NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
Division of the National Health Laboratory Service

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OUTBREAK RESPONSE, DIVISION OF PUBLIC HEALTH SURVEILLANCE AND RESPONSE
CENTRE FOR ENTERIC DISEASES

Typhoid:

NICD recommendations

for diagnosis, management

and public health response

Version 1 (June 2011)
Previously called 'Health Care Workers' Handbook on Typhoid'
Developed by:
The National Institute for Communicable Diseases (NICD)
a division of the National Health Laboratory Service (NHLS),

in collaboration with:
The South African National Department of Health
U.S. Centres for Disease Control and Prevention – South Africa

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a division of the National Health Laboratory Service (NHLS),

Prefix and Disclaimer

This material is intended for use by healthcare professionals. While the greatest care has been taken in the development of the document, the National Department of Health and the National Institute for Communicable Diseases of the National Health Laboratory Service do not accept responsibility for any errors or omissions. All healthcare professionals should exercise their own professional judgement in confirming and interpreting the findings presented in the handbook.

Quick Reference Guide - Typhoid

Typhoid case definitions: Page 6

A typhoid '*case under investigation*':

A person presenting with a documented fever >/= 38.5°C, and any of:

- Gastrointestinal symptoms (abdominal pain, nausea and vomiting or constipation),
- Relative bradycardia,
- 'Rose spots' (erythematous macula-papular lesions) or
- Hepatosplenomegally or leucopaenia.
- A travel history within the last month to an area with a confirmed outbreak of typhoid is highly suggestive.

A confirmed case of typhoid:

The isolation of *Salmonella* Typhi from a clinical specimen in the presence of symptoms compatible with typhoid.

A typhoid carrier:

The isolation of *Salmonella* Typhi from a clinical specimen in a person who is asymptomatic.

REMEMBER TO EXCLUDE MALARIA IN ALL RETURNING TRAVELLERS WHO PRESENT WITH FEVER. At least two negative malaria smears are required

Public health response to a case of typhoid: Page 12

1. Notify the department of health
2. Confirm the diagnosis by verifying laboratory results, and patient details.
3. Review the case management and treatment
4. Interview the patient and complete a case investigation form to ascertain risk factors for exposure and likely source of infection
5. Identify contacts at risk of infection, and confirm that they are well, and are not carrying typhoid.
6. Follow up the patient with three stool specimens to confirm that s/he is not a carrier.

Diagnosis of typhoid Page 7

Typhoid is diagnosed by culture of the organism Salmonella Typhi from any clinical specimen.

1. Blood culture is the specimen of choice. Submit blood cultures as soon as possible. Blood cultures may be positive in up to 50-80% of cases
2. Stool culture may be useful, especially in children. Organisms are shed in the stool only after the first week of illness
3. Bone marrow aspirate is positive in 90% of cases but is an invasive specimen.
4. Urine cultures may be useful.

Serological testing is not recommended for the diagnosis of typhoid

Treatment of a case of typhoid: Page 10

If typhoid is clinically suspected, commence treatment immediately. Do not wait for laboratory results

Ciprofloxacin is the drug of choice for the treatment of uncomplicated typhoid fever in South Africa.

- The paediatric dose if 15mg/kg/day in two divided doses x 7 days.
- Adults are treatment with 500-750mg po bd x 7 days

Refer to page 11 and 12 for treatment of complicated typhoid, and typhoid carriers

Notification of cases and additional support:

Laboratory support: National Institute for Communicable Diseases, Centre for Enteric Diseases, Arvinda Sooka arvindas@nicd.ac.za (011-386-6235), or after-hours, the NICD doctor-on-call 082 883 9920:

Public health support and notification of cases: Notify the Provincial Communicable Diseases Control Officer, or the NICD Outbreak Response unit (011-555-0542) or outbreak@nicd.ac.za.

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1 Background on typhoid fever

1.1 Aetiologic agent

Typhoid fever, also called enteric fever, is caused by a bacterial infection with *Salmonella enterica* subspecies *enterica* serotype Typhi or serotypes Paratyphi A, B or C. For the purposes of these guidelines, hereafter we refer to these only as *Salmonella* Typhi causing typhoid fever disease.

1.2 Clinical features

Few clinical features reliably distinguish typhoid fever from other causes of febrile illnesses. Infection in the absence of treatment manifests after an average incubation period of 10-14 days (range 5-21 days) as a multistage febrile illness.

Acute typhoid fever:
Systemic illness characterised by:

- Fever (30-100% of cases): remittent during the first week, rising in a stepwise fashion and becomes sustained (lasting > 48 hours) after the first week.
- Headache (43-90%).
- Gastrointestinal symptoms (8-79%), including:
    - Abdominal pain/cramps (30-40%),
    - Nausea and vomiting (usually not severe), and/or
    - Constipation (10-38%) or diarrhoea (diarrhoea is more frequent in children and HIV-infected adults).
- Relative bradycardia (17-50%),
- Erythematous maculopapular lesions (rose spots) (≈30%): **f**lat, faint-pink spots 2-4cm in diameter which develop on the chest, abdomen and back. These may be difficult to detect in dark-skinned individuals.
- Hepatosplenomegaly (23-65%).
- Leukopenia (16-46%).
- Nonspecific symptoms, such as chills, diaphoresis, anorexia, cough, weakness, sore throat, dizziness, and muscle pains, are frequent before the onset of fever.

