STOP CHOLERA

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Cholera Surveillance: Detecting and Reporting Cases

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A Note About This Document

The intention of this document is to clarify and outline the steps to effective cholera surveillance. It discusses when, where and why surveillance for cholera is needed and how to establish a useful and cost-effective surveillance system for cholera. To make comments, corrections and additions, please contact the authors at dsack1@jhu.edu

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Introduction

When, where and why is surveillance needed for cholera, and how can one establish a useful and cost-effective surveillance system? The answers to these questions depend on the goals of the system and the epidemiology of cholera in the country or a specific region of interest. For example, a system for characterizing patterns of annual cholera seasonality in Bangladesh will be quite different from a surveillance system in an African country, which has had outbreaks every few years, and is attempting to detect an outbreak at the earliest stage. Both systems will be different from surveillance to understand which districts are "hot spots," or at highest risk for cholera within a given country. All of these scenarios require a surveillance system designed to meet the needs for controlling cholera in the specific area and situation. Each of these systems have recently been assisted with the use of rapid diagnostic tests (RDTs) and polymerase chain reaction (PCR) methods for detecting and confirming cases.

The types of surveillance may be categorized broadly in the following manner:

- Surveillance for early identification of cholera outbreaks
- Monitoring the course of an outbreak
- Detection of "cholera hotspots"
- Routine surveillance of cholera in endemic areas to characterize its epidemiology
- Detection of high-risk groups
- Monitoring the effectiveness of cholera prevention programs
- Surveillance for cholera deaths
- Environmental (water) surveillance

Identifying cholera cases

Before describing an approach to each situation, one must consider the different ways to identify cases in such a surveillance system. Defining how cases will be identified is an important first step for any surveillance system. Broadly, a case can be identified "clinically" if the signs and symptoms are consistent with the clinical definition as described by the World Health Organization. Alternatively, it can be a "confirmed" case of disease if the results of a clinical case are confirmed by microbiological culture of PCR. While a case definition is useful, it must also be considered that severe diarrheal diseases can be caused by other agents, especially enterotoxigenic E. coli; thus, cholera cases will often need to be confirmed. The proportion that need confirmation depends on the situation. Confirming cholera in a patient with diarrheal symptoms has generally required a stool culture to isolate Vibrio cholerae O1 (or rarely O139), and this continues to be the standard method. Recently, rapid diagnostic tests (RDT), the most common of which are the dipstick, are being introduced to detect cholera. These have the advantage of providing a result within 15 minutes. Two RDT are most commonly used (Crystal VC and Bioline but others are also on the market). These have lines for both serotypes O1 and O139. They have a sensitivity of about 85-90% and specificity of about 70% indicating that false positives may occur. Recently, tests are now available that have a line for O1 only (Crysal VC O1 and CholKit) which appear to have improved sensitivity and specificity. Our project at Johns Hopkins and others have evaluated the Crystal VC test when the sample is first incubated in alkaline peptone water (APW) for 6 to 18 hours to enrich the V. cholerae. Methods for this procedure are found in the Manual for Detecting Vibrio cholerae O1 from Fecal Samples Using an Enriched Dipstick Assay found in the StopCholera Toolkit [1]. When this dipstick is used using this "enriched" method, sensitivity remains high, and the specificity increases to over 90% [1]. Though this enrichment test requires a few hours, results are available the same day, and can PCR methods, using either stool samples or APW from the six-hour enrichment, can be used. In the past, it was assumed that bacterial culture was the "gold standard" for detecting cholera, but even cultures are not 100% sensitive. Discrepancies between dipstick and culture can sometimes be resolved with PCR. Currently the PCR methods are not yet adapted to remote areas but drops of the stool or the APW specimens can be placed on filter paper and after drying, can be sent to a central laboratory for PCR testing.

