

An update on typhoid vaccination

JONATHAN COHEN MB BS, FACTM, FRACGP, MastFamMed

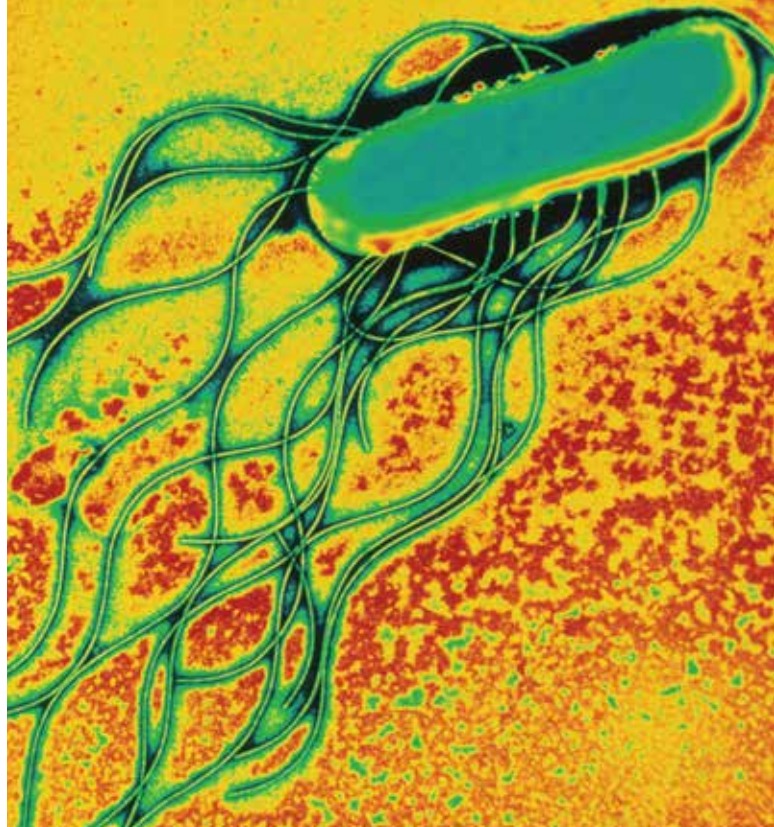
Typhoid fever is a potentially severe illness that occurs primarily in less developed countries. Travellers to endemic areas can reduce their risk through standard precautions and vaccination with live oral or parenteral vaccine.

Typhoid and paratyphoid fever, collectively known as enteric fever, are potentially severe systemic infections caused by the bacteria *Salmonella enterica* serotype Typhi and serotype Paratyphi A, B or C, respectively. The worldwide burden of typhoid fever is reported as between 12 and 22 million cases per year, with a case fatality rate of 20 to 30% if untreated and 1% if treated.^{1,2} Paratyphoid fever is clinically indistinguishable from typhoid fever. The estimated number of cases of paratyphoid fever worldwide and in travellers is approximately 30% of the number of typhoid cases.³

Typhoid fever is associated with poor sanitation, poor food hygiene and inadequate treatment of drinking water. It occurs primarily in less developed countries, with the vast majority of cases in the Indian subcontinent and South-East Asia (Figure). Other areas of risk include Africa, the Caribbean, Central and South America, Papua New Guinea and many Pacific islands. As these are all popular destinations for travellers from developed countries, typhoid fever is one of the more well-known vaccine-preventable diseases.

Paratyphoid fever has a similar geographical distribution to typhoid fever.⁴ There is no vaccine specific for paratyphoid fever but there is evidence suggesting that the live attenuated typhoid vaccine provides some protection against *Salmonella* Paratyphi B.

In Australia, typhoid is generally associated with travel to regions where the disease is endemic.⁴ The number of cases notified in Australia has doubled over the past 10 years, averaging 125 cases annually over the past five years.⁵ This is despite the widespread



availability of typhoid vaccination and may reflect increasing travel to endemic areas. Although the risk of disease increases with duration of travel, infection may occur even with visits of less than a week to an endemic area. The risk appears higher for those who travel to endemic regions to visit friends or family.⁴

Clinical features

Typhoid fever is a prolonged nonspecific febrile illness. The incubation period is generally between one and three weeks, although this can vary on either side. The disease has both systemic and enteric effects. Symptoms are often nonspecific and do not necessarily include diarrhoea. Symptoms and signs are summarised in Box 1.

