



Cholera

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This is a summary of the Global Task Force on Cholera Control's *Interim Guidance on Cholera Surveillance*, available at http://www.who.int/cholera/task_force/GTFCC-Guidance-cholera-surveillance.pdf?ua=1.



DISEASE AND VACCINE CHARACTERISTICS

Cholera is a diarrhoeal disease caused by toxigenic serogroups of the bacterium *Vibrio cholerae*, which can cause rapid dehydration and death. Cholera is closely associated with poverty, poor sanitation and lack of clean drinking water. As such, the cholera burden is concentrated in Africa and southern Asia, accounting for about 99% of worldwide cases. Cholera can be endemic and cause epidemics. Cholera bacteria are spread by direct faecal-oral contamination or ingestion of contaminated water or food. The incubation period is less than 24 hours to 5 days. Only up to 25% of infected persons become symptomatic; of these, 10–20% experience severe disease. Severe disease manifests as acute, profuse watery diarrhoea (“rice water stools”), usually with vomiting. This leads to rapid dehydration, which can result in hypotensive shock, renal failure and death within hours of onset.

The cholera case fatality rate should be below 1% where access to care with proper rehydration services (oral and/or intravenous) is available, but it may reach 5% in the most vulnerable settings. Cholera affects all age groups, although half of the cholera deaths are in

children < 5 years of age. Current estimates of cholera cases range from 1.4 to 4 million, and estimated cholera deaths range from 21,000 to 143,000 (1). However, global burden of cholera is underestimated due to contributing factors such as low reporting, limited epidemiological surveillance and lack of laboratory capacity.

Two types of killed whole-cell oral cholera vaccines are available: a monovalent (O1) vaccine with a recombinant B subunit of the cholera toxin, and a bivalent (O1 and O139) without the B subunit. The vaccines are given as two- or three-dose regimens. Neither vaccine is recommended for infants. Cholera vaccines are recommended in endemic settings, during cholera outbreaks and in humanitarian crises with risk of cholera. WHO has maintained a stockpile of cholera vaccine since 2013 to be used in these situations, upon request of the country. Cholera vaccines should always be used in conjunction with other cholera prevention and control strategies (see Box 1).

BOX
1

Prevention of cholera through non-vaccine strategies

Vaccination is not the primary preventive strategy for cholera. The mainstay of cholera prevention and control is access to clean potable water, adequate sanitation, and promotion of good water, sanitation and hygiene (WASH) practices. Other preventive efforts should include promotion of hand-washing and safe food handling practices. Moreover, cholera can be effectively treated with rehydration, and resources should be devoted to improving access to effective care. Cholera vaccination can be complementary to these activities, implemented in the short-to-medium term while access to primary prevention through WASH and other control measures improves globally (2).



RATIONALE AND OBJECTIVES OF SURVEILLANCE

The objectives of cholera surveillance are to:

- detect and characterize cholera outbreaks
- identify high-risk areas and vulnerable populations to guide preventive and control measures, including better access to safe water and sanitation, health and

hygiene education in the community, immunization of at-risk population, and adequate and timely access to patient care

- monitor disease occurrence and epidemiology
- estimate cholera disease burden.



TYPES OF SURVEILLANCE RECOMMENDED

MINIMAL SURVEILLANCE

Event-based surveillance is the minimal surveillance standard (3) when the objective is to detect cholera outbreaks. Event-based surveillance is not based on standard case definitions to detect cases, but rather on unstructured descriptions, rumours and reports about any event that might indicate a cholera outbreak.

Sources of information include official sources (Ministries of Health, institutes, agencies, international organizations, etc.), formal sources (health facilities, hospitals, laboratories, health care workers, community health workers, non-governmental organizations, etc.) and informal sources (press, radio, TV, blogs, social media, rumours from the community, reports, etc.). Follow up on reported events within 24 hours and take appropriate measures to confirm or rule out a cholera outbreak.

surveillance is facility-based; health facilities keep line lists of suspected cholera cases (see definition of suspected cholera case below). Indicator-based surveillance can take place solely in sentinel sites in areas of risk, or could potentially take place nationwide. Laboratory testing is done to confirm cholera on suspected cases. This type of indicator-based surveillance can detect outbreaks as well as provide information on cholera epidemiology and burden. While it is recommended that case-based data be transmitted to higher levels, lower levels can choose to aggregate the results and report the number of cases in their integrated aggregate diseases surveillance system, like Integrated Disease and Surveillance Response (IDSR).

