STOP CHOLERA

Work Together. Stop Transmission. End Deaths.

Glossary of Terms Related to Cholera and Cholera Vaccine Programs

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A Note About This Document

This glossary is intended to help clarify some commonly used terms for cholera. It is intended to be a "work in progress" and not all readers will agree to the exact meaning of each of the terms included here. There may be terms that have been overlooked and need to be added. In developing this glossary, it is clear that terms like endemic, epidemic, case fatality rate, etc., have not always been clearly defined, or used in standardized ways. This lack of clarity makes comparison of control strategies difficult. The intention of this glossary is to help clarify the meaning of terms and in the process assist in developing improved strategies for the control and eventual elimination of cholera. To make comments, corrections and additions, please contact the authors at dsack1@jhu.edu.

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Why use this glossary: When describing cholera and cholera vaccination programs, consistent use of certain terms may be helpful. This glossary is suggested as a guide to commonly used terms for cholera and cholera vaccine programs. An annex accompanies this glossary, which expands the understanding and concepts of many of these terms.

Acute diarrhea

a) Acute diarrhea is an illness characterized by > 3 loose or watery (non-bloody) stools in a 24-hour period, and generally associated with other symptoms, such as nausea, vomiting, fever, abdominal cramps, fatigue, or weakness.

b) An episode of acute diarrhea for which the date of onset of the episode is three days or more from the end of a previous episode will be considered as a separate episode. If the onset starts within 2 days after the end of the previous episode then this will be considered as continuation of the previous episode.

c) The onset of a diarrheal episode is defined as the day on which it is reported to have begun.

Definition of cholera infection and cholera case

a) A person has a cholera infection if *Vibrio cholerae* O1 or O139 can be isolated from a fecal sample. The person may or may not be symptomatic.

b) A confirmed cholera case is a patient[1] with acute watery diarrhea from whom *V. cholerae* O1 or O139 is isolated from a fecal sample during the illness. The illness may range from very mild to very severe, with life-threatening dehydration.

c) Cholera gravis is a cholera illness with severe dehydration. This is a life-threatening illness associated with a very high risk of death if treatment is not provided immediately. Fever is not a symptom associated with cholera, but could occur if the patient has another concurrent infection.

d) Rarely cholera can occur as "cholera sicca" (dry cholera). This is a condition in which fluid is secreted into the intestine, but the fluid has not yet been passed as stool; rather, it accumulates in the intestine for several hours before it is passed. Thus, the patient may not have diarrhea when first seeking care, but will have other signs of dehydration.

e) The designations of O1 and O139 are the two specific serogroups of the *V. cholerae* that are associated with epidemic cholera. The serogroup is determined by the cell wall of the bacteria; the test for confirming the serotype is agglutination with a specific antiserum. Nearly all cholera cases are caused by serogroup O1; however, a few strains of O139 have been found in the Indian subcontinent. and recently in China. O139 first appeared in 1992 in India and Bangladesh and quickly spread to other countries in Asia but seems to have regressed since then. It has not been isolated from patients in Africa.

f) For additional information about the microbiology, serogroups, and virulence factor of cholera, see the Annex.

[1] A patient is a person who is ill. Similarly, the term *case* typically refers to an ill person. A person with an infection without symptoms will not generally be considered to be a *case* and is not a *patient*.

World Health Organization (WHO) case definitions for cholera

a) In an area where the disease is not known to be present, a patient aged five years or more who develops severe dehydration or dies from acute watery diarrhea is considered a cholera case.[2]

b) In an area where there is a cholera epidemic, a patient aged 5 years or more who develops acute watery diarrhea, with or without vomiting, is considered a cholera case.

c) A case of cholera is "culture confirmed" when *V. cholerae* O1 or O139 is isolated from any patient with diarrhea.

Other terms sometimes used when identifying cases of cholera

a) A suspected case is a patient with symptoms typical of cholera during a time when cholera was not known to be present in the area, and from whom a fecal sample was not obtained for culture; thus, the diagnosis could not be confirmed.

b) A probable case is a patient, like the suspected case, who has symptoms typical of cholera but without a laboratory confirmation of the etiology. The difference between a suspected and probable case is that the probable case is detected during a known cholera outbreak and has symptoms typical of other lab-confirmed cases.

c) A lab-confirmed case is a patient with acute diarrheal symptoms from whom *V. cholerae* O1 or O139 is isolated from a fecal sample.

d) The term "acute watery diarrhea" (AWD) is sometimes used by countries preferring to avoid using the term "cholera." Unfortunately, there is no standard definition for patients meeting this criterion, but it does imply a severe watery diarrhea that would be consistent with either a suspected case or a probable case depending on the epidemiological setting.

Cholera surveillance

a) Generally, surveillance for cholera is conducted among patients who seek care at a health facility for acute watery diarrhea. Thus, the cases that are reported are usually those that have diarrhea of sufficient severity, such that it leads to seeking medical care.

b) The term "passive surveillance" refers to reports of patients who have come to a treatment center and are reported to have met a case definition for cholera.

c) The "active surveillance" has been defined differently by different investigators; thus, a surveillance report which uses the term "active surveillance" needs to define the actual methods employed. For some, active surveillance implies that the records of facilities have been extensively reviewed to detect patients whose illness is consistent with the case definition, rather than relying on routine reports. For other investigators, active surveillance and is the same as "active case finding" in which field workers go to the community to seek out cases of diarrhea in a defined population. Many of these cases will not have come to the facility.

d) Age groups. Cholera rates may differ by age group; thus, it is important to identify patients according to age. Age groups often used are <2 years, 2-4 years, 5-14 years, and >14 years. There is a common misperception that very young children do not get cholera, but young children are, in fact, susceptible.

