33

Typhoid

NOTIFIABLE

The disease

Typhoid fever is a systemic infection caused by the gram-negative bacterium *Salmonella enterica*, subspecies *enterica*, serotype *typhi*. Paratyphoid fever is a clinically similar illness caused by *S. paratyphi* A, B and C.

Following ingestion of contaminated food or water, *S. typhi* penetrates the intestinal mucosa, replicates and enters the bloodstream. The severity of symptoms varies. Clinical features range from mild fever, diarrhoea, myalgia and headache to severe disseminated disease with multi-organ involvement in 10 to 15% of cases. The case–fatality rate (CFR) is less than 1% with prompt antibiotic therapy, but may be as high as 20% in untreated cases or in cases treated with inappropriate antibiotics (WHO, 2018). Children are disproportionately affected by typhoid fever, with peak incidence occurring in individuals aged 5 to less than 15 years of age (WHO, 2018).

Unlike other *Salmonella* species, both *S. typhi* and *S. paratyphi* only colonise humans. Most of the more than 2000 other serotypes of *Salmonella* cause only local infection of the gastro-intestinal tract (gastroenteritis or 'food poisoning') and are commonly found in many mammalian hosts.

Transmission is primarily via the oral route following ingestion of food or water contaminated by faeces and occasionally the urine of persons acutely ill with typhoid or those who are chronic carriers. Direct faecal–oral transmission can also occur. In healthy individuals, one million or more organisms may be required to cause illness; however, ingestion of fewer organisms may still result in illness, especially in susceptible individuals. The incubation period averages from 10 to 20 (range 3-56) days, depending on host factors and the size of the infecting dose (Feasey and Gordon, 2014). In paratyphoid fever it ranges from 1 to 10 days (Feasey and Gordon, 2014).

The risk of contracting typhoid fever is highest for travellers to areas of high endemicity. In the Indian subcontinent, a region of high incidence of typhoid fever (more than 100 cases per 100,000 people per year (Crump et al., 2004)), the attack rate for travellers has been estimated at 1 to 10 per 100,000 journeys (Mermin *et al*., 1998; Steinberg *et al*., 2004; Connor and Schwartz, 2005).

All patients with typhoid and paratyphoid excrete the organisms at some stage during their illness. About 10% of patients with typhoid excrete *S. typhi* for at least three months following the acute illness, and 2 to 5% become long-term carriers (more than one year). The likelihood of becoming a chronic carrier increases with age, especially in females and those with a biliary tract abnormality.

Typhoid can be successfully treated with antibiotic therapy and general medical support. However, strains of *S. typhi* have become increasingly resistant to antibiotics (WHO, 2018).

A recent outbreak of extensively drug resistant (XDR) typhoid in Pakistan with resistance to third-generation cephalosporins demonstrates the importance of preventive measures including vaccination for those at risk of typhoid. Laboratory screening is important to ensure the appropriate antibiotic treatment is selected. Antimicrobial resistance leads to an increased proportion of patients experiencing clinical treatment failure and complications, it may also lead to an increase in chronic carriers (WHO, 2018).

Following natural infection with typhoid, an immune response develops that may partially protect against reinfection and severity of disease (WHO, 2018).

History and epidemiology of the disease

Typhoid is predominantly a disease of countries with inadequate sanitation and poor standards of personal and food hygiene. There are gaps in surveillance and published data but recent reviews found generally high incidence rates in South Asia, sub-Saharan Africa, and East Asia and Pacific where the disease is endemic in many countries. Lower incidence rates are reported in the Middle East, North Africa, Central and South America (Als *et al*, 2018, Mogasale, 2014). Estimates of the global annual incidence of typhoid fever range between 11 and 21 million cases with approximately 128,000 to 161,000 deaths per year (WHO, 2018).

