Typhoid

and other invasive salmonellosis

World Health Organization

DISEASE AND VACCINE CHARACTERISTICS

Enteric fever (typhoid and paratyphoid fever) is caused by *Salmonella enterica* serovar Typhi *(S.* Typhi*)* and *Salmonella enterica* serovar Paratyphi *(S.* Paratyphi). *S.* Paratyphi A and B (and, uncommonly, *S.* Paratyphi C) cause a disease that is clinically indistinguishable from typhoid fever, particularly in parts of Asia. Invasive non-typhoidal[1] salmonellosis (iNTS) is an invasive infection caused by non-typhoidal serovars of *S. enterica,* most commonly *S. enterica* serovars Enteritidis and Typhimurium. Collectively, invasive *Salmonella* infections are responsible for a significant burden of morbidity and mortality worldwide. There are an estimated 11–21 million cases of typhoid fever and approximately 128 000–161 000 deaths annually, compared to an estimated 6 million cases of paratyphoid fever and 54 000 deaths annually *(1, 2, 3, 4)*. The majority of cases occur in South and South-East Asia and sub-Saharan Africa.

An estimated 2.1– 6.5 million cases of iNTS disease occur annually, with the highest incidence in Africa *(5)*. The risk of iNTS is highest in infants, young children and young adults with underlying comorbidities, including severe anaemia, malaria, malnutrition and HIV infection. The case fatality rate is high in those with HIV infection.

Typhoid fever is an acute, life-threatening, febrile illness. Without treatment, the case fatality rate of typhoid fever is 10–30%, dropping to 1–4% with appropriate therapy *(6)*. Young children are at greatest risk. Common symptoms include sustained fever, chills and abdominal pain. The non-specific symptom profile complicates clinical diagnosis, with symptoms that are common to other diseases occurring in typhoid-endemic areas. The mainstay for laboratory confirmation is blood culture but this has limited sensitivity of approximately 40–60% *(7)*, due in part to the widespread use of antimicrobials before patients present to a health service. The emergence of antimicrobial resistance is a significant challenge, with several recent large outbreaks caused by multidrug-resistant *S.* Typhi in Africa and Asia.

There are three types of typhoid vaccines licensed for use:

➤ the newer generation typhoid conjugate vaccine (TCV), with currently licensed products consisting of Vi polysaccharide antigen linked to tetanus toxoid protein

➤ the unconjugated Vi polysaccharide (ViPS) vaccine

➤ the live attenuated Ty21a vaccine.

In 2018, WHO recommended the first prequalified TCV for intramuscular administration of a single dose (0.5 mL) in children ≥ 6 months of age and in adults up to 45 years of age. The ViPS vaccine is recommended for intramuscular or subcutaneous administration in individuals 2 years of age and older. Ty21a vaccine is available in enteric-coated capsules recommended for oral administration on alternate days in a three-dose regimen (or a four-dose regimen in Canada and the US) in persons above 6 years of age. Repeat vaccination is recommended for ViPS every three years, and for Ty21a every three to seven years in most endemic settings or every one to seven years for travellers from non-endemic to endemic areas, depending on national policies *(6)*.

There are currently no licensed vaccines against paratyphoid fever and iNTS disease.

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[1]   *Non-typhoidal refers to* Salmonella *enterica serovars other than* S. *Typhi and* S. *Paratyphi which are known as typhoidal serovars.*

RATIONALE AND OBJECTIVES OF SURVEILLANCE

The objectives of surveillance for typhoid fever and other invasive salmonellosis are to:

➤ determine the epidemiology and disease burden for typhoid fever, paratyphoid fever and iNTS to facilitate and support control strategies

➤ facilitate the rapid detection of outbreaks and response to outbreaks

➤ guide the introduction of vaccination and other control strategies in a country, given significant heterogeneity in disease burden across geographic areas and populations

➤ monitor impact of vaccination on disease and potential changes in epidemiology

➤ evaluate other (non-vaccine) prevention and control measures

➤ monitor antimicrobial resistance patterns among *Salmonella* isolates, which can inform treatment practices and, in some instances, the need for vaccination campaigns

➤ in non-endemic settings, identify imported cases among returned travellers or migrants (which can provide indirect measures of risk in countries visited) and support pre-travel vaccine advice or contact tracing as needed.