Severe illness and extra-intestinal complications:
Up to 10-15% of patients may develop severe illness. This may include gastrointestinal bleeding (10-20%), intestinal perforation (1-3%), septic shock, or acidosis.
Extra-intestinal complications may also occur, including:

- Central nervous system (3-35%): Encephalopathy. Cerebral oedema, subdural empyema, cerebral abscess, meningitis, ventriculitis, transient Parkinsonism, motor neuron disorders, ataxia, seizures, Guillain-Barré syndrome, psychosis.
- Cardiovascular system (1-5%): Endocarditis, myocarditis, pericarditis, arteritis, congestive heart failure
- Pulmonary system (1-6%): Pneumonia, empyema, bronchopleural fistula
- Bone and joint (<1%): Osteomyelitis, septic arthritis
- Hepatobiliary system (1-26%): Cholecystitis, hepatitis, hepatic abscesses, splenic abscess, peritonitis, paralytic ileus
- Genitourinary system (<1%): Urinary tract infection, renal abscess, pelvic infections, testicular abscess, prostatitis, epididymitis
- Soft tissue infections: Psoas abscess, gluteal abscess, cutaneous vasculitis
- Haematological: Haemophagocytosis syndrome

The case fatality rate due to typhoid fever varies depending on presence of complications and timely antimicrobial intervention. If left untreated, 12-30% of all infections may result in death; however, with appropriate treatment mortality rates may be reduced to <1% within developing nations. Up to 32% of severely ill or complicated typhoid cases may be fatal, depending on the country studied.

Chronic carriage:
Approximately 1-5% of infected persons experience a chronic carrier state following recovery from an acute phase illness. These individuals may excrete the organism for years if left untreated, with the potential to infect others, as well as develop recrudescent illness themselves. Chronic typhoid carriage has frequently been associated with gallstones in the biliary tract of infected persons. *Salmonella* Typhi bacilli form biofilms on the surface of gallstones, thereby protecting the bacteria from the host's immune response, as well as antimicrobial therapy. Prolonged *Salmonella* Typhi carriage, with intermittent febrile periods has been also associated with intestinal/urinary schistosomiasis (a.k.a. bilharzia). The bacteria are able to colonise adult *Schistosoma spp.* which shelter the bacteria from the host's immune system and antimicrobials.

1.3 Transmission

Humans are the only known hosts of *Salmonella* Typhi. Bacteria are shed in the faeces of an infected person and transmitted from person to person via ingestion of food or water contaminated by these faeces (faecal-oral route). Large outbreaks of typhoid fever are often associated with contamination of a drinking water. The organism can survive for several days in fresh water (e.g. ground water, pond-water) and seawater. Furthermore, the organism can survive for prolonged periods (up to several months) in contaminated foods. Outbreaks have been associated with contaminated eggs, oysters (fresh and frozen), ice-cream and iced-drinks, raw fruits and vegetables, fish and various meats. Contamination of food can occur through food handlers (e.g. vendors who may be asymptomatic carriers), irrigation of gardens/crops with sewage-contaminated water or fertilizers, as well as the sharing of food items among cases.

1.4 Burden of disease

Worldwide, an estimated 21 million typhoid fever cases, resulting in 200,000 deaths, occur each year. Incidence is highest in developing countries within Asia (including south-central Asia and south-east Asia) and parts of Africa. Typhoid is endemic within South Africa; however, the local burden of disease is unknown. In addition to endemic disease, the epidemic potential of typhoid fever was previously demonstrated in South Africa. Examples include Delmas (Mpumalanga Province), where repeated outbreaks of typhoid fever have been recorded; causing over 1000 cases during 1993, and over 400 suspected cases and three deaths in 2005.

1.5 Epidemiology and high risk individuals

Within endemic settings typhoid fever is closely associated with poor food hygiene, and inadequate water and sanitation infrastructures. In these settings, school-aged children (5-15 years) are most frequently affected. In more industrialised settings with lower transmission rates, travellers make up a large proportion of cases; hence, disease is more frequently observed in older age groups. South Africa observes a mixed pattern of endemic disease (with continued potential for large scale epidemics), and sporadic cases in more industrialised areas of the country. Travellers (local and international) returning from areas with endemic transmission may account for a large proportion of cases in South Africa. Travellers present a risk not only of transmitting illness within our local population, but also of introducing multidrug-resistant strains that are observed more commonly in highly endemic countries (south-central Asia and south-east Asia).

Persons with occupations as food handlers, or those who provide care for patients, children or the elderly, represent specific high-risk groups due to their potential to widely transmit infection. They, therefore, require specific considerations during the public health response to identified cases, and should be restricted form these activities until these investigations have been complete.

2 Case definitions

2.1 A typhoid 'case under investigation':

A person presenting with a documented fever >/= 38.5^{o}C, and any of:

- Clinical symptoms of typhoid, including gastrointestinal symptoms (abdominal pain, nausea and vomiting or constipation), relative bradycardia, 'rose spots' (erythematous macula-papular lesions), splenomegaly and/or hepatomegaly, leucopaenia
- A travel history within the last month to an area with a confirmed outbreak of typhoid;

2.2 A confirmed case of typhoid:

The isolation of *Salmonella* Typhi, *Salmonella* ParaTyphi from a clinical specimen in the presence of symptoms compatible with typhoid.

2.3 A probable case of typhoid

A clinically compatible case that is epidemiologically linked to a confirmed case, in an outbreak situation.

2.4 A typhoid carrier:

Typhoid carriers may be 'convalescent carriers' or 'chronic carriers'.

- A convalescent carrier is a person who is still excreting *Salmonella* Typhi or *Salmonella* Paratyphi after two courses of appropriate antibiotic therapy, but has been excreting for less than 12 months
- A chronic carrier is a person who continues to excrete *Salmonella* Typhi or *Salmonella* Paratyphi for 12 months or more.

3 Diagnosis

3.1 Differential diagnosis

Typhoid fever may be clinically indistinguishable from other causes of an enteric-fever like syndrome, including *Yersinia enterocolitica*, *Yersinia pseudotuberculosis, Campylobacter fetus* or other non-typhoidal *Salmonella* infections. Therefore, laboratory testing is advisable in all patients presenting with clinically compatible characteristics of typhoid fever (see Section 1.2 above).

Supportive laboratory tests and epidemiological clues may also be considered in differentiating typhoid fever from enteric-fever like syndromes. Leukopenia (low white cell count) is reported in 16-46% of cases. The absence of eosinophils is also common among patients. Hepatic transaminases (ALT and AST) may be raised in up to two-thirds of cases. Epidemiological clues may include the patient's age, place of residence and history (e.g. travel, water source, consumption of food outside of the home). Within endemic settings, typhoid fever is more frequently observed in infants and pre-school children than in the older population. Infection is historically associated with households with poor hygiene or poor sanitation and water infrastructures. In areas without wide-spread endemic transmission, including parts of South Africa, typhoid fever frequently affects travellers to highly-endemic settings (e.g. Asia). Food-handlers also play an important role in transmission, and eating outside of the home (e.g. from street vendors) can be important predictors of infection.