Ideally, indicator-based and event-based cholera surveillance are integrated to most efficiently detect and characterize cholera outbreaks and disease.

ENHANCED SURVEILLANCE

Indicator-based surveillance is the routine collection of surveillance data on individual cases that meet the suspected cholera case definition. For cholera,



CASE DEFINITIONS AND FINAL CLASSIFICATION

SUSPECTED CASE DEFINITION FOR CASE FINDING

In areas where a cholera outbreak has **not** been declared, a suspected case is any patient aged ≥ 2 years who has acute watery diarrhoea and severe dehydration or died from acute watery diarrhoea. (Acute watery diarrhoea is characterized by three or more loose or watery, non-bloody stools within a 24-hour period.) In areas where a cholera outbreak is declared, a suspected case is any person presenting with or dying from acute watery diarrhoea.

CONFIRMED CHOLERA CASE

A confirmed cholera case is any suspected case in which *Vibrio cholerae* O1 or O139 is confirmed by culture or polymerase chain reaction (PCR) test. In countries where cholera is not present or has been eliminated, the case is confirmed if *Vibrio cholerae* O1 or O139 is toxigenic. After a cholera outbreak has been identified, assume that all cases of acute watery diarrhoea in the

area have cholera, with only periodic laboratory testing to confirm that cholera transmission persists and thus the outbreak is ongoing.

Certain public health responses are triggered by a cholera alert. A cholera alert is defined by the detection of any of the following:

- ▶ two or more people ≥ 2 years of age linked by time and place (from the same area within one week of one another) with acute watery diarrhoea and severe dehydration, or dying from acute watery diarrhoea
- ▶ one death from severe acute watery diarrhoea in a person ≥ 5 years of age
- ▶ one case of acute watery diarrhoea testing positive for cholera by rapid diagnostic test (RDT) in an area that has not yet detected a confirmed case of cholera, including those at risk for extension from a current outbreak.



CASE INVESTIGATION

Any cholera alert reported through event-based or indicator-based surveillance should trigger a field investigation to confirm or rule out the outbreak. Stool samples from suspected patients should be collected for laboratory confirmation, which will then serve as the basis for outbreak declaration. Ideally, a case's stool is tested with a cholera RDT. If positive, the sample is sent to a laboratory able to conduct confirmatory testing (culture or PCR). If a patient is in a health facility, the patient should be isolated from other patients and

placed under contact precautions (strict handwashing) to prevent spread of cholera. Countries can choose to implement an active case search for other suspected cholera cases in the community if resources allow. Early in the course of an outbreak, case investigations can be done to identify risk factors and sources of transmission like water sources or food, which might be amenable to interventions.



SPECIMEN COLLECTION

Accurate and reliable test results depend on having a sample that has been collected, stored and transported correctly (4). The national reference laboratory should standardize methods for collection and transport of stool samples. The methods should be documented and available to staff or health care providers who collect, package and ship samples.

SPECIMEN TYPES

Faecal specimens (liquid stool or rectal swabs) are used to diagnose cholera. Faecal specimens should be collected in the early stage of the illness, when pathogens are usually present in the stool in highest numbers (ideally within the first four days of illness), and before antibiotic therapy has been started. Do not delay patient rehydration treatment in order to take a specimen.

Specimens may be collected after rehydration has begun.

STORAGE AND TRANSPORT

Place the specimen in a clean, appropriately labelled, leak-proof container and transport to the laboratory at room temperature within two hours. If a container must be cleaned, avoid the use of any solution that contains chlorine. If there will be more than a two-hour delay, place a stool-soaked swab into Cary-Blair transport medium. If kept sterile and properly sealed, Cary-Blair transport medium is stable in storage for several months and does not require refrigeration (before use and once inoculated). If Cary-Blair transport medium is not available and the specimen will not reach the laboratory within two hours, another possible option is to preserve and transport liquid stool samples on a filter paper kept in a moist environment. To do so, dip a blotting paper disc into the liquid stool and place in a screw-cap microtube with two or three drops of normal saline solution to stop the sample from drying out.

Other considerations for storage of stool samples for culture include the following:

- ▶ avoid cold storage (2–8°C) of the samples, as it can greatly decrease the populations of *Vibrio cholerae*
- ▶ do not allow specimen to dry
- ▶ add small amount of normal saline if necessary
- ▶ transport in a well-marked, leak-proof container at room temperature.