TYPES OF SURVEILLANCE RECOMMENDED

MINIMAL SURVEILLANCE

The needs and objectives of each country should guide the recommendations for type of surveillance. In endemic settings, laboratory-based, facility-based surveillance is recommended as a minimum. This may be through routine passive reporting of positive laboratory results for invasive *Salmonella* to a surveillance system, or through an active approach requiring review of laboratory records to identify patients meeting the confirmed case definitions. Countries may decide on the minimum set of clinical data to be collected and reported in laboratory-based surveillance (see section on **Data collection, analysis and use**). Ideally, one or more sentinel sites should be considered for each geographical area of interest. It is important to understand that there is marked heterogeneity of incidence within countries, and greater representation of diverse ecological settings within a country will improve assessment of burden.

ENHANCED SURVEILLANCE

Population-based surveillance is time- and resource-intensive; it is most suited to short periods of time. Passive laboratory or facility-based surveillance may be appropriate as a routine ongoing monitoring system to meet objectives that do not require complete ascertainment of cases.

Population-based surveillance that seeks to estimate incidence of disease and disease outcomes within a given catchment area can generate additional data that may be used to build the case for vaccination or other programmatic interventions. In particular, this may provide baseline disease burden data for monitoring the impact of intervention(s). For countries that are primarily seeking to understand disease burden or vulnerability to outbreaks for different areas or population subgroups, disease burden data across a large area may be needed due to the wide and often unpredictable variation in prevalence of infection between, and even within, geographic areas.

Collection and reporting of antimicrobial susceptibility data can be readily incorporated into any of the types of surveillance outlined above.
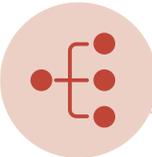
LINKAGES TO OTHER SURVEILLANCE

In order to have a sustainable system for reporting morbidity and mortality from typhoid and other invasive salmonellosis, surveillance should be integrated into existing health events reporting systems, such as the Integrated Disease Surveillance and Response (IDSR) system or Health Management Information Systems (HMIS). Countries that report "enteric fever" through existing surveillance systems should adopt the pathogen-specific case definitions detailed here. Surveillance for invasive *Salmonella* infections can be integrated with surveillance for other invasive bacterial vaccine-preventable diseases, such as pneumococcal disease.

TABLE 1

Other types of surveillance for typhoid and other invasive salmonellosis

TYPE OF SURVEILLANCE	DESCRIPTION
FACILITY-BASED (SENTINEL) SURVEILLANCE	Cases may be identified by retrospective review of health facility records for patients with symptoms consistent with typhoid or paratyphoid fever, or by laboratory registers for patients with positive results. This relies on the information generated through routine clinical care and laboratory findings. No specific effort is made to screen all potential typhoid fever and paratyphoid fever cases meeting pre-defined criteria.
	A more intensive facility-based approach is to identify and document cases meeting defined criteria at the time of presentation or admission, and refer them for laboratory testing. This may be conducted in one or a small number of sites (sentinel site surveillance), rather than nationwide.
	In this approach, the suspected case definition may be used to identify cases for laboratory testing. Cases can then be categorized according to the confirmed case definition.
HYBRID SURVEILLANCE	Hybrid surveillance uses a combination of facility-based surveillance with the collection of additional population epidemiological data, which serves as correction factors in the estimation of incidence rates *(8)*. Additional information collected typically includes health service utilization for symptoms that are consistent with the disease under surveillance and estimation of the catchment population. Follow-up with patients in the community may also be undertaken to document mortality or other morbidities after contact with the health service.
	The suspected case definition may be used to identify cases for laboratory testing. Cases can then be categorized according to the confirmed case definition.
POPULATION-BASED ACTIVE SURVEILLANCE	This aims to identify all enteric fever cases within a defined population. It requires community and household visits to identify cases.
	The suspected case definition may be used to identify cases for laboratory testing. Cases can then be categorized according to the confirmed case definition.