Other causes of febrile illness, and possibly concurrent infections, in returning travellers should also be considered. These alternative diagnoses could include malaria, dengue, hepatitis, etc.

3.2 Specimen collection for laboratory diagnosis

The definitive diagnosis of typhoid fever requires the isolation of *Salmonella* Typhi from blood, bone marrow or a specific anatomical lesion (e.g. abscess). Blood culture is the diagnostic test of choice. The procedures and limitation of the various laboratory tests are described below.

3.2.1 Blood culture – *Diagnostic test of choice*

Blood culture is the diagnostic test of choice given the limitations of testing other specimen types. Furthermore, blood culture provides the means for conducting antimicrobial resistance testing, which is important in treatment choice (see Section 3.1). The sensitivity of blood culture is 50-80%. It is limited by the small numbers of *Salmonella* Typhi bacilli present in blood and the use of antibiotics before specimen collection, and varies by volume of blood collected and the system used for culturing.

Procedures for blood culture with vary depending on the testing system used by the laboratory. Prior to specimen collection, contact your local laboratory (or referral laboratory if blood cultures not performed at local level) and identify the system they use. The majority of NHLS laboratories utilise a BacT/ALERT® system for blood cultures. The following steps apply to this system. If an alternative system is used by your local laboratory, follow the manufacturer's guidelines.

1. **Skin preparation:** Clean the venepuncture site thoroughly with an alcohol prep pad. Allow to air dry. Do not re-palpate the vein after cleaning.

2. **Bottle preparation**: Inspect blood culture bottles prior to use. Ensure the bottle and sensor on the bottom of the bottle is intact. The sensor is normally a uniform greyish-green colour. Discard any bottle found to be damaged or with a yellow sensor (i.e. indicating contamination of the broth).

3. **Venepuncture and bottle inoculation:** Within the BacT/ALERT® system, the choice of blood culture bottle is dependent on the age of the patient and if antibiotics were taken prior to specimen collection. Perform the venepuncture and inoculate the appropriate bottles for your patient as follows:
    a. **Adult and school-aged children <u>without</u> prior antibiotic treatment** – inoculate 2 x standard AEROBIC blood culture bottles (blue top) with 10ml of blood in each bottle (i.e. 20ml blood total).
    b. **Adult and school-aged children <u>with</u> prior antibiotics** – inoculate 2 x FAN® AEROBIC blood culture bottles (green top) with 10ml of blood in each bottle (i.e. 20ml blood total).
    c. **Infants and pre-school children** – inoculate 2 x Paediatric FAN® blood culture bottles (yellow top) with up to 4ml of blood in each bottle.

4. **Labelling and forms:** All specimens should be labelled and accompanied by standard NHLS clinical specimen submission forms, including: patient details, clinical presentation, relevant history and healthcare practitioner's details. Indicate "<u>culture for typhoid</u>" on the form.

5. **Transport:** Once blood culture bottles have been inoculated, they should be incubated immediately at 37°C until transport arrives. <u>Do not refrigerate</u> inoculated bottles. Send specimens to your local NHLS laboratory as per standard procedures. Specimens may be referred to a regional NHLS laboratory depending on capacity at local laboratory.

3.2.2 Stool culture

The isolation of *Salmonella* Typhi from stool is suggestive of acute typhoid fever when associated with a clinically compatible illness; however, stool culture does not replace blood culture as a diagnostic specimen due to a number of limitations. Firstly, bacilli are shed in stool only after the first week of illness. Secondly, only 30% of adult cases, and 60% of paediatric cases, will have a positive stool culture. Thirdly, typhoid carriers may also have a positive stool culture. Nevertheless, stool culture plays a role in public health investigations following identification of a case, and is important in identifying carriers (see Section 4). Where indicated, stool culture may be submitted as per standard procedures:

1. **Specimen collection:** Stools should be collected in a sterile wide-mouthed plastic container.

2. **Inoculation of transport medium (where applicable):** If stool cannot be processed within 2 hours, place the stool specimen in Cary-Blair transport medium. Collect a small amount of stool by inserting a sterile, cotton-tipped, swab into the stool and rotating it. If mucous and shreds of

intestinal epithelium are present, these should be sampled with the swab. Immediately insert the swab into the transport medium. The swab should be pushed completely to the bottom of the medium. Cut off and discard the top portion of the swab-stick that is protruding above the edge of the container, leaving the cotton tip in the transport medium. Replace the screw cap on both containers and tighten firmly. Submit both the stool and the inoculated transport medium containers for laboratory testing.

3. **Labelling and forms:** All specimens should be labelled and accompanied by standard NHLS clinical specimen submission forms, including: patient details, clinical presentation, relevant history and healthcare practitioner's details. Indicate "culture for typhoid" and the nature of the specimen (i.e. stool or rectal swab) on the form.

4. **Transport:** Send specimens to your local NHLS laboratory as per standard procedures. Specimens may be referred to a regional NHLS laboratory depending on capacity at local laboratory. If there is a delay in transport (or processing in the laboratory) immediately place both containers in a refrigerator (at 4°C), or a cold-box, until collected by the courier. Do not freeze.

Rectal swabs may be collected where a stool specimen cannot be obtained, but these are inferior specimens with reduced sensitivity. Rectal swabs should be collected by moistening a sterile swab in transport medium (Cary-Blair). Insert swab gently into the rectal sphincter (2 to 3 cm) and rotate to sample anal crypts. Remove swab and check for visible faeces. Immediately insert the swab into the transport medium, label the specimen, and transport to laboratory as per steps 2-4 above.