[1] https://publichealth.jhu.edu/sites/default/files/2023-09/manual-for-detecting-vibrio-cholera-1.pdf

Availability of Cholera Rapid Tests from GAVI

Since 2023, GAVI is now making cholera RDTs available to countries who plan to improve surveillance through the increased use of RDTs. Applications to GAVI must provide details of their plans for improved surveillance to be considered for this new resource [2].

Declaring a "cholera alert" or declaring a "cholera outbreak"

Because of the public health importance of a cholera outbreak, it needs to be reported immediately to the district, regional and national health authorities. For endemic areas, an outbreak of cholera is said to have occurred if there is a sudden increase in the number of cholera cases that are linked by time and place. For areas where cholera has not been reported recently, an outbreak is declared if a single case is confirmed with culture or PCR, especially if there is evidence of onward transmission. In the past, authorities have often delayed recognition of an outbreak, waiting to see if suspected cases were confirmed, or perhaps in hopes that the case was isolated and not representative of an outbreak. However, delaying outbreak recognition can have harmful repercussions. By recognizing and declaring a cholera outbreak immediately, authorities and agencies can quickly mobilize resources, and an effective response can reduce cholera deaths.

During cholera outbreaks, case fatality ratios tend to be highest at the beginning of the outbreak, but then decrease as treatment and resources improve. Thus, recognizing an outbreak early can save lives by accelerating the proper response. The potential use of vaccine makes rapid recognition of an outbreak even more important since, if it is to be used, vaccine will avert a higher number of cases if given early in the outbreak. When only a few patients meet the case definition of cholera, there should be a notification of an "alert" so that health authorities can begin preparations. If dipstick tests are available, the results of those tests can reinforce the alert. Specimens should be sent for culture and if several (>3 within a week) stool samples at a health facility are positive using the RDT, one can be confident that an outbreak is occurring and can be declared.

Using surveillance for early identification of cholera outbreaks

In many countries, especially in many African countries, nearly all cases of cholera occur during outbreaks but are very rare at other times. Thus, high risk for cholera occurs only during these outbreaks and early identification allows health authorities to respond promptly. The outbreaks may occur as frequently as every year or once every few years. Since they occur infrequently, health providers may not be experienced in recognizing the signs and symptoms of cholera and may not be experts in treatment. As noted above, the case fatality ratio is often highest during the early phases of an outbreak. If the outbreak is detected quickly, providers can be re-trained and additional resources can be provided. Therefore, areas with occasional outbreaks may benefit from a surveillance system geared at detecting the earliest cases of a cholera outbreak. Areas at risk for intermittent cholera outbreaks also need methods for rapidly identifying patients with signs and symptoms of cholera and methods to confirm the cases. This involves training doctors and nurses to recognize patients with dehydrating diarrhea. Although cholera can affect patients of any age, including infants, cholera is more likely to be recognized in patients > 2 years. Thus, if a patient, or a cluster of patients, has severe, acute (less than 48 hours duration), dehydrating, watery diarrhea, cholera should be suspected, and a stool sample should be obtained. Ideally, a rapid test should be performed. If the rapid test is positive when carried out directly from the stool, the diagnosis can be confirmed by retesting with the rapid test after enrichment in APW for six hours. If the rapid test (either direct or after enrichment) is positive, or if a rapid test was not done, a stool sample should be sent for culture and confirmation. If other diarrhea patients have a positive RDT, this can also be used to declare an outbreak. For areas without known cholera in the region for more than 12 months, a single culture confirmed case indicates a cholera outbreak and health authorities should be notified. Once an outbreak is declared, the surveillance system can shift to one that tracks the course of the outbreak. This type of surveillance to rapidly recognize an outbreak is especially critical for areas that have recently experienced deterioration in water and sanitation due to natural disasters (flood, earthquake, or drought), civil strife, or recently established refugee camps. Although this may happen in

[2] https://www.gtfcc.org/wp-content/uploads/2023/02/8th-meeting-of-the-gtfcc-working-group-on-surveillance-2023-beth-evans-lee-hampton.pdf

areas that have not experienced cholera in the past, these situations accentuates cholera transmission should the bacteria be introduced; thus, surveillance for cases of watery diarrhea needs to be enhanced in humanitarian emergencies.