CASE DEFINITIONS AND FINAL CLASSIFICATION

SUSPECTED CASE OF TYPHOID OR PARATYPHOID FEVER FOR CASE FINDING

➤ Fever for at least three out of seven consecutive days in an endemic area or following travel from an endemic area

   OR

➤ Fever for at least three out of seven consecutive days within 28 days of being in household contact with a confirmed case of typhoid or paratyphoid fever

Countries may opt to use additional criteria to exclude other diagnoses that are appropriate to their setting, such as malaria and dengue.

SUSPECTED CASE OF INVASIVE NON-TYPHOIDAL SALMONELLOSIS (INTS) FOR CASE FINDING

A case definition for suspected iNTS is not provided due to the high degree of non-specificity in clinical presentation. iNTS should be considered as a differential diagnosis in the presence of an acute febrile illness in those at risk in an endemic setting, including those immunocompromised by disease or malnutrition.

CONFIRMED CASES

➤ **Typhoid fever:** Laboratory confirmation by culture or molecular methods of *S.* Typhi or detection of *S.* Typhi DNA from a normally sterile site.

➤ **Paratyphoid fever:** Laboratory confirmation by culture or molecular methods of *S.* Paratyphi A, B, or C or detection of *S.* Paratyphi A, B, or C DNA from a normally sterile site.

➤ **Invasive non-typhoidal salmonellosis (iNTS):** Laboratory confirmation by culture or molecular methods of non-typhoidal *Salmonella* or detection of non-typhoidal *Salmonella* DNA from a normally sterile site.

➤ **Relapse of typhoid or paratyphoid fever:** Laboratory confirmation of *S.* Typhi or *S.* Paratyphi from a normally sterile site within one month of completing an appropriate course of antimicrobial treatment and resolution of symptoms.

CHRONIC CARRIERS

➤ **Presumptive carrier:** Evidence of shedding of *Salmonella* spp. (positive stool culture or PCR) of an unknown duration.

➤ **Definitive carrier**

» Evidence of shedding of *Salmonella* spp. (positive stool culture or PCR) at least 12 months after finishing an appropriate course of antimicrobial treatment and the resolution of symptoms following a laboratory-confirmed episode of acute disease

OR

» Two positive stool samples 12 months apart.

➤ **Convalescent carrier:** Evidence of shedding *Salmonella* spp. (positive stool culture or PCR) 1–12 months after finishing an appropriate course of antimicrobial treatment and the resolution of symptoms following a laboratory-confirmed episode of acute disease.

CASE INVESTIGATION

Case and laboratory report forms should be completed (manually or electronically) for patients meeting case definition criteria in the surveillance system. When patients who meet the criteria are identified during contact with the health service, the case and laboratory report forms may be filled to the extent possible at the time of patient contact. Where appropriate, as in active surveillance, the suspected case definition may be used to identify patients for laboratory testing. Relevant clinical specimens should be collected as soon as possible, ideally before the commencement of antimicrobial treatment. It is important for the surveillance team to ensure that appropriate follow-up is done to complete the case or laboratory report forms with the laboratory results when they are available.

Where cases are identified retrospectively through review of clinical or laboratory records, a case report form should be completed at a minimum for each confirmed case, drawing on information from available clinical records. Due to the low positive predictive value of the suspected case definition, only confirmed cases should be reported by passive systems.

More detailed field investigation of cases may be required in outbreaks but is not required for routine surveillance.

SPECIMEN COLLECTION

Blood is the preferred clinical sample for the diagnosis of enteric fever and invasive nontyphoidal *Salmonella* infections *(9)*. Blood should be collected prior to administration of antimicrobials whenever possible; however, this should not delay necessary care for critically ill patients. The blood specimen for culture should be collected as early as possible in the course of the disease.

Bacterial load in acute typhoid is low, an average of < 1 cfu/mL of blood, and is maximal during the first week of illness. For this reason, it is vitally important to ensure that the volume of blood is optimal for inoculation in broth culture bottles. Insufficient blood volumes reduce the likelihood of laboratory confirmation of an enteric fever diagnosis. The commercially prepared blood culture bottles include instructions to determine the appropriate amount of blood to be inoculated into each bottle. Bottles prepared in-house are typically inoculated with a 1:10 ratio of blood to broth. The volume of blood is determined according to patient age, as shown in the table below. If an adult bottle is used for older children, care should be taken to maintain the ratio of blood to broth.

