



Cora A Mayer
Amy A Neilson

Typhoid and paratyphoid fever

Prevention in travellers

This article forms part of our travel medicine series for 2010, providing a summary of prevention strategies and vaccinations for infections that may be acquired by travellers. The series aims to provide practical strategies to assist general practitioners in giving travel advice, as a synthesis of multiple information sources which must otherwise be consulted.

Background

Typhoid and paratyphoid (enteric) fever, a potentially severe systemic febrile illness endemic in developing countries, is associated with poor sanitation, reduced access to treated drinking water and poor food hygiene. It is one of the leading causes of infectious disease in the developing world.

Objective

This article discusses the clinical features and prevention opportunities for typhoid and paratyphoid fever.

Discussion

Travellers to developing countries are at risk of infection. This risk varies from 1:30 000 for prolonged stays in endemic regions to 1:3000 in high endemicity areas such as the Indian subcontinent, where risk is highest. The mainstay of prevention is hygiene and food and water precautions. Vaccines against typhoid fever are discussed. However, when used alone they provide incomplete protection. Treatment and future developments in typhoid fever diagnostics and vaccines are also briefly discussed to provide a general overview of typhoid fever and its prevention for use in travel related consultations in general practice.

Keywords: typhoid fever; paratyphoid fever; typhoid/paratyphoid vaccines; travel



Typhoid and paratyphoid fever, collectively termed 'enteric fever', are similar severe febrile systemic illnesses caused by infection with the invasive Gram negative bacterium *Salmonella enterica*, subspecies *Enterica* serovar *Typhi* (*S. typhi*) and *Enterica* serovar *Paratyphi* A or B respectively. Unlike other salmonella species these infect only humans.¹⁻⁴ Globally, *S. typhi* is the commonest cause of disease, but *S. paratyphi* A infections are common in some parts of the world,⁵ especially Asia,⁶ and are often associated with travellers.

S. paratyphi B (and C) infections occur less frequently.⁵ Typhoid fever is one of the leading causes of infectious disease in developing countries.⁴

Owing to the historical significance of typhoid fever, excellent literary and cinematic descriptions of this disease exist.⁷ The usual incubation period is 7–14 days with a range of 3–60 days. Typical symptoms include:

- fever, which increases with disease progression
- dull frontal headache
- malaise
- myalgia
- anorexia, and
- dry cough.

Constipation (or less commonly diarrhoea, which occurs more often in young children), abdominal pain and tenderness, relative bradycardia, splenomegaly and rash ('rose spots') may also occur. Complications, which include gastrointestinal bleeding, intestinal (usually ileal)⁸ perforation and typhoid encephalopathy tend to occur after 14 or more days of illness in 10–15% of patients. Milder or nonspecific, as well as atypical presentations can occur, so a high index of suspicion is important in febrile travellers (including children) who have visited endemic areas.^{4,9} The overall fatality rate is 10%; less than 1% with appropriate antibiotic treatment.

Relapse may occur 2–3 weeks after initial defervescence in 5–10% of patients. Up to 5%, regardless of treatment, may become chronic, asymptomatic carriers with continued shedding of the organism in the stool or urine for more than 1 year. This is a public health risk, especially if the carrier works in the food industry,^{1,2} as illustrated by the well known case of 'Typhoid

Mary' Mallon early last century.¹⁰ Chronic carriage is more frequent in older people and those with gallstones.²

S. typhi is an immunomodulatory pathogen which seeks to avoid detection by the host immune defences. Tissue invasion is thought to occur via M cells on Peyer's patches in the terminal ileum, and the infection eventually localises to the bone marrow and finally the gall bladder, which explains biliary shedding of organisms. Infection leads to a reduction in host inflammatory response, which explains the lack of classic gastroenteritis symptoms associated with other gastrointestinal pathogens. The Vi capsular polysaccharide of *S. typhi* (not found in *S. paratyphi* A) further limits immune response,⁵ and can be targeted by vaccines.

