Typhoid and Paratyphoid Fever (Enteric Fever)

Manitoba
Public Health Branch

1. Case Definition

1.1 Confirmed Case

Isolation of *Salmonella* Typhi or *Salmonella* Paratyphi A, B or C from a clinical specimen (e.g., feces, urine, blood, bone marrow) with or without clinical illness[a] (1).

1.2 Probable Case

Clinical illness[a] in a person who is epidemiologically linked to a confirmed case (1).

2. Reporting and Other Requirements

Laboratory:

- All positive results from laboratory tests are reportable to the Public Health Surveillance Unit (204-948-3044 secure fax).
- Clinical laboratories are required to submit isolate sub-cultures from individuals who tested positive for *Salmonella* Typhi or Paratyphi A, B or C to Cadham Provincial Laboratory (CPL) within seven days of report.

Health Care Professional:

- Probable cases are reportable to the Public Health Surveillance Unit (form available at: www.gov.mb.ca/health/publichealth/cdc/protocol/form2.pdf) ONLY if a positive lab result is not anticipated (e.g., poor or no specimen taken, person has recovered). Confirmed cases do not require reporting by health care professional as they will be reported to Manitoba Health by the laboratory.

3. Clinical Presentation/Natural History

A systemic bacterial disease with gradual onset of sustained fever, constitutional symptoms (e.g., headache, malaise, anorexia and lethargy), relative bradycardia, abdominal pain and tenderness, hepatomegaly, splenomegaly, non-productive cough in the early stage of the illness and rose spots (on the back, arms and legs) (2-4). Constipation is more likely with typhoid and diarrhea with paratyphoid. The non-specific symptoms of typhoid fever may resemble those of malaria, dengue fever, influenza or other febrile illnesses (5). Clinical presentation varies from unapparent infection or mild illness with low-grade fever to severe clinical disease with abdominal discomfort and multiple complications (2). Continuous high-grade fever can continue for up to four weeks if untreated, followed by a return to normal temperature (4). Malaise and lethargy can continue for several months (4). Severity is influenced by strain virulence, quantity of organisms ingested, duration of illness before effective treatment, age and previous vaccination (2). Non-sweating fevers, mental dullness, slight deafness and parotitis may occur (2). Peyer's patches in the ileum can ulcerate, with intestinal hemorrhage or perforation (about 1% of cases), especially late in untreated cases (into the 2nd and 3rd weeks of illness) (2). Severe forms have been associated with high case-fatality rates (2). Untreated, the fatality rate may rise to 10-20% (5). With prompt antimicrobial therapy, case-fatality rate is less than 1% (2). Up to 10% of patients have a mild relapse, usually within two to three weeks of fever resolution (6).

Enteric fever caused by *S.* Paratyphi is clinically indistinguishable from that caused by *S.* Typhi (7); however, symptoms may be milder (4).

For patients presenting with *S.* Typhi or Paratyphi gastroenteritis with no systemic involvement, refer to the Salmonellosis protocol (http://www.gov.mb.ca/health/publichealth/cdc/protocol/salmonellosis.pdf).

a Characterized by insidious onset of sustained fever, headache, malaise, anorexia, splenomegaly, constipation or diarrhea and non-productive cough. Relative bradycardia and rose spots (less than 25% of individuals) may be seen.

4. Etiology

Typhoid fever is caused by *Salmonella enterica* subsp. *enterica* serotype Typhi (commonly *S*. Typhi) (2). Paratyphoid fever is caused by *Salmonella* Paratyphi A, B and C (2). Of the *Salmonella* Paratyphi B variants, var. Java is associated with routine gastrointestinal disease, not paratyphoid fever. *S*. Paratyphi C infections are rare (2). Globally, *S*. Paratyphi A is the most frequently described of the paratyphoid fever serotypes (8).

5. Epidemiology

5.1 Reservoir

Humans are the only known hosts for both typhoid and paratyphoid fever (6). No animal or environmental reservoirs have been identified (9). Up to 5% of patients continue to harbour *S*. Typhi in their intestinal tract and gallbladder for months or years ("asymptomatic carriers") (5, 7).