3.2.3 Bone marrow aspirate culture

Bone marrow culture is considered the most sensitive (90%) of the clinical specimens for isolation of *Salmonella* Typhi; however, sample collection is painful and invasive, and requires technical expertise and appropriate surgical equipment. Furthermore, the sensitivity of blood culture is approaching that of bone marrow culture due to recent advances in technology. Therefore, bone marrow culture is not routinely recommended to diagnosis of typhoid fever. A bone marrow aspirate may be indicated in patients who have been previously treated, who have a long history of illness and for whom there has been a negative blood culture with the recommended volume of blood. Furthermore, bone marrow aspirates collected for other indications (e.g. cytopenias) may be subjected to culture for *Salmonella* Typhi.

3.2.4 Extra-intestinal complications and focal infections

In patients who present with extra-intestinal complications (e.g. endocarditis, pneumonia, meningitis, arthritis or focal abscesses) an appropriate specimen from the site of the focal infection may be submitted for *Salmonella* Typhi culture. For example, these may include: sputum, CSF, synovial fluid or pus. Blood cultures (as above) should still be obtained for these patients, and laboratory results should be interpreted in line with the patient's clinical presentation/history.

3.2.5 Urine cultures

Salmonella Typhi may be excreted in urine; therefore, although not routinely suggested for laboratory diagnosis, the culture isolation of *Salmonella* Typhi from urine is indicative of acute typhoid fever or chronic carriage depending on the clinical presentation of the patient.

3.2.6 Serology and other tests

Aside from culture, serological (such as the Widal test) and other laboratory tests are not recommended for the diagnosis of typhoid fever due to a number of limitations:

- **High rates of false-negative results.** Up to 10% of true-positive do not produce detectable antibody titres.
- **High rates of false-positive results.** False-positive results are frequent due to cross-reaction with other pathogens (including non-typhoidal *Salmonella* and malaria), immunological disorders and chronic diseases.

- **Results are difficult to interpret.** Quantitative measures of antibody titres, knowledge about the baseline titres present in the local population, and paired sera samples are required to correctly interpret serology test results. Laboratories often do not give quantitative measures of the antibody titre. Background agglutinins and antibodies vary significantly between population groups and are dependent on endemicity and typhoid vaccine use in that population. Paired sera, collected 7-14 days apart, are required to identify a rise in antibody titre.

4 Treatment and case management

Early diagnosis and prompt administration of appropriate antimicrobial therapy prevents severe complications of typhoid fever and results in case-fatality rates of <1%. The choice of antimicrobial therapy depends on the susceptibility of *Salmonella* Typhi strains in the area of residence or travel. Obtaining a thorough patient history including recent travel and previous antibiotic use is, therefore, necessary for all suspected cases to inform treatment choice.

4.1 Supportive management

More than 90% of typhoid patients can be managed with oral antibiotics, reliable care and close medical follow-up for complications or failure to respond to therapy. After initial diagnosis, patients may be discharged home on appropriate treatment, if they are clinically stable. However, patients with persistent vomiting, severe diarrhoea, and complications (intestinal or extra-intestinal) require hospitalisation and intravenous (IV) antibiotic therapy. Supportive measures, such as oral or intravenous hydration, the use of antipyretics, appropriate nutrition and blood transfusions, also play an important role where indicated.

4.2 Treatment of acute uncomplicated typhoid fever

Note: If typhoid fever is clinically suspected, commence treatment immediately. Do not wait for laboratory results.

Multidrug resistant (MDR) *S*. Typhi first emerged in the 1980s, and is defined as *S*. Typhi strains resistant to the three antibiotics that were commonly used to treat typhoid fever, namely: ampicillin, chloramphenicol and cotrimoxazole. MDR-typhoid fever is now widespread globally, including South Africa (where it was first described in 1987).

Strains of *S*. Typhi that are MDR remain susceptible to ciprofloxacin. Therefore, ciprofloxacin is currently the treatment of choice for typhoid fever in South Africa. Ciprofloxacin offers several advantages over other drugs, including: rapid clearance of fever and symptoms, low rates of post treatment carriage (<2%), oral administration, and availability at most healthcare facilities. Treatment should be commenced immediately following a clinical diagnosis of suspected typhoid fever. Do not wait for laboratory results; however, specimens should ideally be collected prior to commencement of antimicrobial therapy.

Of great concern is the widespread emergence of *S*. Typhi strains with decreased susceptibility to ciprofloxacin. Presently, approximately 15% of *S*. Typhi in South Africa have decreased susceptibility to ciprofloxacin (reported as either intermediately resistant or resistant to ciprofloxacin). Studies have shown that patients with *S*. Typhi with decreased susceptibility to ciprofloxacin have delayed response, clinical treatment failure and increased mortality if treated with ciprofloxacin (even if treated with maximal doses for prolonged duration). Recommended treatment for typhoid fever with decreased susceptibility to ciprofloxacin is azithromycin or ceftriaxone/cefotaxime.

Table 1: Recommended antimicrobial treatment for acute uncomplicated typhoid fever according to ciprofloxacin susceptibility*

		Paediatrics		Adults**	
Susceptibility	Antibiotic	Dose	Days	Dose	Days
Susceptible to	Ciprofloxacin	15 mg/kg/day po in two	5-7	500-750 mg po 12	5-7

ciprofloxacin		divided doses (i.e. 12 hourly)		hourly	
Intermediately resistant OR resistant to ciprofloxacin	Ceftriaxone OR Cefotaxime	50-75 mg/kg/day IV in two divided doses (i.e. 12 hourly) 40-80 mg/kg/day IV in 2 divided doses (i.e. 12 hourly)	10-14 10-14	1-2 g IV 12 hourly	10-14

*Ciprofloxacin susceptibility as determined using 2012 CLSI breakpoints for *Salmonella* spp
**Pregnant women should preferably be treated with azithromycin, ceftriaxone or cefotaxime since ciprofloxacin is an FDA-category C agent and not advised for use during pregnancy.

4.3 Treatment of severe and complicated typhoid fever

Severe typhoid fever, patients unable to tolerate oral treatment due to vomiting and/or severe diarrhoea, and/or patients with intestinal/extra-intestinal complications may require hospitalisation and parenteral treatment. Once patients have clinically improved, treatment can be completed with oral antibiotics (e.g. oral ciprofloxacin). Table 2 outlines the treatment recommendations.