Monitoring the course of an outbreak

When a cholera outbreak has been declared, the course of the outbreak should be monitored to understand the pace, detect changes in antibiotic sensitivity, identify its geographic spread, and understand when the outbreak has run its course. The most common practice currently employed once an outbreak is declared, is to identify additional cases by clinical signs and symptoms without confirmation. However, even during outbreaks, some cases with severe diarrhea do not have cholera, and the proportion of these non-cholera diarrhea cases is highly variable. To understand the proportion of suspected diarrhea cases with cholera, fecal samples of a representative sample of diarrhea cases can be tested using RDTs or culture to confirm the etiology. By monitoring the number of clinical cases each day and each week, important information on the severity of the outbreak can be determined, but these estimates can be improved if the proportion of a representative sample of such cases are confirmed. The nature of cholera is to spread; thus, areas adjacent to the outbreak need to be under surveillance so that if the outbreak does spread to neighboring areas, they will also be prepared and can respond quickly. If the risk of spread is high, such neighboring areas may be targeted for vaccine.

In the process of conducting the monitoring surveillance, some isolates should be sent for antibiotic testing. Recent outbreak strains have been sensitive to doxycycline, but sensitivity patterns can change during an outbreak. Utilization of an effective antibiotic is important; thus, sensitivity patterns need to be verified at least every few weeks during an outbreak. As the outbreak continues, there is likely to be peaks and valleys in the daily or weekly number of cases, therefore, the overall trends during the outbreak should be viewed. Since cholera outbreaks in Africa tend to be self-limited to a few months, understanding when the outbreak is over is also reassuring to the health authorities.

Detecting identification of Priority Areas for Multisectoral Interventions (PAMIs, formerly referred to as 'hotspots')

Countries with endemic cholera are not uniformly at risk for cholera. An example is the Democratic Republic of Congo where the high-risk areas are associated with the Great Lakes in the east of the country. When cholera control plans are developed, these PAMIs (hotspots) within the county need to be identified so that resources can be concentrated in these areas. As vaccine supplies increase, these hotspots should be targeted for vaccination. Detection of PAMIs areas can utilize a surveillance system similar to that used to detect outbreaks but the data should be analyzed so that the frequency of outbreaks and rates of disease can be categorized at a regional or district level. If possible, this information should attempt to identify associated risk factors, for example, occupation, season, unusual movement of people (especially refugees and internally displaced people), and distance from large lakes. This information should then lead to the development of maps that identify the hotspots in the country, and most importantly, should lead to specific strategies to control cholera in these areas. In some areas, fishing villages have been especially vulnerable. The Global Task Force for Cholera Control has developed a tool using Excel to identify districts in a country which have high annual rates of cholera and have outbreaks more persistently. This tool can be found at https://www.gtfcc.org/resources/identification-of-priority-areas-for-multisectoral-interventions-pamis-for-cholera-elimination/.

Using routine surveillance in endemic areas to characterize epidemiology

In some countries, especially in South Asia, cholera is endemic, and occurs as "seasonal peaks," and may even be year-round. Diarrheal diseases have many causes, but in some areas, cholera may be less common than other diarrheal diseases, such as rotavirus and enterotoxigenic E. coli. Nevertheless, among these causes, cholera tends to be the most severe and specific interventions are needed to control it. With many causes of diarrhea, a sampling system can be effective to understand the epidemiological characteristics of the disease, specifically, seasonality, age and sex specific rates. For example, in Bangladesh, a systematic sample 5 of diarrhea cases show peak seasons

for cholera is March and April in the southern part of the country, and October to November in the north. In the middle of the country, there are peaks before and after the monsoon which occurs in June through August. Understanding these trends in seasonality helps in the preparation for control. For health centers treating many diarrhea patients, a system in which symptoms and signs of a representative sample of suspected cholera patients are recorded and stool samples are tested for cholera is an efficient way to monitor trends in epidemiology. The representative sample might be every 10th or every 50th patient with watery diarrhea depending on the numbers of patients treated. Another sampling strategy is to monitor all patients being treated at a facility a few days each month. The specific method for testing a representative sample needs to be adapted to the logistic constraints of the facility. In some cases, an electronic data base system using a tablet computer or smart phone may simplify the data management to better understand trends.