Typhoid is rare in resource-rich countries where standards of sanitation are high. Cases of typhoid and paratyphoid disease reported in England, Wales and Northern Ireland are usually imported due to foreign travel or contact with somebody who has travelled. The most frequently reported region of foreign travel for typhoid and paratyphoid was the Indian subcontinent (PHE, 2018). In 2016 and 2017, 93% of confirmed symptomatic cases with travel history recorded were presumed to be acquired abroad (Public Health England, 2018). Between 2008 and 2017, there were an average of 387 laboratory reports of typhoid and paratyphoid each year. Approximately 40-50% of the cases were paratyphoid, of these, most were Paratyphi A (Public Health England, 2018). Occasional small outbreaks of indigenous typhoid occur in the UK. For the latest epidemiological data on typhoid and paratyphoid please see: https://www.gov.uk/government/publications/typhoid-and-paratyphoid-laboratory-confirmed-cases-in-england-wales-and-northern-ireland

Prevention of typhoid and paratyphoid depends primarily on improving sanitation and water supplies in endemic areas and on scrupulous personal, food and water hygiene. Immunisation may be recommended for individuals at risk from typhoid fever. Up to date, country specific recommendations for travellers are available from https://travelhealthpro.org.uk/ and www.travax.nhs.uk.There is no vaccine for paratyphoid infection; there is some evidence for cross protection against *S. Paratyphi B* with the oral typhoid vaccine Ty21a. However, most paratyphoid cases reported in UK travellers are caused by *S. Paratyphi A* and there is currently no evidence for protection against this serovar.

The typhoid vaccination

Worldwide, three types of typhoid vaccine are currently available: a polysaccharide vaccine; an oral, live, attenuated vaccine; and more recently, an inactivated conjugate vaccine which is not licensed in the UK.

Vi polysaccharide vaccine

One of the typhoid vaccines available in the UK is composed of purified Vi capsular polysaccharide from *S. typhi*. Each 0.5ml dose contains 25µg of antigen. A four-fold rise in antibody against Vi antigen has been detected seven days following primary immunisation with Vi vaccine. Maximum antibody response is achieved one month following vaccination and persists for about three years (Keitel *et al*., 1994; Tacket *et al*., 1998).

The efficacy of the Vi vaccine was evaluated in field trials in Nepal (Acharya *et al*., 1987) and in Eastern Transvaal, South Africa (Klugman *et al*., 1987; Klugman *et al*., 1996). In the Nepalese study, vaccine efficacy at 20 months against culture-positive typhoid was 75% (95% CI = 49 to 87%) in adults and children aged five to 44 years. The South African study found the cumulative three-year efficacy of vaccine against culture-positive typhoid to be 55% (95% CI = 30 to 71%) in children aged six to 15 years.

Protective antibody titres to Vi antigen fall over time. Re-vaccination is necessary when continuing protection is required. Additional doses of Vi vaccine do not boost serum antibody levels; re-vaccination returns antibody levels to those achieved after the primary immunisation (Keitel *et al*., 1994).

Non-conjugated polysaccharide vaccines are poorly immunogenic in infants and young children. There is little definitive data on the efficacy of Vi vaccine in children aged less than 18 months (Cadoz, 1998).

Furthermore, in 2008, the lower age limit for Typhim Vi was increased from 18 months to two years.

Protection by vaccination may be less if a large number of infective organisms are ingested. Because of the limited protection offered by the vaccine, the importance of scrupulous attention to personal, food and water hygiene must still be emphasised for those travelling to endemic areas.

Oral typhoid vaccine (Ty21a)

Oral typhoid vaccine contains a live, attenuated strain of *S. typhi* (Ty21a) in an enteric-coated capsule. Large scale field trials in Chile and Indonesia have estimated a vaccine effectiveness of 33-67% for the three dose course after 3 years (Levine *et al*.,1987; Levine *et al*.,1990; Simanjuntak *et al*.,1991). A systematic review and meta-analysis by the Cochrane institute estimated the cumulative efficacy of the Ty21a vaccine over 2.5 to 3 years was 48% (95% CI 34% to 58%) (Anwar *et al*.,2014). The vaccine is indicated for persons from five years of age.