Epidemiology

Transmission occurs via ingestion of faecally contaminated food or water, as *S. typhi* is shed in the faeces during acute illness and by asymptomatic chronic carriers.¹ There is an associated apparent risk of sexual transmission through oral or anal intercourse.⁴

Enteric fever is endemic in less developed countries where poor sanitation and food hygiene and reduced access to treated water facilitate spread.^{1,6} Approximately 1.2 billion people do not have access to clean drinking water, while a further 2.6 billion lack adequate sanitation services.¹¹ An estimated 16–22 million cases of typhoid^{2,5,9} and 200 000–600 000 deaths occur annually,^{2–4,9,12} while paratyphoid caused approximately 5.4 million illnesses in 2000.^{3,5} Surveillance information is sparse due to poor reporting and diagnostic inaccuracy.^{3,5}

The highest incidence (more than 100 cases per 100 000 population/year) occurs in the Indian subcontinent, including India, Pakistan, Bangladesh and Sri Lanka.^{2,3} Incidence is also high in southeast Asia (except Japan and Singapore), including Indonesia¹³ and Papua New Guinea, with moderate prevalence in Malaysia, South Korea and Mongolia. Incidence is also high in the African continent (moderate in Mediterranean north Africa including Morocco, Algeria, Tunisia, Libya and Egypt,¹⁴ and excluding South Africa) and the Middle East (except Kuwait and Bahrain). Incidence is moderate in Latin America.^{2,3}

Risk to travellers

Cases of typhoid fever in developed countries (where the incidence of typhoid fever has steeply declined) are usually travel related, as are most of the 50–80 cases of typhoid fever reported annually in Australia,^{1,15} where it is a notifiable disease.¹ Rarely, nontravelling family members of travellers develop the disease.¹⁶ Risk to the traveller is associated with exposure, especially when prolonged, to potentially contaminated food and drink.⁴ Overall risk is about 1:30 000 for those staying for 4 weeks or more in typhoid endemic countries, but rises to 1:3000 in the Indian subcontinent, north and west Africa, and South America.² The risk is highest for extended stays in the Indian subcontinent,^{12,15} and is increased in postdisaster areas where typhoid is already endemic.¹⁷ The incidence of paratyphoid fever, which is not covered by available vaccines, is increasing in parts of Asia.¹⁸ Severe complications and death due to enteric fever are rare in travellers,¹⁹ probably because they tend to present early and have access to high quality medical care.¹⁵ Among travellers, those visiting friends and relatives, particularly in the Indian subcontinent, are at greatest risk;^{9,12,20} as this group is less likely to present for pretravel advice²⁰ or may present late.²¹

Specific destinations found to be associated with typhoid fever in returning travellers include India, Pakistan, Mexico, Bangladesh, the Philippines and Haiti.⁴

Persons with decreased gastric acid barrier due to gastric atrophy, acid suppressive medications or gastrectomy, and immunocompromised individuals (eg. due to human immunodeficiency virus [HIV] infection or chemotherapy) are at greater risk of severe illness.^{1,2} Children are at high risk of typhoid fever, and account for a considerable proportion of cases associated with travel.²²

Prevention in travellers

Hygiene and food and water precautions are most important, especially for prevention of paratyphoid fever, as there is no vaccine available for this. Vaccination further reduces the risk of typhoid fever in visitors to endemic areas but provides incomplete protection.^{2–4,12,15} Data on the effectiveness of typhoid vaccines in travellers is sparse, as this population has

not been studied sufficiently.³ It is especially important to give appropriate preventive information to travellers visiting friends and relatives where possible.^{3,20,21}

Vaccine recommendations

Vaccination is recommended for most people (including military personnel) over 2 years of age travelling to moderate to high risk countries.¹ Especially included are areas where outbreaks of typhoid fever are currently occurring.³ The vast majority of travel related typhoid cases occur in people more than 2 years of age, for whom typhoid vaccine is available.¹² As the vaccines are well tolerated, they should be considered even for short trips to endemic areas of less than 2 weeks duration.^{3,9,12} Household contacts of returned travellers with typhoid fever or a known carrier should be vaccinated. Vaccine efficacy varies from 50–80% for currently available vaccines, but this is likely to be less in travellers.^{2,4,9} Where possible, vaccination should be completed at least 2 weeks before travel.¹