5.2 Transmission

Infection with *S*. Typhi is usually acquired through ingestion of food or water contaminated with excreta from typhoid fever cases or asymptomatic carriers of the bacterium (4, 5). Important vehicles in some countries include shellfish (particularly oysters) from sewage-contaminated beds, fruit and vegetables fertilized by night soil and eaten raw, and milk/milk products contaminated through hands of carriers (2). Transmission through sexual contact, especially among men who have sex with men, has been documented (9).

5.3 Occurrence

General: An estimated 22 million cases of typhoid fever and 200,000 related deaths occur worldwide each year; an additional six million cases of paratyphoid fever are estimated to occur annually (9). Areas of risk include East and Southeast Asia, Africa, the Caribbean and South and Central America (9). The main burden of disease is in the developing world (2). Approximately 90% of the deaths occur in Asia and most deaths occur in children of school age or younger (5).

Most cases of typhoid/paratyphoid fever that occur in developed countries follow travel to endemic disease areas (2, 4). The Indian sub-continent (India, Pakistan, Bangladesh) accounts for the majority of all reported cases of typhoid that are a result of travel to endemic disease areas (10). In addition, persons and their families who return to their birth country for the purpose of visiting friends and relatives (VFRs) are at increased risk for developing typhoid and are disproportionately over-represented in reported cases of typhoid as compared to other travellers (10 -12).

During the past four decades, both the incidence of *S*. Paratyphi A infection and its relative frequency among enteric fever cases have increased in the United States and other countries (8). In some parts of China, the incidence of paratyphoid fever has surpassed that of typhoid fever (8). Peak incidence occurs in individuals between five and 19 years (4, 13) and young adults (4); however, age-specific incidence rates vary from one country to another (13).

Canada: In 2009, 164 cases of *S*. Typhi were reported to the National Enteric Surveillance Program (NESP) representing 2.7% of *Salmonella* isolates reported (14). As reporting to NESP is voluntary and not all provinces/territories report cases, the cases reported are an under-representation of the actual number of infections in Canada (14).

Manitoba: Thirty-seven cases of typhoid fever and 41 cases of paratyphoid fever were reported to Manitoba Health for 2000-2011 inclusive. The highest number of typhoid fever cases was reported in the 5-19 and 20-44 year age groups. The highest number of paratyphoid fever cases was reported in the 5-19 year age group. Of reported typhoid and paratyphoid fever cases, 65% and 24% respectively were identified as being related to international travel on the case investigation form. No outbreaks of typhoid or paratyphoid fever were reported between 2000 and 2011.

5.4 Incubation Period

The incubation period for typhoid fever averages 8-14 days, but ranges from 3 days to over 60 days (2). The incubation period for paratyphoid fever is 1-10 days (2).

5.5 Host Susceptibility

All humans are susceptible (2). Lifelong immunity usually follows natural infection if the primary infection is not aborted by early antibiotic treatment; reinfections are rare (5). Immunocompromised individuals and individuals suffering from achlorhydria are susceptible to lower infectious doses of *S*. Typhi and are at increased risk of severe disease (5). Immunization with *S*. Typhi vaccine confers protection against *S*. Typhi for two to three years or longer (5). Because *S*. Paratyphi lack the Vi antigen, Vi antigen based *S*. Typhi vaccines are unlikely to provide protection against paratyphoid fever (15). The live oral typhoid fever vaccine has shown some protection against paratyphoid B infection (2).

5.6 Period of Communicability

The period of communicability lasts as long as the bacilli appear in excreta, usually from the first week throughout convalescence, variable thereafter (commonly one to two weeks for paratyphoid fever) (5). Between 1% and 5% of typhoid fever patients become chronic carriers (e.g., "Typhoid Mary") (defined as excretion of *S*. Typhi in urine or stools for more than one year) and the rate is higher for women, those older than 50 years, and patients with schistosomiasis, cholelithiasis, carcinoma of the gallbladder and other gastrointestinal malignancies (4).