Detecting high-risk groups

Cholera occurs among the most vulnerable groups who lack basic sanitation and safe water. While this is a general principle, just as there are geographic hotspots, there may be specific groups of people who suffer a disproportionately high risk of disease or a high risk of death if they develop cholera. People living in very remote areas who lack access to health services constitute one such vulnerable group. Due to their remote location, surveillance of these populations is challenging. Innovative methods are needed to understand the risks of cholera in these areas and to understand how to prevent cholera deaths in this group. Just as some may be geographically remote, others may be socially excluded from health care and thus have a higher case fatality risk if they develop the disease. Identifying these groups will also require innovative strategies for surveillance.

Monitoring the effectiveness of cholera prevention programs

As interventions are developed, they need to be monitored to document the outcome of the program. Determining the effectiveness of oral cholera vaccine (OCV) is an obvious need, and it would seem that whenever OCV is used, there should be plans for detecting and counting cases in the vaccinated and neighboring areas using a system of identifying cases clinically as well as confirming a representative sample. If the intent of the campaign is to conduct a true effectiveness analysis, all cases should be confirmed using either culture, PCR, or an enriched dipstick procedure.

Equally important to documenting the effectiveness of OCV, is determining the effectiveness of water, sanitation and hygiene (WASH) interventions, clinical treatment, or other interventions that may be attempted to curb cholera. Ideally, countries will develop national plans for cholera control that include indicators to monitor progress with their interventions in terms of cholera cases or cholera deaths averted. If, for example, the national plan sets targets for reducing rates of cholera nationally, or for reducing the number of areas with endemic cholera, surveillance will need to determine if these targets are being met. The national plans should include the methods to be used to conduct surveillance to fit the needs of the plan.

Surveillance for cholera deaths

Without treatment, severe cholera can kill up to 50% of its victims. With adequate and appropriate treatment, no one should die of cholera. Although the benchmark for cholera treatment is a case fatality ratio of <1%, in reality, deaths from dehydration from cholera should not occur.

Case fatality ratios (CFRs) (also called case fatality rates) are commonly reported during outbreaks. The reported CFRs in Africa have generally ranged between 2% to 10% with most being around 4%. However, the method for determining these rates is not standardized. Generally, the CFR is determined using the number of patients treated at the health facility as the denominator and the number of these patients who died as the numerator. This methodology is not always used; however, since cholera deaths among patients who did not come to the health facility may also be counted, which tends to increase the CFR. On the other hand, since those seeking treatment may include patients with diarrhea who do not have cholera, the CFR will tend to be lower by including more patients in the denominator. Ideally, surveillance for cholera deaths would identify deaths occurring in the facility and those occurring in the community separately. The reason for this separation relates to the different

interventions needed to improve cholera treatment. If deaths are occurring in the facility, improved treatment procedures are needed. The corrective action may be more training or improved provision of supplies and medicines. The timing of the deaths is also important since a death that occurs in a patient who has been hospitalized for a day represents a different problem than a cholera death that occurs 15 minutes after arrival. On the other hand, if deaths are occurring in the community, a different intervention is needed, such as improving transportation, communication, or developing new treatment facilities closer to patients. Standard methods to detect and to enumerate cholera deaths are still needed. Until these methods are developed, we recommend calculating CFR based on cases of those that die in the treatment facility, adjusting the denominator according to the proportion of diarrhea cases confirmed to have cholera. Furthermore, the number of cholera cases in the community that did not receive treatment at a facility and died, should be counted separately; however, their numbers should also be included in reports to health authorities.