Whole-cell typhoid vaccine

The injectable, killed, whole-cell typhoid vaccine contains heat-inactivated, phenol-preserved *S. typhi* organisms. A two-dose regimen gives a cumulative three-year efficacy of about 70%, and provides protection for up to five years (Engels *et al*., 1998). This vaccine is highly reactogenic and is no longer used in the UK.

Storage

Both Vi polysaccharide and oral typhoid (Ty21a) vaccines should be stored in the original packaging at +2˚C to +8˚C and protected from light. All vaccines are sensitive to some extent to heat and cold. Heat speeds up the decline in potency of most vaccines, thus reducing their shelf life. Effectiveness cannot be guaranteed for vaccines unless they have been stored at the correct temperature. If Vi vaccines have been frozen they should not be used as this can reduce their potency and increase local reactions. If a blister containing Ty21a vaccine capsules is not intact, it should not be used.

Presentation

Vi vaccines are supplied in pre-filled syringes, each containing a single dose of 0.5ml. Vaccines are available as a single antigen product or combined with hepatitis A vaccine.

Ty21a vaccines are supplied in blister packs containing three capsules.

Dosage and schedule

Vi vaccine

A single dose of 0.5ml of Vi vaccine is recommended for adults and children over the age of two years.

Ty21a vaccine

The Ty21a capsule is taken on alternate days (the first capsule on day 0, the second capsule on day 2 and the third on day 4). The vaccine is recommended for children over the age of five years and adults. Reinforcing doses of three capsules should be given as recommended.

Dosage of injectable monovalent typhoid vaccines

Vaccine product	Ages	Dose	Volume
Typhim Vi	Two years and older*	25µg	0.5ml
Typherix (discontinued in 2018)	Two years and older*	25µg	0.5ml

Dosage of oral monovalent typhoid vaccine

Vaccine product	Ages	Dose
Vivotif	Five years and older	Three capsules on days 0, 2 and 4

Dosage of combined typhoid and hepatitis A vaccines**

Vaccine product	Ages	Dose typhoid	Dose HAV†	Volume
Hepatyrix (discontinued In 2018)	15 years and older	25µg	1440 ELISA units	1ml
ViATIM	16 years and older	25µg	160 antigen units	1ml

* Children between the ages of 12 months and two years should be immunised off-license if following a detailed risk assessment the risk of typhoid fever is considered high.

** For booster doses of either typhoid or HAV, single antigen vaccines can be used

† HAV – hepatitis A vaccine

Administration

Vi vaccines are routinely given intramuscularly into the upper arm or anterolateral thigh. Intradermal injection may cause a severe local reaction and should be avoided. Vaccines should be given by deep subcutaneous injection to individuals with a bleeding disorder. Vaccines must not be given intravenously. Injectable vaccines should be given at separate sites, preferably in different limbs. If given in the same limb, they should be given at least 2.5cm apart (American Academy of Pediatrics, 2003). The site at which each vaccine was given should be noted in the individual's records.

Ty21a vaccine capsules are taken orally. An optimal immune response may not be achieved unless the immunisation schedule of three vaccine capsules is completed. Capsules should be taken about one hour before a meal with a cold or lukewarm drink (temperature not to exceed 37˚C). The vaccine capsule should not be chewed, and should be swallowed as soon as possible after placing in the mouth. This may be difficult for some young children.

Disposal

Equipment used for vaccination, including used vials, ampoules, or partially discharged vaccines should be disposed of at the end of a session by sealing in a proper, puncture resistant 'sharps' box according to local authority regulations and guidance in Health Technical Memorandum 07-01: Safe management of healthcare waste (Department of Health, 2013).