6. Laboratory Diagnosis

S. Typhi and Paratyphi can be isolated from the blood early in the disease and from urine and feces after the first week. In suspected typhoid/ paratyphoid fever, cultures of blood, feces and urine are indicated. Outbreaks should be noted on the requisition.

Serologic testing has limited sensitivity so is of little diagnostic value and generally, not available. Serological methods may be used to support determination of chronic carriage; this must be requested in consultation with Cadham Provincial Laboratory (CPL) (204-945-6123).

7. Key Investigations for Public Health Response

- Source of infection (e.g., travel history, especially visiting friends and relatives; history of contaminated water, milk, shellfish consumption) with emphasis on the investigation of source of infection for cases unlikely to be travel related (16).
- Identification and follow-up of household, intimate and travel contacts.
- Immunization history.

8. Control

8.1 Management of Cases

Treatment:

Antibiotic treatment is indicated to resolve clinical symptoms and to prevent severe complications and death, relapse and fecal carriage (4). Initial choice of antibiotic depends on the sensitivity patterns of *S*. Typhi and Paratyphi isolates in the area (4). With increasing multidrug resistance (MDR) (resistant to ampicillin, chloramphenicol and trimethoprim-sulfamethoxazole) (17), these previously effective antimicrobial agents are no longer recommended for treatment of enteric fever (8).

- Fluoroquinolones are the drug of choice for oral therapy in adults; however, increasing antimicrobial resistance requires therapy to be guided by appropriate antimicrobial susceptibility testing (2, 4, 6, 18). Ciprofloxacin resistance is increasing among both *S*. Typhi and *S*. Paratyphi (15), and is highest in the Indian subcontinent (15). Isolates reported to be naladixic acid resistant but ciprofloxacin susceptible should not be treated with a fluoroquinolone because of high failure rates.
- For adult patients with severe symptoms, ceftriaxone should be initiated pending susceptibility results for the organism.
- In the face of resistance to ciprofloxacin and other fluoroquinolones, parenteral ceftriaxone and oral cefixime are effective (6). Oral azithromycin is effective for treating uncomplicated enteric fever (19).

- Ceftriaxone is the preferred treatment for children with suspected typhoid fever.
- Patients with concurrent schistosomiasis must also be treated with praziquantel to eliminate possible schistosome carriage of *S*. Typhi (2).
- Short-term high-dose corticosteroid treatment combined with specific antibiotics and supportive care reduces mortality in critically ill patients (2).
- **Chronic Carriers:** It is important to consult with an Infectious Diseases specialist when managing chronic carriers. Administration of 750 mg of ciprofloxacin or 400 mg of norfloxacin twice daily for 28 days provides successful treatment of carriers in 80-90% of cases (2). Limited studies have suggested 14-21 days of treatment to be equally efficacious (2). In children, chronic (one year or longer) *S*. Typhi carriage may be eradicated by high-dose parenteral ampicillin. (3).

Public Health/Infection Control Measures:

- Patients must be advised of the importance and effectiveness of washing hands with soap and water after defecation and before preparing, serving or eating food (2).
- Contact Precautions are indicated for pediatric patients who are incontinent or too immature to comply with hygiene and for incontinent adults if stool cannot be contained or with poor hygiene who contaminate their environment. Otherwise, Routine Practices are adequate. Refer to the Manitoba Health document *Routine Practices and Additional Precautions: Preventing the Transmission of Infection in Health Care* available at: http://www.gov.mb.ca/health/publichealth/cdc/docs/ipc/rpap.pdf).
- Persons excreting typhoid bacilli in stools or urine should be excluded from handling food. Exclusion should be based on no fewer than three consecutive negative stool cultures (and urine cultures in patients with schistosomiasis) taken at least 24 hours apart and at least 48 hours after any antimicrobial therapy has ended, and not earlier than one month after onset of symptoms (2). Individuals who continue to excrete the organism should be handled on a case-by-case basis by the regional Medical Officer of Health.
- For child care facility attendees younger than five years of age, three negative stool specimens are recommended for return (3). For those over five years old with symptoms, exclusion should be until 24 hours after resolution of symptoms (3).
- Individuals providing patient or child care should be assessed on an individual basis by the regional Medical Officer of Health.
- Instruct patients, convalescents and carriers in personal hygiene and hand washing before preparing and serving food.