Severe complications of typhoid fever include gastrointestinal bleeding, intestinal perforation and encephalopathy.⁴

Chronic asymptomatic biliary carriage occurs in up to 5% of patients, even after treatment, and is defined by continued shedding of the bacteria for longer than one year.⁴ As humans are the only reservoir for the organism, carriage has important implications for public health, and carriers should be excluded from handling food for others. An excellent review of the history of typhoid and 'typhoid Mary' was recently published.⁶

Diagnosis

The diagnosis of typhoid or paratyphoid fever should be considered in travellers with a relevant history and relies on laboratory confirmation through isolation or detection of *Salmonella* Typhi or Paratyphi. Blood culture is the mainstay of diagnosis but a single culture is positive in only about 50% of cases, and multiple cultures may be needed. Stool culture is often negative in the early stages.

Confirmed cases of typhoid fever are notifiable in Australia. Confirmed cases are defined as those with laboratory definitive evidence (isolation or detection of *Salmonella* Typhi).

MedicineToday 2015; 16(12): 53-55

Dr Cohen is Medical Director, Travel Clinics Australia, Melbourne, Vic.

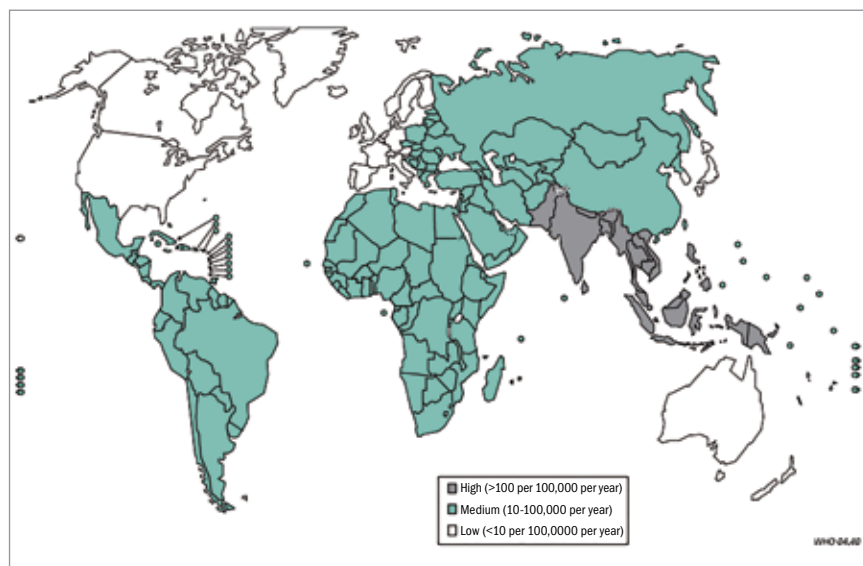


Figure. Geographical distribution of typhoid fever.

Reproduced with permission of the WHO from Bull World Health Organ 2004; 82: 346-353. The global burden of typhoid fever. Crump JA, Luby SP, Mintz ED. Available online at: <http://www.who.int/rpc/TFDisBurden.pdf> (accessed December 2015).

Treatment

Treatment with antibiotics is usually effective in shortening the duration of illness and decreasing the risk of death. However, antibiotic resistance is increasingly reported and can limit treatment options. In particular, reduced susceptibility to fluoroquinolones such as ciprofloxacin is common in infections acquired in the Indian subcontinent or South-East Asia.

The *Australian Antibiotic Guidelines* recommends treating patients with typhoid fever with:⁷

- azithromycin 1 g (child: 20 mg/kg up to 1 g) orally, daily for five days; or azithromycin 500 mg intravenously, daily until oral azithromycin can be tolerated
- (if susceptibility is confirmed) ciprofloxacin 500 mg (child: 12.5 mg/kg up to 500 mg) orally, 12-hourly for seven days; or ciprofloxacin 400 mg (child: 10 mg/kg up to 400 mg) intravenously, 12-hourly until oral ciprofloxacin can be tolerated
- (as an alternative, including for infections acquired on the Indian subcontinent or in South-East Asia) ceftriaxone 2 g (child 1 month

or older: 50 mg/kg up to 2 g) intravenously, daily.