Table 2: Recommended antimicrobial treatment for severe or complicated typhoid fever according to ciprofloxacin susceptibility*

		Paediatrics		Adults**	
Susceptibility	Antibiotic	Dose	Days	Dose	Days
Susceptible to ciprofloxacin	Ciprofloxacin***	15 mg/kg/dose (max 500 mg) po 12 hourly OR 10 mg/kg/dose (max 400 mg) IV 8 hourly	10-14 10-14	500-750 mg po 12 hourly OR 400 mg IV 8 hourly	10-14 10-14
Intermediately resistant OR resistant to ciprofloxacin	Ceftriaxone OR Cefotaxime	50-75 mg/kg/day IV in two divided doses (i.e. 12 hourly) 40-80 mg/kg/day IV in 2 divided doses (i.e. 12 hourly)	10-14 10-14	1-2 g IV 12 hourly	10-14

* Ciprofloxacin susceptibility as determined using 2012 CLSI breakpoints for *Salmonella* spp
** Pregnant women should preferably be treated with ceftriaxone or cefotaxime since ciprofloxacin is an FDA - category C agent and
not advised for use during pregnancy
***Oral or intravenous ciprofloxacin may be used for severe disease
.

Intestinal bleeding, perforations or ulcerations are life-threatening and may require immediate fluid resuscitation, surgical interventions (e.g. closure, drainage of peritoneum, and/or small-bowel restriction for multiple-perforations) and broad-spectrum antimicrobial coverage for polymicrobial peritonitis.

Concurrent treatment with high-dose dexamethasone (initial dose 3mg/kg followed by eight doses of 1mg/kg every 6 hours for 48 hours) should be considered for patients with severe typhoid fever with sign of typhoid-meningitis (e.g. shock, obtundation, stupor or coma). Administering dexamethasone has been shown to reduce fatalities among such patients; however if used, patients must be monitored closely because dexamethasone may mask abdominal complications. Furthermore, steroid treatment beyond 48 hours may increase the relapse rate.

4.4 Treatment of persistent infections and chronic carriers

Up to 1-5% of acute cases develop convalescent or chronic carriage of *Salmonella* Typhi. These patients should be treated for a prolonged duration with an appropriate oral antimicrobial, the strain specific resistance profile dictating the choice of antimicrobial. In the case of convalescent or chronic carriers infected with *S*. Typhi strains susceptible to ciprofloxacin, the recommended treatment is ciprofloxacin (15mg/kg/day po in two divided doses) for 4-6 weeks. At present, there is no data as to which treatment is optimal for *S*. Typhi carriers of strains with decreased susceptibility to ciprofloxacin, and expert advice should be sought in such cases.

Investigation and management of anatomic abnormalities and concurrent infections also plays and important role in treatment of chronic carriers. Antimicrobial agents will likely be ineffective in patients with gallbladder, biliary or kidney stones. In these patients, surgery (e.g. cholecystectomy) combined with antimicrobial treatment may be indicated. Concurrent schistosomal infections (a.k.a. bilharzia) also play an important role in development of urinary carriage of *Salmonella* Typhi in South Africa. Such cases should be treated first with an appropriate dose of praziquantel to eradicate *Schistosoma* spp prior to initiating antimicrobial treatment. Chronic suppressive antimicrobial therapy may be considered in patients with persistent carriage, or relapse, after appropriate investigations and treatment to eradicate *Salmonella* Typhi infection has been attempted.

4.5 Infection prevention and control

Hospitalised patients should be cared for using standard precautions. Contact precautions should be used for diapered or incontinent persons for the duration of illness or to control institutional outbreaks.

It is important to educate the case and care givers with regards to the preventative steps to reduce the risk of transmission (see Section 6), including good hiegne practices (e.g. handwashing).

4.6 School and work restrictions

Suspected and confirmed cases that do not require hospital admission for treatment, should be restricted from school/work until 24 hours after symptoms (especially diarrhoea) subside, in order to minimise the risks for transmission. Persons who work as food handler, or if the case provides care for patients, children or the elderly, should be excluded from those activities until at least 3 consecutive negative cultures, meeting the criteria outlined in Step 6 below, are obtained (see Section 4).

5 Public health response to a single case

All cases of typhoid fever infection pose a public health risk in terms of spreading infection and potentially causing an outbreak. The following steps should be followed by healthcare workers following the identification of a suspected or confirmed case.

1. **Notify the Department of Health:** Typhoid fever is a category B notifiable medical condition; therefore all healthcare professionals are required by law to notify any suspected or confirmed case of typhoid fever to their local Department of Health. Complete a GW17/5 form and fax/mail this to the local health

authority within 7 days of identifying the case. If a laboratory diagnosis is available, attached the laboratory report to the notification; however, notifications should not be withheld pending laboratory results. Should a laboratory diagnosis be obtained after the initial notification is sent, complete a second GW17/5 form and resend this, and the laboratory report, to the local authority.

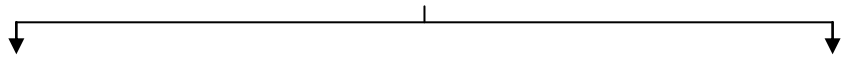
2. **Confirmed the diagnosis:** Review laboratory results with reference to Section 2. Request a blood culture if a laboratory diagnosis has not yet been obtained or if a non-confirmatory test has been done (e.g. serology).

3. **Review case management and treatment:** Ensure the case is receiving appropriate treatment for typhoid fever and any concomitant infections (see Section 3).

4. **Interview the case:** Interviews may be conducted utilising the case investigations form provided (Appendix 1). It is especially important to obtain the following information:
    a. **Occupation.** If the case is a food handler, or if the case provides care for patients, children or the elderly, they should be excluded from those activities until at least 3 consecutive negative cultures, meeting the criteria outlined in Step 6 below, are obtained.
    b. **Source of infection.** Investigate the source of infection, perform additional environmental investigations where indicated and intervene where a source can be identified.