Note: Redeployment to avoid activities that involve an unacceptable risk in the workplace/care facility (e.g., food handler touching unwrapped or raw food that will not be cooked further) should always be considered as an alternative to exclusion (16).

8.2 Management of Contacts

- Contacts are defined as household members, sexual partners and members of a travel party the case has travelled with to an endemic country.
- Public Health will identify contacts and make arrangements for specimen collection if necessary.
- Contacts (especially close travel contacts) should be questioned regarding symptoms (headache, fever, diarrhea, constipation and malaise) and investigated for infection if symptomatic.
- Two negative stool cultures taken at least 24 hours apart should be obtained from symptomatic contacts before allowing them to be employed in high risk settings (e.g., as food handlers) (2). Depending on an individual assessment, this requirement may also be extended to persons occupied in child or patient care. If contacts test positive for *S*. Typhi or Paratyphi, follow *Management of Cases* in Section 8.1 above.
- Asymptomatic contacts who work in high risk settings (e.g., food handlers) should be screened (i.e., stool specimen collected and tested), but not excluded (as per case management) unless a positive result is received.

- Immunization of contacts with typhoid fever vaccine is not generally recommended, but should be considered for individuals with ongoing household and intimate exposure to a known *S*. Typhi carrier (2, 3, 13).

8.3 Management of Outbreaks

An outbreak is defined as the occurrence of case(s) in a particular area and period of time in excess of the expected number of cases.

- Outbreaks should be investigated to identify a common source of infection and prevent further exposure to that source. The extent of outbreak investigations will depend upon the number of cases, the likely source of contamination and other factors.
- Refer to the *Enteric Illness Protocol* available at: www.gov.mb.ca/health/publichealth/cdc/protocol/enteric.pdf
- Public notification should occur. The level of notification will usually be at the discretion of regional Public Health and/or provincial Public Health for local outbreaks but may be at the discretion of the Federal Government for nationally linked foodborne outbreaks as per *Canada's Foodborne Illness Outbreak Response Protocol (FIORP) 2010: To guide a multijurisdictional response* available at: www.phac-aspc.gc.ca/zoono/fiorp-pritioa/index-eng.php
- Cases and contacts should be managed as above (sections 8.1 and 8.2 respectively). In large outbreaks, it may not be practical or necessary to obtain laboratory clearance in every case before persons are allowed to return to work or school.
- Typhoid immunization is not recommended for the control or containment of typhoid outbreaks in Canada (13).
- Education on preventive measures should occur (refer to Section 8.4 below).

8.4 Preventive Measures

- Immunization for typhoid fever (currently there is no licensed vaccine for paratyphoid fever):
  - before traveling to endemic areas;
  - for persons working with the organism in laboratory settings; and
  - for persons with ongoing household or intimate exposure to an *S*. Typhi carrier (3, 13).

  This vaccine is not publicly funded by Manitoba Health for travel or occupational purposes.
- The identification and treatment of *S*. Typhi carriers in low-incidence settings, particularly those involved in food production (15).
- Public health supervision and restriction of high risk occupation of chronic carriers until three consecutive negative stool specimens (and urine in areas endemic for schistosomiasis) have been obtained at least one month apart and at least 48 hours after antimicrobial therapy has stopped (2).
- Protection, purification and chlorination of public water supplies (2).
- Education of the public on the importance of hand washing, emphasizing routine hand washing after defecation and before preparing, serving or eating food (2).
- Education of the public on safe food handling practices (2).
- Consumption of pasteurized milk and milk products only (2).
- When traveling to endemic areas:
  - Drink bottled, boiled or purified water only;
  - Avoid ice;
  - Avoid raw vegetables and fruits that cannot be peeled or thoroughly cooked and eaten steaming hot;
  - Avoid foods and beverages bought from street vendors (9).
- Boiling or steaming shellfish for at least 10 minutes (2).
- Encouraging breast-feeding of infants (2).

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