For patients who acquired the infection in the Indian subcontinent or South-East Asia, azithromycin or ceftriaxone should be used until ciprofloxacin susceptibility is confirmed.

Prevention

Prevention of typhoid and paratyphoid fever rests with following standard precautions on food hygiene, water treatment and hand washing.⁶ In addition, the WHO recommends offering typhoid vaccination to travellers to areas of high risk, especially if staying for longer than one month and/or where antibiotic-resistant strains of *Salmonella* Typhi are prevalent.⁸

In contrast, both the US Centers for Disease Control and Prevention and the *Australian Immunisation Handbook* recommend typhoid vaccination for travellers to areas where there is increased risk of exposure, with no requirement for a minimum duration of stay.^{2,4} This would include most developing countries and parts of many westernised countries. Current Australian recommendations on typhoid vaccination are shown in Box 2.⁴

1. SYMPTOMS AND SIGNS OF TYPHOID AND PARATYPHOID FEVERS

- Low-grade fever that increases over time
- Headache
- Malaise
- Anorexia
- Myalgia
- Cough (rare)
- Transient macular rash on the trunk ('rose spots'; occurs in up to one-third of patients in the second week after symptom onset and hence may be missed)
- Constipation or diarrhoea (constipation is more likely in adults versus diarrhoea in children)
- Abdominal tenderness
- Bradycardia
- Hepatosplenomegaly

In considering the risk–benefit ratio of typhoid vaccination for an individual, factors to take into account include the destination and itinerary. There is a heightened risk of typhoid in regions such as the Indian subcontinent, where antibiotic resistance is also common, and for travellers who visit friends and family.

All guidelines emphasise that vaccination does not offer 100% immunity, so even travellers who have been vaccinated should be advised to follow routine food and water hygiene precautions.

Typhoid vaccination

Both parenteral and oral vaccination options are available for typhoid fever in Australia.

Oral live attenuated typhoid vaccine

An oral typhoid vaccine containing live attenuated *Salmonella* Typhi strain Ty21a is registered for use in Australia in adults and children aged 6 years and older. It has 50 to 80% efficacy against typhoid fever. It has also been shown to have partial efficacy against *Salmonella* Paratyphi B in a number of studies, which may be an additional benefit.⁹⁻¹¹

The oral live attenuated typhoid vaccine

2. AUSTRALIAN RECOMMENDATIONS ON TYPHOID VACCINATION⁴

Typhoid vaccination is recommended for:

- all travellers to endemic areas where food hygiene may be suboptimal and drinking water may not be adequately treated
- travellers to endemic regions to visit friends and relatives
- military personnel
- laboratory personnel routinely working with *Salmonella* Typhi

is available in Australia as a three-dose packet. Doses are given on days 1, 3 and 5, with booster doses recommended after three years. A fourth dose can be given on day 7, and the boosters after five years.¹² This fourth dose is recognised as an option in the *Australian Immunisation Handbook*, and is routinely offered at most travel clinics in Australia and the USA.^{2,4}

Patients prescribed the oral vaccine need to be advised to keep it refrigerated and take it with a cup of cool water one hour before food on each alternate day. It must be swallowed whole and not chewed as the organism is sensitive to gastric acid.

Antibiotics effective against *Salmonella* Typhi and some antimalarials should be avoided for at least three days after the last dose of oral vaccine. However, both mefloquine and atovaquone/proguanil have been shown not to interfere with immune response or efficacy of the oral typhoid vaccine. The oral cholera vaccine should not be given within eight hours after a dose of the oral typhoid vaccine because of the potential effect of the cholera vaccine's buffer on the typhoid vaccine.

The oral typhoid vaccine is contraindicated in pregnant women, people who are immunocompromised and those taking antibiotics.

Adverse events following immunisation with the oral typhoid vaccine include abdominal discomfort, diarrhoea, nausea, vomiting and rarely rashes.

Notably, because studies of the durability of typhoid vaccination have never been performed in travellers, it is prudent to err

on the side of revaccinating earlier for higher risk situations.