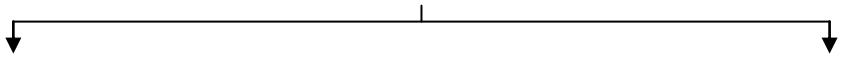
5. **Educate the case and care-givers:** Conduct health promotion to educate the case/care-givers about typhoid fever infection and transmission. Emphasise the importance of good hygiene practices, in particular hand washing before eating and preparing food, and after going to the toilet to prevent further infections.

6. **Case follow-up:** All confirmed typhoid fever cases should be followed-up as outlined below:
    a. Collect three clearance stool samples for *Salmonella* Typhi culture (as per Section 2.2.2). Rectal swabs may be collected if stool cannot be obtained. The first sample should be obtained one week after completion of antibiotics. Subsequent samples should be collected 48 hours apart. If case originally had a positive urine culture, a history of urinary tract infection and/or a history of schistosomiasis (bilharzia), collect urine samples for culture in addition to stool samples.



All three cultures negative: If three consecutive cultures are all negative as per above criteria → release the case from surveillance

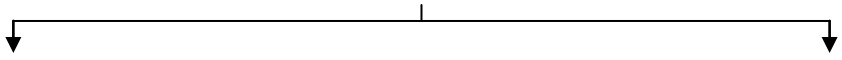
Any of the three samples culture-positive::
1. Consider retreatment (second course of antibiotics – as per section 3.2, Table 1).
2. Collect another three clearance stool samples (first sample one week after completing antibiotics; subsequent samples collected 48 hours apart).



All three cultures negative: If three consecutive cultures are all negative → release the case from surveillance

Any of the three samples culture-positive

Convalescent carrier:
1. Consider 4-6 weeks of treatment with appropriate antimicrobial (see section 3.4).
2. Repeat stool samples monthly.



A negative monthly sample
Collect two further samples 48 hours apart

All three samples negative
→ release the case from surveillance

Positive monthly samples

1. Continue monthly stool sample collection
2. Consider investigation for possible causes of prolonged carriage (see section 3.4)

Positive monthly samples after 12 months of repeat sampling: Chronic carrier
Refer for specialist opinion and management.

7. **Contact management:** Identify contacts at risk of infection, which may include: household members, care givers of the case, and people who may have eaten the implicated food/water/beverages. The following response should be completed for all contacts at risk of infection:
    a. Collect 2 stool/rectal swab samples, ≥48 hours apart, for *Salmonella* Typhi culture (as per Section 2.2.2).
    b. Interview all contacts by completing the line-list at the end of the case questionnaire (Appendix 1)
    c. Educate all contacts on typhoid fever infection, transmission, prevention, and recognising symptoms and seeking medical care if these occur.
    d. If any cultures are found to be positive, refer that contact for treatment and complete the response steps 1-7 for that person. If any laboratory-confirmed contacts are employed as food handlers, or caring for patients/children/elderly, they should be excluded from these activities and redeployed as far as possible. Identification of *Salmonella* Typhi from stool is suggestive of typhoid fever when associated with a clinically compatible illness. *Salmonella* Typhi in the absence of clinical illness may be suggestive of *Salmonella* Typhi carriage.

6 Public health response to a cluster or outbreak

An outbreak of typhoid fever is defined as two or more epidemiologically-linked suspected or confirmed cases. All outbreaks must be immediately notified to health authorities for investigation and response. These activities should be coordinated by the local level Department of Health offices in collaboration with stakeholders, which may include:

- District, Provincial and National Department of Health: Communicable Disease Control, Environmental Health, Epidemiology and Surveillance, Disaster Management, Infection Control, etc.
- NHLS diagnostic laboratories, NICD-NHLS Outbreak Response Unit and Enteric Diseases Reference Unit (EDRU), private laboratories.
- Intersectoral stakeholders when required, e.g.: Department of Water Affairs, Department of Agriculture, Department of Education, etc.

Investigation and response efforts will differ depending on the situation; however, the following elements should always be included:

- **Verify the diagnosis and confirm the existence of an outbreak:**
    - Conduct laboratory testing on all (or as many as possible) suspected typhoid fever cases as per Section 2.

- Conduct preliminary interviews to establish if any epidemiological links between cases exists. Links between cases may include: common place of residents, gatherings, foods consumed, travel, etc.

- **Communication:** Rapid communication and reporting of information, even if only preliminary, is essential to coordinating an efficient and effective response to potential outbreaks. Communicate findings frequently to all stakeholders concerned.

- **Case finding, investigations and follow-up:**
  - Establish systems at local level for detecting new cases and for recording existing cases. This may should include establishing a line-list at each local healthcare facility (clinic and hospitals) for monitoring the outbreak.
  - Investigate cases using a standardised case investigation for (see appendix 1 for example) to identity factors/histories that are common between cases (i.e. identify the source). Data collected should be rapidly analysed and shared with stakeholders to inform ongoing and future response.
  - If feasible (i.e. a small cluster of cases), complete the steps outlines in section 4 for each case.

- **Review case management and treatment:** Ensure all cases are receiving appropriate treatment for typhoid fever and any concomitant infections (see Section 3) to reduce morbidity and mortality.

- **Conduct environmental investigations:** Where indicated food, water and/or other environmental samples may be collected for the *Salmonella* Typhi culture. Such samples should be collected by qualified Environmental Health practitioners as per standard protocols.

- **Control and prevention:**
  - If a source infection can be identified, respond rapidly to interrupt this, and prevent additional infections.
  - Conduct health promotion campaigns on the prevention of typhoid fever in the local community (see section 6.

7 Prevention and control

The prevention of typhoid fever is primarily based on ensuring access to safe water, food safety and proper sanitation infrastructures. Health promotion and education is paramount to raising public awareness about these practices and inducing behaviour change within a community. This intervention should especially be implemented for each and every known case and his/her contacts. Vaccination against typhoid are available in South Africa; however, these are only indicate for laboratory staff that work regularly with the pathogen and may also be considered for travellers for highly endemic settings. The limitations of these vaccines should be noted and should note detract against the primary measures of preventing infections.

