capsule contains ≥2 x 10⁹ viable organisms of attenuated *S. Typhi* strain Ty21a; gelatin (bovine derived); ethylene glycol; sucrose. 3 capsules in a blister pack.

- **Typherix** – GlaxoSmithKline Australia Pty Ltd (purified Vi capsular polysaccharide vaccine). Each 0.5 mL pre-filled syringe contains 25 µg Vi polysaccharide of *S. Typhi* strain Ty2; phenol; phosphate buffer.

- **Typhim Vi** – Sanofi-Aventis Australia Pty Ltd (purified Vi capsular polysaccharide vaccine). Each 0.5 mL pre-filled syringe contains 25 µg Vi polysaccharide of *S. Typhi* strain Ty2; ≤1.25 mg phenol; phosphate buffer.

### Combination vaccine that contains *S. Typhi*

- **Vivaxim** – Sanofi-Aventis Australia Pty Ltd (formaldehyde-inactivated hepatitis A virus [GBM strain] and typhoid Vi capsular polysaccharide). Supplied in a dual-chamber syringe which enables the two vaccines to be mixed just before administration. Each 1.0 mL dose of mixed vaccine contains 160 antigen units of inactivated hepatitis A virus antigen, 25 µg purified typhoid Vi capsular polysaccharide strain Ty2; 0.3 mg aluminium as aluminium hydroxide; 2.5 µL phenoxylethanol; 12.5 µg formaldehyde; ≤5 µg neomycin; ≤10 ng bovine serum albumin; traces of polysorbate 80.
The attenuated non-pathogenic S. Typhi strain Ty21a was derived by chemical attenuation of a wild-type strain. Attenuated features of Ty21a include the absence of the enzyme UDP-galactose-4-epimerase and the Vi capsular polysaccharide antigen (an important virulence determinant of S. Typhi). These features partially contribute to the non-pathogenicity and, therefore, the safety of the oral live vaccine.\textsuperscript{12} The oral vaccine Ty21a strain cannot be detected in faeces more than 3 days after administration of the vaccine. It stimulates serum IgG, vigorous secretory intestinal IgA and cell-mediated immune responses.\textsuperscript{12} Clinical trials, with different formulations of the vaccine and with a variety of schedules, have been undertaken in several countries with endemic typhoid fever (Egypt, Chile, Indonesia). These have documented varying degrees of protection against the disease.\textsuperscript{5,12} Parenteral Vi polysaccharide vaccines are produced by fermentation of the Ty2 strain, followed by inactivation with formaldehyde, and then extraction of the polysaccharide from the supernatant using a detergent.\textsuperscript{12} The vaccines elicit prompt serum IgG anti-Vi responses in 85 to 95% of adults and children >2 years of age. The vaccines have also been used in clinical trials in endemic regions (Nepal, South Africa, China), indicating moderate protection against typhoid fever.\textsuperscript{5,12} As with oral typhoid vaccine, herd protection of unvaccinated persons living in areas with moderate coverage of parenteral vaccine has been demonstrated.\textsuperscript{13,14} Neither the oral nor the parenteral vaccines have been studied in prospective clinical trials in travellers to endemic regions. Because many travellers do not have any naturally acquired immunity, the protection conferred through typhoid vaccination may be less than that documented in the clinical trials mentioned above. However, there is circumstantial evidence that the vaccines do provide protection to travellers to endemic regions,\textsuperscript{8,9} and that 3-yearly revaccination is necessary to prolong the protection.\textsuperscript{15}

4.21.5 Transport, storage and handling

Transport according to National vaccine storage guidelines: Strive for 5.\textsuperscript{16} Store at +2°C to +8°C. Do not freeze. Protect from light.

Because the person to be vaccinated will be responsible for looking after the course of the oral live attenuated vaccine following purchase, details of how it should be transported (from the pharmacy to home) and stored in the refrigerator (at home) must be carefully explained.

4.21.6 Dosage and administration

Oral live attenuated vaccine

The vaccine is registered for use in persons ≥6 years of age; it is presented in a pack of 3 capsules. Each dose (a whole capsule) is the same for both adults and children.