TABLE 2

Guide to volumes of blood to be collected for blood culture according to age of the patient

PATIENT AGE	BLOOD VOLUME FOR CULTURE BOTTLES CONTAINING 40 ML OF BROTH (PAEDIATRIC)	BLOOD VOLUME FOR CULTURE BOTTLES CONTAINING 80 ML OF BROTH (ADULT)
3 MONTHS–< 2 YEARS	1–2 mL	
2 YEARS–< 5 YEARS	2–3 mL	
5–< 15 YEARS	5–10 mL	
ADULT (> 15 YEARS)		8–10 mL

Blood specimens should be transported in the sealed bag to the microbiology laboratory as soon as possible, to initiate the incubation period at proper temperature. Bottles should be kept at room temperature during transport and should never be refrigerated after inoculation. If transportation to the laboratory is likely to be delayed by > 4 hours, contact the laboratory for guidance on interim storage of inoculated bottles.

Stool culture may be used for the detection of chronic carriers and to monitor faecal shedding in patients following acute typhoid fever. Faecal shedding may be sporadic, and different guidelines exist on the number and frequency of specimens to be submitted for culture. As general guidance, countries may consider initially screening three stool samples taken 24 hours apart, or at least seven samples after completion of antimicrobials. If any of these initial samples are positive, testing of additional specimens (collected at longer intervals) may be advised *(10)*.

LABORATORY TESTING

Laboratory confirmation should always be sought for clinically suspected cases. Confirmation by culture (or validated molecular methods, as available) is essential as typhoid fever, paratyphoid fever and other invasive salmonellosis can present as a non-specific febrile illness, and current serological tests lack diagnostic specificity. Confirmation is essential to assess the proportion of enteric fever caused by these different organisms, determine antimicrobial susceptibility and do molecular epidemiology studies.

Blood culture is currently the preferred laboratory method in most endemic settings for the diagnosis of enteric fever and invasive nontyphoidal *Salmonella* infections. While bone marrow culture has been shown to be approximately 50% more sensitive than blood culture, it is an invasive procedure that is impractical in most endemic settings and not appropriate for public health surveillance *(9)*. Bone marrow specimens may still be submitted for culture when clinically indicated, for example, if other reticuloendothelial infection or malignancy is suspected. The test's enhanced sensitivity may also be useful in selected patients who have been heavily treated with antimicrobials.

While blood culture is the most common method for laboratory confirmation, it has several limitations including relatively poor sensitivity, particularly when only one sample is collected and there is extensive use of antimicrobials prior to health centre or hospital presentation. As such, many clinically suspected enteric fever cases may lack laboratory confirmation and be culture-negative.

Stool culture is not recommended for the diagnosis of acute enteric fever. A brief period of asymptomatic faecal shedding typically occurs following *Salmonella* infections; a subset of these patients will progress to long-term, asymptomatic carriage. Stool culture may thus be used for the detection of chronic carriers and to monitor faecal shedding in patients following acute typhoid fever.

Although serologic tests are commonly used in many settings, current evidence suggests that these tests are limited by poor sensitivity and inadequate specificity, and so are inappropriate for use in routine surveillance *(11)*.

Several investigational serologic assays appear to show promise, but these are not commercially available at this time.

All microbiology laboratories reporting *Salmonella* data should have an external quality assurance and quality control system implemented at all stages, including:

➤ The minimum standard recommended for blood culture confirmation is to use a semi-automated system that will support isolation of common pathogens associated with vaccine preventable diseases.

➤ Biochemical testing algorithms used for bacterial identification should be able to at least differentiate between *Salmonella* serovars Typhi, Paratyphi A and *Salmonella* spp. (not serovar Typhi or Paratyphi A).

➤ Steps should be taken to minimize blood culture contamination rates, including the setting of target contamination rates.

ANTIMICROBIAL SUSCEPTIBILITY TESTING

It is recommended that antimicrobial susceptibility testing be routinely done and reported to national authorities and international networks such as the Global Antimicrobial Resistance Surveillance System (GLASS) (www.who.int/glass/en/). This is critical given the rise in multidrug-resistant *S.* Typhi. Susceptibility results from clinical samples are critical for patient management. Understanding local and regional susceptibility trends can also guide empiric therapy, particularly when individuals may have acquired the infection during travel. Monitoring and reporting of antimicrobial susceptibility can guide public health decision-making on the need for control strategies including vaccination.