Recommendations for use of the vaccine

Typhoid vaccine is indicated for active immunisation against typhoid fever and is recommended for:

- travellers visiting typhoid-endemic areas whose planned activities put them at higher risk (please check the country information pages (https://travelhealthpro.org.uk/ and www.travax.nhs.uk). Those at increased risk include travellers visiting friends and relatives, frequent or long-stay travellers to areas where sanitation and food hygiene are likely to be poor
- laboratory personnel who may handle *S. typhi* in the course of their work

Primary immunisation

The immunisation schedule of Vi vaccine consists of a single dose; for Ty21a vaccine, a three-dose course.

Vi vaccine

Children aged from two years and adults

A single dose of Vi vaccine is recommended for children and adults.

Ty21a vaccine

Children aged from five years and adults

One capsule on alternate days (first capsule on day 0, the second on day 2 and the third on day 4). An optimal immune response may not be achieved unless the immunisation schedule of three vaccine capsules is completed. Protection commences about seven to ten days after completion of the third dose.

Not all recipients of typhoid vaccines will be protected against typhoid fever, and travellers should be advised to take all necessary precautions to avoid contact with or ingestion of potentially contaminated food or water.

The CDC and WHO advise that most widely used oral live vaccines can be given simultaneously and at any time before or after oral and parenteral live vaccines. Guidance from Public Health England states that the oral typhoid vaccine can be given at any time before or after other live vaccines (PHE, 2015).

Reinforcing immunisation

Vi vaccine

A single dose of Vi vaccine should be administered at three-year intervals in adults and children over two years of age who remain at risk from typhoid fever.

Individuals who have received other non-Vi typhoid vaccines may receive reinforcing doses of Vi vaccine at three-year intervals.

Ty21a

In the case of travel from a non-endemic area to an area where typhoid is endemic, a booster consisting of three doses is recommended every three years (Fraser *et al.*, 2007).

Children under two years of age

Young children may show a sub-optimal response to polysaccharide antigen vaccines. Children between the ages of 12 months and two years should be immunised 'off license' with the polysaccharide vaccine if following a detailed risk assessment the risk of typhoid fever is considered high. Immunisation is not recommended for children under one year of age. When children are too young to benefit fully from typhoid vaccination, scrupulous attention to personal, food and water hygiene measures should be exercised by the caregiver.

Contraindications

There are very few individuals who cannot receive typhoid vaccine. When there is doubt, appropriate advice should be sought from a travel health specialist. Severe reactions to a previous dose of non-Vi typhoid vaccine do not contraindicate the subsequent use of a Vi-containing vaccine. Most severe reactions to typhoid vaccines will have been associated with the inactivated whole-cell vaccine which is no longer available in the UK. Typhoid Vi vaccine should not be given to those who have had:

- a confirmed anaphylaxis to a Vi antigen-containing vaccine

Ty21a vaccine should not be given to those :

- who are immunosuppressed (see Chapter 6 for more detail)
- who have had confirmed anaphylaxis to any component of the Ty21a vaccine or enteric-coated capsule, including gelatin

Precautions

Minor illnesses without fever or systemic upset are not valid reasons to postpone immunisation. If an individual is acutely unwell, immunisation should be postponed until they have fully recovered. This is to avoid confusing the differential diagnosis of any acute illness by wrongly attributing any sign or symptoms to the adverse effects of the vaccine.

In the event of a gastrointestinal illness, vaccination with the Ty21a vaccine should be postponed until after recovery. Ty21a vaccine should not be commenced within three days of completing any antibacterial agents, and similarly, antibacterial therapy should not commence within three days after the last dose of vaccine.

If malaria prophylaxis is also required, the fixed combination of atovaquone and proguanil can be given concomitantly with Ty21a. Doses of mefloquine and Ty21a should be separated by at least 12 hours. For other anti-malari als, there should be an interval of at least three days between the last dose of Ty21a and the first dose of malaria prophylaxis.

Pregnancy and breast-feeding

No data are available on the safety of Vi polysaccharide and Ty21a typhoid vaccines in pregnancy or during lactation. There is no evidence of risk from vaccinating pregnant women or those who are breast-feeding with inactivated viral or bacterial vaccines or toxoids (Plotkin, Orenstein and Offit, 2013).