For culture, the sample must not be allowed to dry out. However, for DNA detection by PCR, dry filter papers can be used for transport of faecal specimens. All specimens should be accompanied by a laboratory request form containing at minimum the following information:

- ▶ patient name or initials
- ▶ age
- ▶ place of residence
- ▶ date and time of collection
- ▶ symptoms
- ▶ date of onset of symptoms
- ▶ type of testing requested (culture, PCR or both).



LABORATORY TESTING

The objectives of the laboratory diagnosis of cholera include confirming alerts and declaring outbreaks, monitoring antibiotic susceptibility, characterizing the circulating strains, identifying changes in the virulence, supporting epidemiologic investigations and declaring the end of an outbreak.

Stool culture is the gold standard for testing for *Vibrio cholerae* but requires selective media; thiosulfate-citrate-bile salts agar (TCBS) is ideal for isolation and identification. Cholera isolation is important for characterization of antibiotic susceptibility and subtyping, usually done through the use of antisera.

PCR can be used in place of culture to detect toxigenic *Vibrio cholerae*. However, while it is sensitive and specific for this bacteria, it cannot provide information on antibiotic susceptibility.

Cholera RDTs such as dipsticks are based on immunochromatographic tests and are intended for use at primary health care sites for the following purposes:

- surveillance
- early outbreak detection
- tool for initial alerts
- outbreak monitoring, including potential new foci and seasonal peaks in highly endemic areas.

Cholera RDTs do not replace stool culture or PCR to confirm cholera and should not be used for individual diagnosis. However, culture confirmation is rarely accessible in peripheral healthcare facilities where most of the cholera patients present. The use of cholera RDTs can improve the reliability of cholera alerts by permitting the triage of specimens while waiting for culture or PCR confirmation (5). Given the high sensitivity of RDTs, countries can choose to send stool samples for confirmatory testing from only those patients who screen positive on the RDT. Culture results should be available within a maximum of two to four days after the specimen arrives at the laboratory.

False negatives using RDTs or culture can occur if specimens are collected:

- in receptacles containing chlorine residues
- after initiating antibiotic therapy
- in case of poor sampling or handling practices of the specimen, such as a long delay.

Stool may be tested for other enteric pathogens, but the requirements of transport and testing will differ from the requirements for cholera testing and should be planned for accordingly.

At least one laboratory in the country should be operational and capable of isolating and identifying *Vibrio cholerae* by culture or PCR if available and testing for antibiotic susceptibility. The designated reference laboratory should be able to provide transport media and reagents, train technicians and monitor the quality of examinations. While there is no global laboratory network for cholera, there are WHO collaborating centres and regional reference labs that can provide support in laboratory diagnostics for cholera. Establish collaboration with these international laboratories that can perform quality assurance, provide training and conduct molecular testing for characterization and genotyping of circulating *Vibrio cholerae* strains.



DATA COLLECTION, REPORTING AND USE

RECOMMENDED DATA ELEMENTS

Each health facility should create and regularly update a line list register of cases that contains at least demographic, clinical and laboratory information for each case, as follows:

- Unique case identifier
- Age in years or age in months
- Sex
- Place of residence to the smallest administrative area (GPS is ideal)
- Signs and symptoms
- Date of symptom onset
- Hospitalization status
- Level of dehydration (none, some, severe) or treatment plan (A, B, C) (6)
- Outcome (survived or died)
- Laboratory results

The following additional case-based data may also be collected:

- Risk factors
- Activity or profession
- Displaced or living in camps
- Cholera vaccination status, including date vaccinated and type of vaccine
- Pregnancy status

Sample data collection tools can be found elsewhere, such as the *Interim Guidance Document on Cholera Surveillance* (3). If reporting is aggregate, transmit the following data to higher levels: age (< 5 years of age; ≥ 5 years of age), district, month and year of onset and outcome.

REPORTING REQUIREMENTS AND RECOMMENDATIONS

In a previously **unaffected area** or area with no recent reported cases, any cholera alert should be immediately reported (within 24 hours) to the next higher level health authorities (provincial or national), so they can conduct field investigations to confirm and declare the outbreak.

In an area where a **cholera outbreak** is declared, report the number of cases and deaths – both registered at the health facility and occurring in the community – daily or weekly to monitor the disease incidence, mortality, case fatality ratio and any prevention or case management interventions.