Susceptibility testing should be conducted using quality control guidelines such as the European Committee on Antimicrobial Susceptibility Testing (www.eucast.org) or the Clinical and Laboratory Standards Institute (www.clsi.org). Below are recommendations for antimicrobial susceptibility testing:

➤ *S.* Typhi and *S.* Paratyphi A should be tested for their susceptibility to ampicillin, chloramphenicol, co-trimoxazole, ciprofloxacin or pefloxacin,

ceftriaxone and azithromycin. This panel may be expanded based on local resistance patterns or prescribing practices. In a resource-limited setting, this panel may be abbreviated to only include drugs used for empiric therapy (such as ceftriaxone and ciprofloxacin). It is very important to store bacterial isolates or refer them to a national or regional reference laboratory if further testing is needed.

➤ For other invasive *Salmonella* serovars, antimicrobial susceptibility testing should be further supplemented with a carbapenem, tigecycline, an aminoglycoside, and three additional third-generation cephalosporins such as ceftazidime, cefpodoxime or cefotaxime.

THE USE OF REFERENCE LABORATORIES

➤ *Salmonella* isolates from sporadic cases can be sent to a reference laboratory for further characterization. Information derived from

reference laboratory characterization may assist in identifying unsuspected outbreaks. Similarly, further characterization of isolates collected during a suspected outbreak is recommended to support epidemiological investigations. In each case, work with the reference laboratory to determine whether it is best to submit all isolates or just a representative subset. Whenever possible, strains with unusual resistance should be sent for confirmatory testing at a reference laboratory.

➤ The selected reference laboratory should have the capacity to 1) serotype *Salmonella* using conventional or molecular methods, 2) molecularly subtype *Salmonella* using standardized, internationally comparable molecular epidemiology techniques, and 3) conduct confirmatory susceptibility testing, including molecular characterization of resistance mechanisms.

DATA COLLECTION, REPORTING AND USE

RECOMMENDED DATA ELEMENTS

In systems where case-based data are collected for reporting and investigation, the following parameters are recommended for collection. It is important to ensure that clinical data are linked to laboratory data for each case.

➤ Unique identifier

➤ Date of report

➤ Age/date of birth

➤ Sex

➤ Country of birth

➤ Place of residence (city, district and province)

➤ Travel history within the last 28 days before illness onset for persons not living in endemic settings (places and dates)

➤ Household contact with a confirmed case of typhoid or paratyphoid fever in the 28 days before illness onset

➤ Fever for at least three out of seven consecutive days

➤ Date of fever onset

➤ Hospitalization (including date of admission and date of discharge)

➤ Complications (intestinal perforation, encephalopathy)

➤ Abdominal surgery

➤ Outcome/discharge status

➤ Type of specimen(s) collected

➤ Date of specimen(s) collection

➤ Date specimen(s) received in laboratory

➤ Laboratory test(s) undertaken

➤ Laboratory findings, including antimicrobial susceptibility

➤ Final case classification (suspected or confirmed as typhoid fever, paratyphoid fever or iNTS, relapse, etc.[2])

➤ Typhoid vaccination status (if yes, what vaccine used, number of doses and date(s) when each dose was administered)

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[2]   *Depending on the laboratory capacity for serovar identification, biochemical testing may only be able to differentiate between* Salmonella *serovars Typhi, Paratyphi A and* Salmonella *spp. (not serovar Typhi or Paratyphi A) – see* **Laboratory testing** *section.*

REPORTING REQUIREMENTS AND RECOMMENDATIONS

Optimally, data should be reported from a local level to a regional level monthly. Recording and storage of data should be via an electronically stable format.

There are no International Health Regulations (IHR) requirements for reporting of typhoid fever, paratyphoid fever or iNTS. Countries are encouraged to report antimicrobial resistance data to GLASS.

RECOMMENDED DATA ANALYSES

➤ Tabulate confirmed case data by age and geographic area, and report at a national and global level. Suspected case data need not be reported beyond the local level.

➤ As much as possible, case-based data (ideally, linking clinical and laboratory data) should be available for analysis at the national level. If case-based data are not available, then at a minimum aggregate data should be stratified by age, sex and geographical location.