The vaccination schedule consists of 1 capsule of vaccine on days 1, 3 and 5, taken 1 hour before food. 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. If possible, antibiotics and other relevant drugs should be delayed for 3 days after the last dose of the vaccine (refer to 4.21.10 Precautions below).

A 4th capsule taken on day 7 has been shown in one large clinical trial to result in a lower incidence of typhoid fever compared with 3 doses.\textsuperscript{12,17} However, giving a 4th dose requires partial use of a second pack.

Co-administration with other vaccines

Oral typhoid vaccine can be administered at the same time as any of the live parenteral vaccines (including yellow fever vaccine or BCG).\textsuperscript{12} The oral live attenuated typhoid vaccine should be separated from the administration of inactivated oral cholera vaccine by an interval of at least 8 hours, and separated from the administration of antibiotics by an interval of at least 3 days (refer to 4.21.10 Precautions below).

The oral live attenuated typhoid vaccine may be given concurrently with mefloquine or with atovaquone/proguanil combination (Malarone) (refer to 4.21.10 Precautions below).

Parenteral Vi polysaccharide vaccines

Both monovalent typhoid vaccines (Typherix and Typhim Vi) are registered for use in persons ≥2 years of age. The dose of both vaccines is 0.5 mL (for both adults and children), to be given by IM injection.

The dose of the combination typhoid Vi polysaccharide/hepatitis A vaccine (Vivaxim) is 1 mL to be given by IM injection. Vivaxim is registered for use in persons aged ≥16 years. (Refer also to 4.4 Hepatitis A.)

Co-administration with other vaccines
Parenteral Vi polysaccharide typhoid vaccines can be given with, or at any time before or after, other travel vaccines, such as oral cholera or yellow fever vaccines.

### 4.21.7 Recommendations

It is recommended that travellers be advised about personal hygiene, food safety and drinking boiled or bottled water only. They should be advised that raw (or undercooked) shellfish, salads, cold meats, untreated water and ice (in drinks) are all potentially ‘high-risk’, as are short (day) trips away from higher quality accommodation venues.

#### Oral live attenuated vaccine

**Children aged <6 years**

Oral typhoid vaccine is not recommended for use in children aged <6 years.

**Children aged ≥6 years and adults**

Oral typhoid vaccine in either a 3- or 4-dose schedule is recommended for children aged ≥6 years and adults who are:

- travelling to endemic regions, where food hygiene may be suboptimal and drinking water may not be adequately treated
- travelling to endemic regions to visit friends and relatives
- military personnel
- laboratory personnel routinely working with *S. Typhi*.

The addition of a 4th oral dose, on day 7, is an option as there is evidence that 4 doses provides greater protection.\(^{12,17}\)

**Revaccination of children aged ≥6 years and adults**

The optimal timing of revaccination against typhoid fever is uncertain and, therefore, international recommendations vary considerably.\(^{5,7,9,12}\)

Where continued exposure to *S. Typhi* exists (such as occurs with either prolonged travel or residence in an endemic region) and the oral live attenuated vaccine was used initially, a repeat 3-dose or 4-dose course can be given 3 years after a 3-dose course, or 5 years after a 4-dose course.

**Parenteral Vi polysaccharide vaccines**

For further recommendations on the use of the combination typhoid Vi polysaccharide/hepatitis A vaccine refer to 4.4 Hepatitis A.

**Children aged <2 years**

The parenteral typhoid vaccine is not recommended for use in children aged <2 years.

**Children aged ≥2 years and adults**

A single dose of parenteral typhoid vaccine is recommended for children aged ≥2 years and adults who are:

- travelling to endemic regions, where food hygiene may be suboptimal and drinking water may not be adequately treated
- travelling to endemic regions to visit friends and relatives
- military personnel
- laboratory personnel routinely working with *S. Typhi*.

**Revaccination of children aged ≥2 years and adults**

The optimal timing of revaccination against typhoid fever is uncertain and, therefore, international recommendations vary considerably.\(^{5,7,9,12}\)

Where continued exposure to *S. Typhi* exists (such as occurs with either prolonged travel or residence in an endemic region) and the parenteral vaccine was used initially, revaccinate with the parenteral vaccine every 3 years. Refer also to 4.4 Hepatitis A for more information.