It is not known if Ty21a vaccine (which is live) can cause fetal harm when administered to pregnant women or affect reproductive ability. If the risk of typhoid is high, vaccination should be considered if there is no alternative vaccine.

Immunosuppression and HIV infection

Vi vaccine does not contain live organisms and may be given to HIV-positive individuals and those considered immunosuppressed, in the absence of contraindications.

Immunosuppressed individuals may have a sub-optimal immune response to Vi vaccine. The importance of scrupulous attention to personal, food and water hygiene must be emphasised for immunosuppressed persons travelling to endemic areas.

Ty21a vaccine should be avoided in immunosuppressed and HIV-infected individuals.

Further guidance is provided by the Royal College of Paediatrics and Child Health (www.rcpch.ac.uk), the British HIV Association (BHIVA) immunisation guidelines for HIV-infected adults (BHIVA, 2015; https://www.bhiva.org/vaccination-guidelines) and the Children's HIV Association of UK and Ireland (CHIVA) travel guidelines (https://www.chiva.org.uk/guidelines/travel-children-and-adolescents/).

Adverse reactions

Based on pooled estimates from clinical trials and post-marketing surveillance data, local reactions (pain, swelling, erythema and induration at injection site) are the most commonly reported symptoms following Vi vaccine (Engels *et al*., 1998; Tacket *et al*., 1986; Begier *et al*., 2004). These symptoms are usually mild and transient. Systemic reactions following the vaccine are infrequent. Fever occurs in about 1% of vaccine recipients. Headache, nausea, diarrhoea and abdominal pain have been reported but are uncommon.

There have been rare reports of anaphylaxis following administration of Vi vaccine (Begier *et al*., 2004).

Following Ty21a vaccine, the most commonly reported adverse events are gastro-intestinal symptoms, fever, influenza-like symptoms and headache. All severe reactions should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card scheme at http://yellowcard.mhra.gov.uk/

Management of cases, carriers, contacts and outbreaks

The local health protection team (HPT) or UK country equivalent should be informed immediately whenever a patient is suspected of having typhoid fever. Reporting should not wait until there is laboratory confirmation. Early identification of the source of infection is vital in containing this disease. Reports should contain a travel history, including country of travel.

Cases, carriers and their close contacts in the following groups may pose an increased risk of spreading infection and may be considered for exclusion from work or school (Working Party of the PHLS *Salmonella* Committee, 1995):

- food handlers
- staff of healthcare facilities
- children aged less than five years of age who attend nurseries or other similar groups
- older children or adults who cannot maintain good standards of personal hygiene

Advice on exclusion from work or school must be sought from the local HPT. Both cases and carriers of *S. typhi* should be advised to be scrupulous in their hygiene practices. Carriers should be referred for specialist clinical management.

Typhoid vaccine is not recommended for close contacts of either cases or carriers, or during an outbreak of typhoid fever in the UK.

Supplies

Vi-containing vaccines

- Typhim Vi (typhoid vaccine)
- ViATIM (combined hepatitis A/typhoid vaccine)

These vaccines are available from Sanofi Pasteur (Tel: 01483 505 515) (Fax: 01483 535432)

- Typherix (typhoid vaccine)
- Hepatyrix (combined hepatitis A/typhoid vaccine)

These vaccines are no longer available, supplied previously by GlaxoSmithKline UK (Tel: 0800 221 441) (Fax: 0208 990 4321)

Medical information e-mail: customercontactuk@gsk.com and MASTA (Tel: 0113 238 7500) (Fax: 0113 238 7501).

Ty21a vaccine

- Vivotif (oral typhoid vaccine)

This vaccine is available form Emergent BioSolutions

Vaccine orders via Clarity Pharma: 0845 080 5190

enquiries@clarity-pharma.com

Medical information: safety@ebsi.com

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