Pregnancy

Typhoid may be a more serious disease during pregnancy with a higher incidence of diarrhoea, complications such as gastrointestinal bleeding, hepatic dysfunction and intestinal perforation as well as maternal death. There is also an increased risk of abortion and fetal death, and potential transplacental infection of the fetus,²³ although a recent study showed that typhoid fever does not appear to affect pregnancy outcome.²⁴ While the risk of disease must outweigh the potential risk of the vaccine, generally the use of Vi vaccine in pregnancy is advised for women travelling to endemic areas.^{1,23}

Vaccines

Vaccines available in Australia for the prevention of typhoid fever are listed in *Table 1*.

Booster doses

Efficacy of oral and parenteral vaccines has not been studied in travellers to endemic regions; protection may be less in this group as travellers usually lack naturally acquired immunity. Booster doses for both monovalent typhoid vaccines are necessary every 3 years.^{1,2} The Centers for Disease Control and Infection recommends

Table 1. Vaccines available to prevent typhoid^{1–4,9,25}

Name and type	Protection	Dosing	Adverse effects	Contraindications	Other
Vivotif® Oral (GSK/Berna), Ty21a – oral live attenuated typhoid vaccine	Stimulates secretory IgA and cell mediated immune responses and provides varying degrees of protection against typhoid fever. There may be modest cross protection against paratyphoid fever	Pack (refrigerated, not frozen) contains three capsules, to be swallowed whole (not chewed) with water on days 1, 3 and 5; 1 hour before food. A fourth dose given on day 7 may increase vaccine efficacy but also expense. If >3 weeks passed since the last dose of an incomplete course, the course should be restarted	- Usually well tolerated - Abdominal pain - Nausea - Vomiting - Diarrhoea - Rashes	- Not recommended in immunosuppressed persons (may be given to HIV positive individuals with CD4+ counts >200/microL) - Safety in pregnancy has not been determined (pregnancy category C) – use parenteral vaccine - Age <6 years - Current acute gastroenteritis or other febrile illness - History of anaphylactic reactions to the vaccine or any of its components	May be given at the same time as oral polio vaccine, yellow fever vaccine and antimalarials May not be given at the same time as antibiotics or other drugs active against salmonella (delay for 3 days after the last vaccine dose) 8 hours should separate this vaccine from administration of inactivated oral cholera vaccine
Typhex® (GlaxoSmithKline) and Typhim Vi® (Sanofi Pasteur) – parenteral purified Vi (for 'virulence') capsular polysaccharide vaccines (ViCPS)	Protection against typhoid fever is moderate. There is no cross protection against paratyphoid fever as <i>S. paratyphi</i> has no Vi antigen. ³ Certain strains of <i>S typhi</i> also lack Vi antigen, but they are less likely to cause severe disease and their prevalence is low to moderate	Intramuscular stat dose of 0.5 mL. IgG anti-Vi response is rapid (by day 7, with maximum neutralising antibodies by day 28 in 85–95% of adults and children >2 years of age	- Pain at the injection site - Myalgias - Fever (3%) - Malaise - Nausea	- Current acute febrile illness - History of anaphylactic reactions to the vaccine or any of its components - Individuals <2 years (while not a contraindication, also note the vaccine may be less effective in children aged 2–5 years) - Pregnancy category is also C, so the risk of disease must outweigh potential vaccine risks (see text discussion)	The Vi vaccine is preferable to oral vaccine if the timeframe before travel is short, in children 2–6 years of age; those on antibiotic therapy or other medications precluding the use of the oral vaccine; immunocompromised or HIV infected travellers; pregnant women; if the traveller's preference is for a single dose vaccine; and where compliance with the dose regimen or refrigeration requirements are a potential issue (30% chance of noncompliance with Ty21a)
Vivaxim® (Sanofi Pasteur) – combination vaccine containing both inactivated hepatitis A virus and typhoid Vi capsular polysaccharide	Vaccine components in the combination vaccine are of similar efficacy as when administered as monovalent vaccines	Intramuscular stat dose. Follow up dose of monovalent hepatitis A vaccine is required 6–12 months later to prolong immunity to hepatitis A	As per individual components	As per individual components	Uptake of both vaccines may be increased with a combination vaccine