7.1 Safe water

Both sporadic cases and outbreaks of typhoid fever have been associated with poor quality water for drinking and other domestic activities (cooking, washing, etc.). An overall reduction in disease burden may be achieved through ensuring access to safe water throughout the community. Likewise, provision of safe water may play a role in controlling outbreaks (when suspected as the source) as well as preventing additional settings within the household setting. Response measures may include:

- **In areas with access to municipal water systems:** enhanced monitoring of water throughout the supply systems (from point of treatment to consumer outlets), and ensuring appropriate water treatment (e.g. adequate chlorine concentrations to disinfect the water).
- **In areas without access to treated water:**

- Monitoring of drinking water sources, and treating of these if practical (e.g. in the case of JoJo tanks, wells).
- Provision of alternative water sources (e.g. supply safe/treated water using water-tankers, JoJo tanks)
- Distribute resources and conduct health promotion activates for point-of-use disinfection water within households. Disinfection methods may include boiling and/or chemical disinfectants (chlorine bleach, tablets, etc.). Safe storage and use of water also plays an important role in preventing secondary spread in households (for example: use plastic narrow-mouthed containers with covers to avoid recontamination after treatment).

7.2 Food safety

Contaminated food plays and important role in the transmission of typhoid fever. Following identification of a case, food safety should be promoted with households to prevent transmission to close contacts. This should include:

- Wash hands with soap and clean water before preparing and eating food, and after going to the toilet.
- Wash all surfaces and equipment used for food preparation with soap and clean water.
- Cook food thoroughly, avoid raw (uncooked) food (especially shellfish and meats). Eat only cooked and still hot food or reheat it.
- Use only safe water for preparing food, beverages and ice (or treat water before using).
- Wash and peel all fruit and vegetables before eating (especially when eaten raw)
- Do not use fertilisers that contain human-waste (excreta or faeces) on vegetable gardens or crops.

Acute cases and proven carriers who handle, process and/or serve food (especially in commercial settings) should be excluded from these activities pending treatment and follow-up testing (as per Section 4).

In outbreak situations, food safety behaviours should be reinforced at a community level. Food safety inspections at restaurants and street vendors, and ensuring compliance with regulations, will also play an important role in preventing infections.

7.3 Sanitation

Provision of proper sanitation infrastructures will also reduce the burden of typhoid fever, as well as other enteric diseases, within a community. Ensure appropriate systems for human-waste disposal and sewage treatment for all community members, monitor these systems continually, and maintain proper functioning at all times. In areas without municipal sewage systems, toilets (e.g. pit-latrines) should be built, regularly serviced and maintained to ensure safe functioning. Restrict access of the general public to sanitation infrastructure to prevent human-excreta from being used as fertilisers. Rapid provision of safe sanitation infrastructures (e.g. building pit-latrines) or investigating, and fixing faults in existing sanitation systems, may also play a role in controlling outbreaks.

7.4 Vaccination

Vaccination is indicated for laboratory staff that work regularly with *Salmonella* Typhi. It may also be considered for travellers to highly endemic countries (see Section 6.5).

The Vi purified polysaccharide antigen vaccine (available as Typhim Vi® (Sanofi Pasteur) and Typhix® (GlaxoSmithKline)) is currently the only typhoid vaccine registered for use in South Africa. This vaccine is administered as single dose (deep subcutaneous or intramuscular) and becomes effective 2-3 weeks after injection. It offers protection against *Salmonella* Typhi for 60-75% of recipients, and remains effective for a minimum duration of 3 years, but may be as long as 10 years. Children < 18 months old may show a suboptimal response to polysaccharide antigen vaccines. Furthermore, typhoid is rare in children < 2 years old; therefore, the decision to immunise should be based on risk of exposure. Limited data are available on use during pregnancy; therefore, should only be considered when benefits outweigh risks. This vaccine does not protect against *Salmonella* Paratyphi infection.

Typhoid vaccination is not recommended for contacts of identified cases due to the extended duration required to infer protection. However, vaccinations may be considered in the control of outbreaks in certain situations, but the limited effectiveness of this strategy must be acknowledged and such campaigns should not detract from the primary control interventions (i.e. safe water, food safety and proper sanitation). Routine typhoid vaccinations have shown to be effective in controlling disease in endemic settings; however, this is currently not recommended in South Africa.

7.5 Travellers

Returning travellers make up a large proportion of typhoid fever cases detected in South Africa. Travellers should be advised to:

- Drink only water that is bottled or bring it to a rolling boil for at least 1 minute. Bottled carbonated water is generally safer than uncarbonated water.
- Avoid ice and food products (e.g. ice cream) that are potentially made with contaminated water.
- Eat foods that have been thoroughly cooked and that are hot and steaming. Avoid raw vegetables and fruits that cannot be peeled.
- Peel the fruit and vegetables yourself after washing your hands with soap. Do not eat the peelings.
- Avoid foods and beverages from street vendors and informal sellers.

Travellers to highly endemic areas (including south-central Asia, south-east Asia and parts of Africa), or areas with ongoing typhoid fever outbreaks, may consider vaccination. These may be obtained from most travel clinics and should be given at least 2 weeks before departure. Given the limitations of vaccination, it is important to emphasise scrupulous personal, food and water hygiene at all times during travel.

7.6 Post exposure prophylaxis

Post exposure prophylaxis for health care workers and contacts of persons with confirmed typhoid is not advised. The infective dose of typhoid is 10^5 organisms/ml. Therefore the risk of transmission is low. A 'watch and see' approach is advised, with investigation of any febrile illness occurring within 21 days of contact.

8 Resources and additional information

Further questions from health professionals can be addressed to:

- The NICD Hotline - 082 883 9920 ***strictly for use by health professionals only***

Further questions from the general public and all other queries can be directed to:

- The Department of Health Communicable Disease Control hotline: 0861-DOH-CDC (0861-364-232)

Additional information on typhoid fever is available from the following references:

- Centers for Disease Control and Prevention (CDC). Typhoid fever: General information. Available online: http://www.cdc.gov/nczved/divisions/dfbmd/diseases/typhoid_fever/. Last accessed 29 April 2011.
- World Health Organization (WHO). Background document: The diagnosis, treatment and prevention of typhoid fever. Available online: http://whqlibdoc.who.int/hq/2003/WHO_V&B_03.07.pdf. Last accessed 29 April 2011.
- World Health Organization (WHO). Health topics: Typhoid fever. Available online: http://www.who.int/topics/typhoid_fever/en/. Last accessed 29 April 2011.
- World Health Organization (WHO). Typhoid vaccines: WHO position paper. Weekly epidemiological record, 2000: 75(21), 257-264.