➤ Report the number of deaths associated with confirmed typhoid or paratyphoid fever and iNTS.

➤ Report and summarize antimicrobial resistance data.

USING DATA FOR DECISION-MAKING

➤ Guide decision-making regarding typhoid vaccine introduction or other control strategies.

➤ Monitor antimicrobial susceptibility patterns.

➤ Following TCV introduction in routine immunization, surveillance is important to assess impact of the vaccine on disease burden and antimicrobial resistance. This will be of particular importance in countries that are early adopters of the TCV, and will provide further data for other countries.

SURVEILLANCE PERFORMANCE INDICATORS

TABLE 3

Surveillance performance indicators for typhoid and other invasive salmonellosis

SURVEILLANCE ATTRIBUTE	INDICATOR	TARGET	HOW TO CALCULATE (NUMERATOR / DENOMINATOR)	COMMENTS
COMPLETENESS OF OUTCOME	Percentage of enrolled cases with outcome recorded	≥ 80%	# of enrolled cases with outcome recorded / # of enrolled cases x 100	Based on active surveillance that aims to identify all patients (inpatients and outpatients) who meet pre-defined case definition
BLOOD CULTURE PERFORMED	Percentage of enrolled cases with blood culture performed	≥ 80%	# of enrolled cases with blood culture performed / # of enrolled cases x 100	Based on active surveillance that aims to identify all patients (inpatients and outpatients) who meet pre-defined case definition
COMPLETENESS OF BLOOD CULTURE RESULTS	Percentage of enrolled cases with blood culture performed who had the test result recorded	≥ 80%	# of enrolled cases with blood culture results recorded (positive Salmonella, positive for other pathogen, negative) / # of enrolled cases with blood culture performed x 100	Based on active surveillance that aims to identify all patients (inpatients and outpatients) who meet pre-defined case definition
COMPLETENESS OF ANTIMICROBIAL SUSCEPTIBILITY TESTING	Percentage of laboratory-confirmed cases with antimicrobial susceptibility testing done	≥ 80%	# of laboratory-confirmed cases with antimicrobial susceptibility testing done / # of laboratory-confirmed cases x 100	Based on active or passive surveillance

CLINICAL CASE MANAGEMENT

Treatment of a confirmed case of invasive *Salmonella* infection should be guided by antimicrobial susceptibility testing. Pending case confirmation and antimicrobial susceptibility test results, treatment of suspected cases should be informed by locally recognized patterns of antimicrobial susceptibility. Treatment regimens should be updated if local patterns change. From a public health perspective, a further aim of appropriate antimicrobial treatment is to limit onward transmission, for example, by reducing the duration of faecal shedding and incidence of chronic biliary carriage of *S.* Typhi.

In suspected cases without laboratory confirmation, it is important to perform tests for alternate locally relevant causes of non-specific fever, and to monitor the response to any empirical treatment given. Repeat blood cultures may be considered if the patient is not improving clinically at 72 hours and initial susceptibility results are not available.

CONTACT TRACING AND MANAGEMENT

Contact investigation may be needed (such as in outbreak response), but it is not recommended as standard for routine surveillance.

SURVEILLANCE, INVESTIGATION AND RESPONSE IN OUTBREAK SETTINGS

DEFINITION OF AN OUTBREAK
The definitions below aim to identify typhoid fever occurrence that should trigger an investigation to determine the appropriate public health response. Similar definitions may be adapted for the identification of paratyphoid fever and iNTS outbreaks to trigger the appropriate investigation and response.

The definition of a suspected typhoid fever outbreak should be based on the general definition for a disease outbreak, as follows: an increase in the absolute number of cases occurring in a population over a defined time period, above what would normally be expected for the particular community, geographical area or season. A minimum of two cases confirmed by blood culture should be documented before an outbreak of typhoid fever is confirmed.

Many endemic countries do not have sufficiently established surveillance systems to be able to assess the baseline threshold of typhoid fever occurrence. Potential changes in the existing surveillance system during the periods of comparison should be considered. For example, strengthening the surveillance system may result in increased case ascertainment.