2 yearly boosters.⁹ After administration of Vivaxim, hepatitis A vaccine booster doses are not required after a completed primary vaccination course,²⁶ whereas monovalent typhoid boosters are required every 3 years if there is ongoing risk of exposure.¹

Treatment

With the emergence of resistant strains, fluoroquinolones and third generation cephalosporins, particularly ciprofloxacin and ceftriaxone, are used as first line antibiotics. However, significant resistance to these drugs is emerging, especially in Asia,^{6,12,19} although fluoroquinolones remain superior for preventing clinical relapse²⁷ and are still recommended for empirical therapy in adults.¹² Children may be treated with third generation cephalosporins.¹² Azithromycin has been shown to be an effective alternative for treatment of uncomplicated typhoid fever⁶ and may perform better than ceftriaxone in this setting.²⁸

Australian guidelines recommend:²⁹

- azithromycin 1 g (child: 20 mg/kg up to 1 g) orally or intravenous (IV) until oral azithromycin can be tolerated, daily for 10 days

OR (if not acquired in the Indian subcontinent and southeast Asia)²⁹

- ciprofloxacin 500 mg (child: 15 mg/kg up to 500 mg) orally, 12 hourly for 7–10 days, or
- ciprofloxacin 400 mg (child: 10 mg/kg up to 400 mg) IV, 12 hourly until oral ciprofloxacin can be tolerated.

As an alternative regimen for initial IV therapy, or if the clinical response is delayed (eg. fever longer than 7 days) use:

- ceftriaxone 2 g (child: 50 mg/kg up to 2 g) IV, daily.

Defervescence takes 3–5 days despite antibiotic therapy; patients may feel more unwell during this time. Alternative antibiotics or causes of infection should be considered if fever does not subside within 5 days.⁹ Antibiotic treatment is combined with supportive therapy, and complications are treated as required (such as operative closure of ileal perforations).⁸ Treatment is continued until adequate clinical response and then, depending on susceptibilities, azithromycin or ciprofloxacin, orally as above, are used for a further 7 days. Expert advice should be sought for treatment of carriers.²⁹

Diagnostic tests and vaccines in development

The clinical and laboratory diagnosis of typhoid fever remains challenging.^{4,9} The present gold standard is direct blood culture followed by microbial identification, but this is expensive and impractical in many settings; *S. typhi* and *S. paratyphi* may also be difficult to culture. Bone marrow culture is most sensitive, but invasive and impractical.⁵ The organism may be shed in stools or urine for culturing,^{5,12} but only sporadically.⁵

Typhoid serology is not ideal as antibody response may be weak, and in addition, exposure to *S. typhi* in endemic areas may lead to serological evidence of past exposure despite a lack of clinical illness. The first typhoid diagnostic, the Widal test, was developed in 1896; it is a visual test that monitors agglutinating antibodies that react with *S. typhi*. It has a high false positive rate due to cross reactivity of antibodies, and remains a controversial diagnostic tool.^{4,9,30} Polymerase chain reaction (PCR) is also of limited value as none are as yet validated for use and interpretation. Current research is directed at all of the above modalities including culture, DNA methodologies and serological approaches.⁵ Antigen based rapid diagnostic test kits in particular could potentially save lives, time and money.³¹ Rapid detection methods, including multiplex PCR and stool dipstick tests^{30,32} as well as a fast blood culture PCR method,³³ are currently being developed to aid early diagnosis. An onsite food testing kit has also been developed.³⁴ Newer assays are rarely available in developing countries.⁹

New vaccines are needed, especially to target infants aged 5 years or less in endemic regions, who are at greatest risk of disease. Fifty percent or more typhoid cases occur in this age group,⁶ which also has the highest case fatality rate.⁴ Previously, children aged 5–19 years were considered at greatest risk.² Vaccines that are immunogenic in infants less than 2 years of age after a single dose are being developed⁶ to improve on current vaccination programs.³ A Vi conjugate vaccine has been trialled³ and a Vi conjugate/diphtheria toxoid combination vaccine may soon be available,³⁵ while others are being developed.³⁶ A more effective vaccine is also needed for travellers with the rise of multidrug

resistant organism strains, as well as a vaccine for *S. paratyphi*.¹⁵ Single dose oral typhoid vaccines M01ZH09, CVD 908, CVD 908-htrA, CVD 909 and Ty800 have undergone preliminary testing in adults.^{3,37–39}