In an area where cholera disease is **endemic**, the number of cases and deaths – both registered at the health facility and occurring in the community – must be reported weekly (or monthly if the number of cases is low) in order to estimate basic surveillance indicators (incidence rate, case fatality ratio and attack rates) and describe the situation in terms of time, place and person. If cholera surveillance is part of IDSR, follow the IDSR reporting schedule.

Reporting for cholera can be either case-based or aggregate based on the resources in the country. WHO does not require that cholera cases be reported through International Health Regulations (IHR) unless a cholera outbreak is deemed a public health emergency of international concern. Cholera cases are not routinely collected through the WHO/UNICEF Joint Reporting Form (JRF).

RECOMMENDED DATA ANALYSES

The following data analysis should be completed:

- the aggregated number of confirmed cholera cases and deaths – both registered at the health facility and occurring in the community – by age group (< 5 years of age; ≥ 5 years of age)
- incidence and attack rates, overall and stratified by age group and location
- case fatality ratios by age group and by facility
- proportion of cases that have received vaccine (if vaccine introduced in area of outbreak).

See the *Interim Guidance Document on Cholera Surveillance* (3) for details on how to calculate the incidence, attack rates and case-fatality ratios.

USING DATA FOR DECISION-MAKING

Analysis should be used to monitor facility-level performance (striving for a low case fatality ratio), as well as to monitor trends, identify populations at risk and initiate or adjust response interventions.

**SURVEILLANCE PERFORMANCE INDICATORS**

Regular monitoring of surveillance indicators might identify specific areas of the surveillance and reporting system that need improvement. Some suggested

surveillance indicators to monitor are listed in the table below, and may be modified based on the type of surveillance conducted.

TABLE
1

Recommended surveillance performance indicators

SURVEILLANCE ATTRIBUTE	INDICATOR	TARGET	HOW TO CALCULATE (NUMERATOR / DENOMINATOR)	COMMENTS
COMPLETENESS OF REPORTING	Percentage of designated sites reporting cholera data, even in the absence of cases	≥ 80%	# sites reporting cholera data / # designated reporting sites for cholera surveillance x 100 (for given time period)	
TIMELINESS OF REPORTING	Percentage of surveillance units reporting cholera data to the national level on time even in the absence of cases	≥ 80%	# of surveillance units in the country reporting cholera data by the deadline / # of surveillance units in the country x 100	At each level reports should be received on or before the requested date.
TIMELINESS OF INVESTIGATION (OF ALERTS)	Percentage of all cholera alerts that have had an investigation initiated within 48 hours of notification	≥ 80%	# of cholera alerts for which an investigation is initiated within 48 hours of notification / # of suspected cholera alerts x 100	
TIMELINESS OF REPORTING LABORATORY RESULTS	Percentage of specimens with results reported within 4 days of receipt of specimen	≥ 80%	# of specimens with results reported within 4 days of specimen receipt / # of specimens received x 100	



CLINICAL CASE MANAGEMENT

Effective treatment for cholera exists and should be initiated as soon as possible. The mainstay of cholera treatment is rehydration. Treatment depends on severity of illness and level of dehydration. Severe cases need intravenous rehydration and antibiotics. Milder cases can be treated with an oral rehydration solution; zinc supplementation should also be given to children < 5 years of age. Information regarding the antimicrobial

susceptibility profile should be provided to clinicians to guide case management and treatment of patients who require antibiotics. Patients should be isolated from other patients and placed under contact precautions to prevent spread. Further details can be found in *Cholera Outbreak (7)* at <http://www.who.int/cholera/publications/final%20outbreak%20booklet%2020260105-OMS.pdf>.



CONTACT TRACING AND MANAGEMENT

Contact tracing is not currently a strategy recommended as part of cholera control.



SURVEILLANCE, INVESTIGATION AND RESPONSE IN OUTBREAK SETTINGS

DEFINITION OF AN OUTBREAK

A cholera outbreak is defined by the occurrence of at least one confirmed case of cholera and evidence of local transmission (3). Outbreaks can also occur in areas with sustained year-round transmission. These outbreaks are defined by an unexpected increase in the magnitude or timing of suspected cases over two consecutive weeks, with some cases being confirmed by the laboratory. Investigate and respond to such increases appropriately through additional outbreak response and control measures.