Conducting environmental (water) surveillance

Since cholera is primarily a water borne infection, water surveillance to detect spread of the bacteria is a logical surveillance activity. For example, if the municipal water supply or a particular well is contaminated with V. cholerae, the first action should be to correct the contamination or close the water source. Unfortunately, there has not been a convenient and efficient method to detect cholera in water such that it can be applied to public health programs to investigate outbreaks, or as an early warning for an outbreak. Recently, cholera projects developed dipstick methods for detecting V. cholerae in water in which 1 to 2 liters of environmental water is passed through gauze pads. The pads are then incubated in APW for 6 to 18 hours, following which the APW is tested for cholera using a rapid test. If positive, the APW is then sent to the lab for culture or PCR using either Cary Blair transport media or by spotting the APW on filter paper[2].

Taking action based on surveillance.

Data from surveillance systems should be organized and reported to the national authorities and to the World Health Organization. Just as there are several categories of surveillance, different types of reporting may be needed. Some of these reports require an urgent notification to authorities in the Ministry of Health, while others will require more careful analysis prior to publication. Whenever possible, the reports should be expressed as both rates and numbers, but often the denominators for rates are not well-documented. For each of these types of surveillance, there are opportunities for innovation in terms of use of mobile phone reporting and unique ways of detecting, reporting, and analyzing the data.

Type of surveillance	Outcome	Type of Report
Rapid identification of an outbreak	Detection of an outbreak in an area without known cases.	An urgent report to the Ministry of Health to declare a cholera alert or cholera outbreak confirmed.
Monitoring the outbreak	Preparation of situation reports to describe its severity, acceleration, spread, and decline.	Weekly situation reports in tabular form and graphs. Include breakdown by age, sex, and geographic location. Include number tested and proportion confirmed as cholera.
Detection of "cholera hotspots"	Rates and seasonality of cholera by district within the country. All ages should be included.	Map of districts, within a country with increased rates. Use methods recommended by the GTFCC
Routine surveillance of cholera in endemic	Using representative sample determine rates of cholera by season, age, and sex.	Weekly (or monthly) reports on the number of cases clinically defined and the proportion confirmed using a representative sample.
Detection of high-risk groups	Rate of cholera among different social or geographic groups.	Rates of disease by group or geographic area.
Monitoring the effectiveness of cholera prevention programs	Rate of disease in intervention group compared to a suitable comparison group which is also under surveillance, or alternatively, rate of disease over time.	Percent change in rates of cholera, or reduction in the geographic areas with cholera.
Surveillance for cholera deaths	Detection of deaths among cases reporting for treatment, or detection of cholera deaths in the community who do not come for treatment.	Calculation of case fatality rate among those who arrive at the treatment center alive. If possible, this should be adjusted to reflect only those with confirmed cholera. Also report the total number of cholera deaths in the region or district over time.

Conclusion

Surveillance for cholera is a critical component for its control, and there are different types of surveillance systems that can be employed. Outbreaks must be detected quickly so that appropriate and rapid responses can be undertaken. Implementing new control programs requires the ability to detect PAMIs (hot spots), understand the basic epidemiology of cholera in the country, and reliably evaluate new control programs.

1. Bwire G, Orach CG, Abdallah D, et al. Alkaline peptone water enrichment with a dipstick test to quickly detect and monitor cholera outbreaks. BMC Infect Dis 2017;17(1):726. DOI: 10.1186/s12879-017-2824-8.
2. Debes AK, Ateudjieu J, Guenou E, et al. Clinical and Environmental Surveillance for Vibrio cholerae in Resource Constrained Areas: Application During a 1-Year Surveillance in the Far North Region of Cameroon. Am J Trop Med Hyg 2016;94(3):537-543. DOI: 10.4269/ajtmh.15-04