Water and sanitation

Progress toward the World Health Organization's Millennium Development Goal number seven – to 'halve the proportion of people without secure access to safe drinking water and adequate sanitation by 2015' – appears slow, but would make the most appreciable difference toward the control of the global burden of enteric fever and many other infective illnesses.^{3,11,12,36}

Patient resources

- www.cdc.gov/ncidod/dbmd/diseaseinfo/typhoidfever_g.htm
- <http://jama.ama-assn.org/cgi/content/full/302/8/914>.

Authors

Cora A Mayer MBBS(Hons), FRACGP, MPH&TM, DRANZCOG, CTH, is a general practitioner and postgraduate student, Melbourne, Victoria. coramayer@yahoo.com.au

Amy A Neilson MBBS, BSc, MPH&TM, is Principal House Officer, Department of Emergency Medicine, Royal Brisbane and Women's Hospital, Queensland.

Conflict of interest: none declared.

References

1. National Health and Medical Research Council. The Australian Immunisation Handbook. 9th edn. Canberra: National Health and Medical Research Council, 2008.
2. Yung A, Ruff T, Torres J, et al. Manual of travel medicine: a pre-travel guide for health care practitioners. 2nd edn. Melbourne: IP Communications, 2004.
3. Whitaker JA, Franco-Paredes C, del Rio C, et al. Rethinking typhoid fever vaccines: implications for travelers and people living in highly endemic areas. *J Travel Med* 2009;16:46–52.
4. Luxemburger C, Dutta AK. Overlapping epidemiologies of hepatitis A and typhoid fever: the needs of the traveler. *J Travel Med* 2005;12:S12–21.
5. Baker S, Favorov M, Duigan G. Searching for the elusive typhoid diagnostic. *BMC Infect Dis* 2010;10:45.
6. Crump JA, Mintz ED. Global trends in typhoid and paratyphoid fever. *Clin Infect Dis* 2010;50:241–6.
7. Mann T. Buddenbrooks. Berlin: S. Fischer Verlag, 1901.
8. Nuhu A, Dahwa S, Hamza A. Operative management of typhoid ileal perforation in children. *Afr J Paediatr Surg* 2010;7:9–13.
9. Centers for Disease Control and Prevention. Travelers' health: yellow book. In: Centers for