CHANGES TO SURVEILLANCE DURING AN OUTBREAK

If the existing cholera surveillance is case-based, shift to aggregate reporting during an outbreak. Not all acute watery diarrhoea cases need laboratory confirmation in the setting of an outbreak.

LABORATORY TESTING IN THE SETTING OF AN OUTBREAK

Rapid confirmation of cholera is important in the setting of a potential outbreak. If RDTs are available, send the RDT positive samples to the reference laboratory

to increase the probability of identifying the outbreak as a true alert. If the RDT is negative, cholera can be ruled out. If at least one sample tests positive by culture or PCR by the reference laboratory, then declare the outbreak and immediately implement control measures in the affected area. Once *Vibrio cholerae* is confirmed by the laboratory and the outbreak is declared, there is no need to confirm all suspected cases. All individuals with acute watery diarrhoea should be registered and reported as suspected cholera cases. For each new district or region affected by the outbreak, confirm the outbreak with laboratory confirmation by culture or PCR of suspected cases.

Do periodical sampling and testing on suspected cases to monitor the outbreak, determine the antibiotic susceptibility profile and carry out continuous monitoring of strains. If you are using RDTs, prioritize RDT-positive samples for transport to the laboratory. RDT-negative samples may also be sent if no positive samples are available. The number of samples collected and tested depends on the laboratory capacity and the extent of the outbreak. Ideally, a minimum of five samples from suspected cases per week per health

facility should be sent for laboratory confirmation and antimicrobial susceptibility testing. Ideally, pre-select samples based on RDT results. When there is a large or nationwide outbreak or when lab capacity is limited, consider designating a number of Cholera Treatment Centres, which represent different demographic and geographic populations, for collection and shipment of samples for testing. When the number of suspected cases in the epidemic area significantly declines and all samples from all cases of acute watery diarrhoea test negative by RDT, culture or PCR for at least two weeks, the outbreak can be considered ended. About 20 stool samples should be tested negative to declare the outbreak over (7), at which point the laboratory can resume testing of suspected case as part of routine surveillance.

Of note, the first few suspected cases appearing in a new district should be culture confirmed to detect outbreak extension.

PUBLIC HEALTH RESPONSE

Implement control measures rapidly as soon as there is indication of a cholera outbreak, even before laboratory confirmation. Cholera control measures are aimed at reducing mortality and the spread of the disease. These measures include setting up cholera treatment units and oral rehydration points, ensuring early detection and transfer of severe cases, training health professionals, applying standard case-management protocols, strengthening epidemiological and laboratory capacity for surveillance, ensuring access to water in quantity and

quality, and promoting hygiene conditions and practices (7). Good hygiene practices include hand-washing, safe preparation of food, safe burials, and improved sanitation and excreta disposal.

Consider the use of oral cholera vaccine as part of a reactive campaign. The use of the vaccine should complement other control strategies, such as WASH and community mobilization. Cholera vaccination can help prevent the spread of current outbreaks to new areas (7). Make a decision to implement vaccination only after a thorough investigation of the current and historical epidemiological situation. Clearly identify the targeted geographical areas and populations, and assess the feasibility of organizing a vaccination campaign given the local infrastructure and other factors. Mass vaccination with a single dose for short-term protection is the preferred strategy for reactive campaigns during outbreaks to help control the outbreak until long-term WASH can be established (2). If the risk of cholera persists, an additional vaccination may be needed to ensure longer-term protection.

SPECIAL ASPECTS OF INVESTIGATION

In the beginning of an outbreak, a field epidemiological and environmental investigation on the first cases can be useful to explore the risk factors and exposures to identify the source of contamination. When available, spatial data collection using GPS will support the outbreak investigation and help describe the geographical pattern. If possible, record inhabited areas, water sources and any other relevant features.

SPECIAL CONSIDERATIONS FOR CHOLERA SURVEILLANCE



SURVEILLANCE IN EMERGENCY SETTINGS

Because of the increased risk of cholera outbreaks in humanitarian and complex emergencies, consider establishing prospective cholera surveillance to detect outbreaks early. If a risk assessment in such settings shows an increased risk of cholera, consider vaccination with oral cholera vaccine as an additional preparedness measure for outbreak prevention when local infrastructure allows, even if there is not a current outbreak.

ENVIRONMENTAL TESTING

Given that cholera is primarily a waterborne disease, monitoring the presence of *Vibrio cholerae* in specific environmental water sources may identify sources or vehicles of infection and aid with the early detection of cholera transmission in some areas (3).



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