9 Appendix 1: Suspected/confirmed typhoid fever case investigation form

INTERVIEWER DETAILS	
1. Interviewer name:	**2. Date of interview:** DD / MM / YYYY
3. Interviewer phone no.:	**4. Department:**

PATIENT DETAILS		
5. First name & Surname:		
6. Age/DOB:	**7. Gender:** ☐ Male ☐ Female	
8. Phone no.:		
9. Town/City:	**District:**	**Province:**
10. Occupation:	**11. Place Of Work:**	
12. Works in a food handling trade? ☐ Y ☐ N		
13. Works in a child/elderly/health care-giving setting? ☐ Y ☐ N		
If yes to 12 or 13, was the case restricted from these activities? ☐ Y ☐ N		

DISEASE PRESENTATION

14. Date of onset? DD / MM / YYYY

15. Symptoms: ☐ Fever ☐ Vomiting ☐ Abdo Cramps ☐ Malaise/Fatigue

(tick all that apply) ☐ Headache ☐ Constipation ☐ Myalgia ☐ Respiratory symptoms (e.g. cough)

☐ Nausea ☐ Diarrhoea ☐ Anorexia ☐ Rose Spots

☐ Other, Specify: _____

16. Complications (list all)**:**

17. Outcome: ☐ Recovered ☐ Still ill ☐ Died, date of death: DD / MM / YYYY

CLINIC/HOSPITAL DETAILS	
18. Name of the clinician:	**15. Phone no.:**
19. Facility name:	**17. Date of 1st consultation:** DD / MM / YYYY
20. Name of referring facility (if applicable):	
21. Admitted to hospital? ☐ Y ☐ N	**If yes, duration of stay?** _____days
22. Was the case notified to DoH? ☐ Y ☐ N ☐ Unknown	

LABORATORY INVESTIGATIONS

23. Date of specimen collection: DD / MM / YYYY

24. Lab name:	**25. Lab number:**

27. Test performed for typhoid diagnosis: ☐ Blood Culture ☐ Stool Culture

☐ Other, specify:_____

29. Result of above test: ☐ Pos ☐ Neg ☐ Unknown ☐ Other, Specify:

30. Follow-up testing: (tick all tests performed)

☐ Stool culture 1 Date collected: DD / MM / YYYY Result: ☐ Pos ☐ Neg

☐ Stool culture 2 Date collected: DD / MM / YYYY Result: ☐ Pos ☐ Neg

☐ Stool culture 3 Date collected: DD / MM / YYYY Result: ☐ Pos ☐ Neg

☐ Additional/other follow-up tests, give details: _____

EXPOSURE QUESTIONS

31. Have you travelled outside of your home town/city within 1 month before your illness started? (include local and international travel)

☐ Y ☐ N

If yes, list all places/countries visited: _____

date departed: DD / MM / YYYY **date returned:** DD / MM / YYYY

32. Have you had any visitors from outside your home town/city within 1 month before illness onset? (include local and international travel)

☐ Y ☐ N

If yes, where did they come from: _____

33. Have you been in contact with anyone with similar illness to yours in the 1 month before your illness started? ☐Y ☐N

If yes, list names and contact details:

Name	Phone no.	Address

34. Have you eaten at any of the following places within 1 month before your illness started?

Type		Name/Address/Phone no.
Café / Restaurant	☐ Y ☐ N	
Street vendor / Market place	☐ Y ☐ N	
Fast food	☐ Y ☐ N	
Other, specify:		

35. Housing type: ☐Formal housing ☐Dwelling outside house ☐Informal settlement ☐Traditional house ☐Hostel/Institution

36. Number of people living in the house: _____

37. Source of drinking water: ☐ Municipal tap in house or on property ☐ Municipal tap off the property (communal tap)

☐ Jo-Jo tank ☐ Borehole water ☐ Open source water (e.g. from a river, stream, dam, etc.)

☐ Other, specify? _____

38. Do you store water in your home? ☐Y ☐N

If yes, in what type of container is water stored? (tick all that apply)

☐ Plastic container ☐ Metal container ☐ Open container ☐ Closed container with lid

How is water removed from the container? (tick all that apply)

☐ With hands ☐ With a spoon/cup/jug ☐ With a tap ☐ Other, specify: _____

39. What type of toilet do you have in your home?

☐ Flush toilet ☐ Chemical toilet ☐ Pit latrine ☐ No toilet ☐ Other, specify: _____

40. Do you have a kitchen/special area for preparing food only in your home? ☐Y ☐N

41. Who prepares most of the meals in your home? (name and relationship to case): _____

Does he/she wash hands before preparing food? ☐Y ☐N

Has he/she ever had a similar illness to yours? ☐Y ☐N

42. Do you grow your own vegetables at home? ☐Y ☐N

If yes, from where do you get the water for your vegetable garden? _____

What do you use to fertilise your vegetable garden? _____

Additional notes / comments / actions taken:

ENVIRONMENTAL ASSESSMENT

45. List all environmental samples collected: (if applicable)

Type of sample (food/water/milk)	**Place / Address where collected**	**Lab no.**	**Result**

Name of lab(s) processing samples: _____

CONTACT TRACING

1. Identify contacts at risk of infection, including: household members, care-givers of the case, and people who may have eaten the implicated food or water/beverages.
2. Investigate all contacts as per guidelines. List all below:

Name	**Age** (years)	**Sex** (M/F)	**History of typhoid fever** (Y/N)	**Occupation**	**Address**	**Stool sample collected** (Y/N)	**Lab result**	**Referred for treatment** (Y/N)