- Disease Control and Prevention Health Information for International Travel, 2010.
10. Brooks J. The sad and tragic life of Typhoid Mary. *Can Med Assoc J* 1996;154:915–6.
 11. The PLoS Medicine Editors. Clean water should be recognized as a human right. *PLoS Med* 2009;6(6):e1000102. Epub 2009 Jun 30.
 12. Lynch MF, Blanton EM, Bulens S. Typhoid fever in the United States, 1999–2006. *JAMA* 2009;302:859–65.
 13. Moehario LH. The molecular epidemiology of *Salmonella* Typhi across Indonesia reveals bacterial migration. *J Infect Dev Ctries* 2009;3:579–84.
 14. Ghenghesh KS, Franka E, Tawil K, et al. Enteric fever in Mediterranean north Africa. *J Infect Dev Ctries* 2009;3:753–61.
 15. Connor BA, Schwartz E. Typhoid and paratyphoid fever in travellers. *Lancet Infect Dis* 2005;5:623–8.
 16. Byers DK, Petersen K. A case of *salmonella enterica* serotype typhi in a patient without a history of international travel. *J Travel Med* 2009;16:223–5.
 17. Sutiono AB, Qiantori A, Suwa H, et al. Characteristics and risk factors for typhoid fever after the tsunami, earthquake and under normal conditions in Indonesia. *BMC Res Notes* 2010;3:106.
 18. Basnyat B, Maskey AP, Zimmerman MD, et al. Enteric (typhoid) fever in travelers. *Clin Infect Dis* 2005;41:1467–72.
 19. Clark TW, Daneshvar C, Pareek M, et al. Enteric fever in a UK regional infectious diseases unit: a 10 year retrospective review. *J Infect* 2010;60:91–8.
 20. Leder K, Tong S, Weld L, et al. Illness in travelers visiting friends and relatives: a review of the GeoSentinel Surveillance Network. *Clin Infect Dis* 2006;43:1185–93.
 21. Hagmann S, Benavides V, Neugebauer R, et al. Travel health care for immigrant children visiting friends and relatives abroad: retrospective analysis of a hospital-based travel health service in a US urban underserved area. *J Travel Med* 2009;16:407–12.
 22. Giovanetti F. Immunisation of the travelling child. *Travel Med Infect Dis* 2007;5:349–64.
 23. Carroll ID, Williams DC. Pre-travel vaccination and medical prophylaxis in the pregnant traveler. *Travel Med Infect Dis* 2008;6:259–75.
 24. Sulaiman K, Sarwari AR. Culture-confirmed typhoid fever and pregnancy. *Int J Infect Dis* 2007;11:337–41.
 25. Van Hoecke C, Lebacqz E, Beran J, et al. Concomitant vaccination against hepatitis A and typhoid fever. *J Travel Med* 1998;5:116–20.
 26. Van Damme P, Banatvala J, Fay O, et al. Hepatitis A booster vaccination: is there a need? *Lancet* 2003;362:1065–71.
 27. Thaver D, Zaidi AK, Critchley J, et al. A comparison of fluoroquinolones versus other antibiotics for treating enteric fever: meta-analysis. *BMJ* 2009;338:b1865.
 28. Effa EE, Bukirwa H. Azithromycin for treating uncomplicated typhoid and paratyphoid fever (enteric fever). *Cochrane Database Syst Rev* 2008;4:CD006083.
 29. Australian Therapeutic Guidelines: Antibiotic. Version 13. Melbourne: Therapeutic Guidelines Limited, 2006. Available at www.tg.org.au [Accessed 16 February 2010].
 30. Olopoenia LA, King AL. Widal agglutination test – 100 years later: still plagued by controversy. *Postgrad Med J* 2000;76:80–4.
 31. Wilde H, Suankratay C. There is need for antigen-based rapid diagnostic tests to identify common acute tropical illnesses. *J Travel Med* 2007;14:254–8.
 32. Kumar A, Balachandran Y, Gupta S, Khare S, Suman. Quick PCR based diagnosis of typhoid using specific genetic markers. *Biotechnol Lett* 2010;32:707–12.
 33. Zhou L, Pollard AJ. A fast and highly sensitive blood culture PCR method for clinical detection of *Salmonella enterica* serovar Typhi. *Ann Clin Microbiol Antimicrob* 2010;19:14.
 34. Wang S, Singh AK, Senapati D, et al. Rapid colorimetric identification and targeted photothermal lysis of *Salmonella* bacteria by using bioconjugated oval-shaped gold nanoparticles. *Chemistry* 2010;16:5600–6.
 35. Schaetti C. Vaccines for enteric diseases: update on recent developments. *Expert Rev Vaccines* 2009;8:1653–5.
 36. Guzman CA, Borsutzky S, Griot-Wenk M, et al. Vaccines against typhoid fever. *Vaccine* 2006;24:3804–11.
 37. Lyon CE, Sadigh KS, Carmolli MP, et al. In a randomized, double-blinded, placebo-controlled trial, the single oral dose typhoid vaccine, M01ZH09, is safe and immunogenic at doses up to 1.7x10¹⁰ colony-forming units. *Vaccine* 2010;28:3602–8.
 38. Kirkpatrick BD, Tenney KM, Larsson CJ, et al. The novel oral typhoid vaccine M01ZH09 is well tolerated and highly immunogenic in 2 vaccine presentations. *J Infect Dis* 2005;192:360–6.
 39. Jain SK. M-01ZH09, an oral live attenuated *Salmonella enterica* serovar Typhi vaccine for the prevention of typhoid fever. *Current Opinion Mol Ther* 2009;11:565–71.

correspondence afp@racgp.org.au