Parenteral typhoid vaccines

Two monovalent parenteral typhoid vaccines are available in Australia. Both contain Vi capsular polysaccharide from *Salmonella* Typhi strain Ty2. They are registered for use in individuals from the age of 2 years and are given as a single 0.5 mL intramuscular dose. Both vaccines offer 60 to 80% protection at one year after vaccination, decreasing to 50 to 77% protection at two years. Adverse events following immunisation tend to be mild and transient and include local reactions (10 to 20%), such as pain, swelling and redness, and less often systemic reactions (3%), such as fever, malaise and nausea.⁴ Revaccination is recommended after two to three years.⁴

A multivalent vaccine combines the Vi capsular polysaccharide vaccine with hepatitis A vaccine. It is registered for use in travellers aged 16 years and over. Off-label use in children aged 6 years and over is common in travel clinics in Australia and internationally.

Although the parenteral Vi typhoid vaccines are not recommended for women who are pregnant or breastfeeding, they can be given if considered necessary.⁴

Summary

Typhoid and paratyphoid fever are serious diseases and largely avoidable with preventive strategies. As well as offering advice on precautions to be taken regarding food hygiene and water treatment, clinicians should discuss vaccination and offer it to travellers as appropriate for their individual circumstances.

Clinicians who are unsure about endemic areas or vaccine recommendations should refer patients who are about to travel to a travel clinic or medical practitioner who is well versed in travel health to discuss the relevant risks and benefits of vaccination.

MT

References

1. Mogsale V, Maskery B, Ochiai RL, et al. Burden of typhoid fever in low-income and middle-income

countries: a systematic, literature-based update with risk-factor adjustment. *Lancet Glob Health* 2014; 2: e570-e580.

2. US Centers for Disease Control and Prevention. Typhoid fever. Atlanta, GA: CDC; 2013. Available online at: <http://wwwnc.cdc.gov/travel/diseases/typhoid> (accessed December 2015).

3. Newton AE, Routh JA, Mahon BE. Typhoid and paratyphoid fever. Available online at: <http://wwwnc.cdc.gov/travel/yellowbook/2016/infectious-diseases-related-to-travel/typhoid-paratyphoid-fever> (accessed December 2015).

4. Australian Technical Advisory Group on Immunisation. Typhoid (updated July 2015). In: Australian immunisation handbook. 10th ed. Canberra: Australian Government Department of Health; 2013 (updated January 2014). Available online at: <http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/Handbook10-home~handbook10part4~handbook10-4-21> (accessed December 2015).

5. National Notifiable Diseases Surveillance System. Number of notifications for all diseases by year, Australia, 1991 to 2014 and year-to-date notifications for 2015. Available online at: http://www9.health.gov.au/cda/source/rpt_2.cfm?RequestTimeout=500 (accessed December 2015).

6. Marineli F, Tsoucalas G, Karamanou M, Androutsos G, Mary Mallon (1869-1938) and the history of typhoid fever. *Ann Gastroenterol* 2013; 26: 132-134.

7. Antibiotic Expert Groups. Therapeutic guidelines: antibiotic. Version 15. Melbourne: Therapeutic Guidelines Ltd; 2014.

8. World Health Organization. Typhoid vaccines: WHO position paper. *Wkly Epidemiol Rec* 2008; 83(6): 49-59. Available online at: <http://www.who.int/wer/2008/wer8306.pdf> (accessed December 2015).

9. Levine MM, Ferreccio C, Black RE, Lagos R, San Martin O, Blackwelder WC. Ty21 live oral typhoid vaccine and prevention of paratyphoid fever caused by salmonella enteric serovar paratyphi B. *Clin Infect Dis* 2007; 45 Suppl 1: S24-S28.

10. Meltzer E, Sadik C, Schwartz E. Enteric fever in Israeli travelers: a nationwide study. *J Travel Med* 2005; 12: 275-281.

11. Schwartz E, Shlim DR, Eaton M, Jenks N, Houston R. The effect of oral and parenteral typhoid vaccination on the rate of infection with *Salmonella* typhi and *Salmonella* paratyphi A among foreigners in Nepal. *Arch Intern Med* 1990; 150: 349-351.

12. Ferreccio C, Levine MM, Rodriguez H, Contreras R. Comparative efficacy of two, three or four doses of TY21a live oral typhoid vaccine in enteric-coated capsules: a field trial in an endemic area. *J Infect Dis* 1989; 159: 766-769.

COMPETING INTERESTS: Dr Cohen is Medical Director, Travel Clinics Australia.