### 4.21.8 Pregnancy and breastfeeding

The oral live attenuated typhoid vaccine is contraindicated in pregnant women (refer to 4.21.9 Contraindications below).

The oral live attenuated typhoid vaccine can be given to breastfeeding women.
Parenteral Vi polysaccharide vaccines are not routinely recommended for pregnant or breastfeeding women, but can be given where vaccination is considered necessary (refer to 4.21.7 Recommendations above).

Refer to 3.3 Groups with special vaccination requirements, Table 3.3.1 Recommendations for vaccination in pregnancy for more information.

### 4.21.9 Contraindications

The only absolute contraindications to typhoid vaccines are:

- anaphylaxis following a previous dose of any typhoid vaccine
- anaphylaxis following any vaccine component.

#### Oral live attenuated vaccine

The oral live attenuated vaccine should not be administered to:

- children <6 years of age; parenteral Vi polysaccharide vaccine should be used instead in children 2–5 years of age
- pregnant women; parenteral Vi polysaccharide vaccine should be used instead
- persons who are immunocompromised, including those with known HIV infection; parenteral Vi polysaccharide vaccine should be used instead
- persons taking antibiotics; parenteral Vi polysaccharide vaccine should be used instead.

#### Parenteral Vi polysaccharide vaccines

The parenteral Vi polysaccharide vaccines should not be administered to children <2 years of age.

### 4.21.10 Precautions

The oral live attenuated vaccine strain may be destroyed by gastric acid, so capsules must be swallowed whole, rather than chewed or opened.

There should be an interval of at least 8 hours between the administration of the oral live attenuated typhoid vaccine and the inactivated oral cholera vaccine, as the buffer in the cholera vaccine may affect the transit of the capsules of oral typhoid vaccine through the gastrointestinal tract.

The oral live attenuated typhoid vaccine may be susceptible to inactivation by some antibiotics and antimalarial agents, although concurrent administration of either mefloquine or atovaquone/proguanil combination (Malarone) has not been shown to interfere with immune responses or efficacy. If the oral vaccine is used, it is recommended that vaccination should be timed so that the last dose of vaccine is administered at least 3 days before starting antibiotics or antimalarial prophylaxis.

### 4.21.11 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. Abdominal discomfort, diarrhoea, nausea, vomiting and rashes have occasionally been reported.

#### Oral live attenuated vaccine

Abdominal discomfort, diarrhoea, nausea, vomiting and rashes have occasionally been reported.

#### Parenteral Vi polysaccharide vaccines

Local adverse events such as erythema, swelling and pain at the injection site are occur very commonly in 10 to 20% of vaccine recipients. Systemic adverse events are common and include fever (3% of recipients), malaise and nausea.

### 4.21.12 Public health management of typhoid fever

Typhoid fever is a notifiable disease in all states and territories in Australia.

Further instructions about the public health management of typhoid fever, including management of cases of typhoid fever and their contacts, should be obtained from state/territory public health authorities (refer to Appendix 1 Contact details for Australian, state and territory government health authorities and communicable disease control).

### 4.21.13 Variations from product information

The Australian product information for Vivotif Oral live attenuated vaccine does not mention the use of a 4-dose course of the vaccine for either initial or repeat vaccination, although this vaccine is registered for use in some other countries (e.g. Canada and the United States) in a 4-dose schedule. The ATAGI recommends that a 4-dose course can be given to provide increased protection against typhoid fever.
The product information for Vivotif Oral live attenuated vaccine does not include pregnancy among the listed contraindications. The ATAGI recommends that pregnancy is a contraindication to the oral live attenuated typhoid vaccine.

The product information for Typhim Vi recommends a booster dose every 2 to 3 years, and the product information for Vivotif Oral live attenuated vaccine recommends a booster every 3 years. The ATAGI also recommends, for those at continuing risk, revaccination with a dose of parenteral Vi polysaccharide vaccine every 3 years after a previous dose, or revaccination with a 3- or 4-dose course of the oral live attenuated vaccine 3 years after a 3-dose course or 5 years after a 4-dose course.

References
A full reference list is available on the electronic Handbook or website www.immunise.health.gov.au.