The above definition may be adapted by each country according to the robustness of surveillance data that can improve the understanding of the epidemiology of typhoid fever in the specific setting.

A change in epidemiological, clinical or microbiological patterns, despite having no increase in overall expected occurrence (absolute numbers or incidence rates), should also warrant an outbreak response. In an institutional setting, a lower threshold of change may be warranted to trigger a response.

CHANGES TO SURVEILLANCE DURING AN OUTBREAK
➤ The numbers of confirmed, probable and suspected cases should be recorded and reported a minimum of once per week to the appropriate level (to facilitate the appropriate outbreak response).

➤ Risk factor data should be recorded for all cases. The choice of risk factors to be included is at the discretion of the investigation team.

➤ Information on antimicrobial susceptibility should continue to be collected.

- Surveillance should be enhanced to an active system if possible.

- In an outbreak, environmental surveillance may be useful to identify potential environmental sources of infection. Sampling should be guided by epidemiological or empirical evidence of common sources (for example, sampling of water sources). In the absence of *S.* Typhi detection following environmental sampling, the presence of faecal coliforms should be used as a marker for contamination and a proxy for water quality.

Response to an outbreak should be based on the risk factors identified. Typhoid vaccination is recommended in response to confirmed outbreaks and should be implemented in the context of other interventions such as health education; water, sanitation and hygiene (WASH) improvements; and training of health professionals in diagnosis and treatment.

CASE DEFINITIONS IN OUTBREAKS

The recommended surveillance case definitions during an outbreak are similar to those for routine surveillance, but with additional features when applicable.

- **Suspected case of typhoid or paratyphoid fever**
  - » At least three out of seven consecutive days of fever (with or without additional clinical features observed in the specific outbreak)

    OR

  - » A physician's suspicion of enteric fever (typhoid or paratyphoid)

- **Probable case of typhoid or paratyphoid fever:** Meets the suspected case definition, plus an epidemiological link to the outbreak.

- **Confirmed case of typhoid or paratyphoid fever or iNTS:** Definition is the same as for routine surveillance.

SPECIAL CONSIDERATIONS FOR SURVEILLANCE OF TYPHOID AND OTHER INVASIVE SALMONELLOSIS

- Where laboratory facilities are available, storing of isolates can enable future investigations or studies.

- Where possible, the collection of data on local antimicrobial treatment practices may be helpful for understanding local resistance patterns.

SURVEILLANCE OF CHRONIC CARRIERS

- In non-endemic settings, Vi-antigen testing with stool culture confirmation has been used to identify chronic carriage.

- Microbiological tests on gallbladder samples for *Salmonella* spp. following cholecystectomy performed for routine indications may provide useful information for understanding the local prevalence of chronic carriers.

ILEAL PERFORATION

All cases of non-traumatic ileal perforation in endemic areas or in returning travellers may be considered probable cases of typhoid or paratyphoid fever. Such cases may be tabulated and notified at a national level. This can be done, for example, in the context of outbreaks, and has been used to identify typhoid fever outbreaks *(12, 13)*. The following case definition is recommended:

The presence of non-traumatic ileal perforation in a patient resident in a typhoid-endemic country or in a traveller recently returned from a typhoid-endemic country.

HUMANITARIAN EMERGENCIES

In circumstances of increased typhoid risk such as in humanitarian emergencies, there may be a need to implement a more intensive type of surveillance (for example, facility-based active surveillance) than the existing routine surveillance.

The risk of typhoid fever in humanitarian settings is considered high under any of the following conditions *(14)*:

- large scale contamination of water supply and poor sanitary conditions (as during flooding)

- a typhoid-endemic region

- an area that has experienced one or more large outbreaks in the past five years

- an ongoing typhoid outbreak or an outbreak of diarrhoea, constipation and high-grade fever (≥ 38°C) lasting three or more days, as a proxy for an ongoing outbreak.

ENVIRONMENTAL SURVEILLANCE

Due to the difficulties in culturing typhoid bacteria from environmentally sourced samples, there is not enough evidence to currently recommend environmental sampling of water on a routine basis to test for *S.* Typhi and *S.* Paratyphi (over and above routine water tests, which may already be taking place to ensure basic water standards and requirements are met). Environmental sampling can, however, be part of a response to outbreaks, as described above.

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