[2] The reason for excluding younger children from this definition is the frequent occurrence of other causes of acute diarrhea in young children. For older children and adults, other causes of severe diarrhea are much less common, thus there is high specificity of a diagnosis of cholera in older children and adults.

Cholera: endemic, epidemic, or outbreak (also see Annex 1)

a) An area is said to have endemic cholera if cholera cases were detected during 3 out of the last 5 years.[3] The "area" may be a region, district or an entire country, depending on the epidemiological setting. Thus, a country might have specific endemic areas while other areas of the same country may not be endemic.

b) An *outbreak*[4] 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. An outbreak may be expected or unexpected. An expected increase may also be termed a seasonal peak or increase. An outbreak may have only a few cases or may have many thousands of cases.

c) An epidemic of cholera is said to have occurred when there is a much higher rate of cholera than usual in an area where cholera is known to occur, or when there is a new outbreak of cholera in an area that has not had cholera during the last 5 years.

Cholera seasonality

Cholera outbreaks in an endemic area generally have a seasonal pattern. Seasons may be quite specific to particular regions in the country. The underlying causes for the seasonality are still being studied, but historical data can be especially useful in determining when and where seasonal peaks are most likely to occur. Detecting seasonal peaks early accelerates a more rapid and appropriate response, and identifying these seasonal patterns allows agencies to anticipate the appropriate responses.

Rates of cholera

a) Determining the true rate of cholera depends on a high standard of surveillance. The calculation assumes that the numerator and denominator come from the same defined population, and that all patients with moderate or severe diarrhea from this population will seek care at the health facilities under surveillance. To determine this, all patients living in a demographically defined population will be able and willing to come for treatment at health facilities whenever they have moderate or severe diarrheal illness. The facility will carry out fecal cultures for *V. cholerae* on all cases of watery diarrhea (all ages) from the demographically defined population.

b) The best estimate rate of cholera uses a numerator based on clinical surveillance at health facilities utilizing a standardized case definition and the ability to culture a representative sample of cases along with a reasonably good estimate of catchment population. The denominator population may need to be adjusted for healthcare utilization pattern for diarrheal illness/distance to the health facility. A certain proportion of patients with cholera will not be seen at the facility and adjustments may be needed to account for this. The numerator may also need to be adjusted for the proportion of the patients with cholera documented by fecal culture. Since young children have diarrhea due to a variety of agents, additional fecal samples may be needed from this age group to determine the proportion of cases due to cholera.

c) The approximate rate of cholera can be estimated based on routine surveillance for cholera using WHO case definitions. The denominator for this calculation will use government data (e.g. census) for the catchment area. However, this rate needs to provide caveats concerning limitations of the data. Counting only patients >5 years will underestimate the true rate and counting all cases of "acute watery diarrhea" will overestimate true rates.

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[3] The definition 3 out of 5 years is generally accepted, but whether this is a better definition than 2 of 5 or 3 of 6 is mainly based on convenience, not science. From the standpoint of cholera epidemiology, it would seem most logical to assume that an endemic area is one which has cholera from time to time. Many feel that this implies that the area has either ongoing transmission from human to human, or has an environmental reservoir able to maintain the infection without its being introduced from the outside.

[4] Some cholera experts have suggested that the term, "outbreak" not be used when referring to cholera since the exact definition is not well defined. However, the term continues to be used.

d) A group specific rate of cholera may be calculated for specific groups. For example rates may calculated by age group, sex, profession, or geographic-area. The numerator and denominator should be from the same group. A group specific rate is useful when targeting a vaccine campaign to a specific group since one would intend to provide vaccine to certain groups with an especially high rate.

Case fatality rate (CFR) and cholera-specific mortality rate

a) The case fatality rate of cholera is the number of cholera patients who die divided by the total number of cholera cases. When making this calculation, some agencies only include deaths occurring among patients who were treated at a health facility. Others, attempt to count all cholera deaths (at least those that they know about) regardless of whether the death occurred in the health facility or in the community. Thus, the published CFR is not always calculated consistently.

b) The cholera-specific mortality rate is the number of cholera patients who die in a defined population divided by the population at risk. These patients may have died after reaching a health facility, but others may have died in the community without reaching a facility.

Vaccine campaign coverage

a) The vaccine coverage is the number of vaccine recipients divided by the number eligible for vaccination (both medically and by age[5]) in the target communities at the start of vaccination campaign.

b) The *community coverage*[6] is the number of vaccine recipients divided by all individuals in the target communities at the start of the vaccination program.

c) Certain terms are used when calculating coverage rates to explain different groups who may or may not have been fully immunized:

Medically ineligible population related to pregnancy refers to women who were not offered vaccine during the campaign because the campaign organizers decided against providing vaccine to pregnant women. Pregnancies were generally determined verbally, not by urine testing.

Medically ineligible population related to illness refers to individuals too sick to come to the vaccination center (or too ill to leave bed if the vaccine is being distributed house-to-house).

Non-participants refer to individuals who were eligible and present in the community at the time of vaccination, but did not receive any dose.

Incomplete dose recipients refer to individuals who did not ingest the full amount of any one of the administered doses (including those who spit out or vomited after dosing).

One-dose recipients refers to individuals who drank and swallowed the full amount of at least 1 dose of the cholera vaccine.

Two-dose recipients refers to individuals who drank and swallowed 2 complete doses (full amounts) of the cholera vaccine.

Counting cases before and after vaccination

a) When evaluating efficacy/effectiveness of an oral cholera vaccine (OCV) it may be desirable to count the numbers of cholera cases detected following vaccination. Since cases may be defined in different ways, please refer to the definitions used above (section 2, 3, and 4). The case definition used should be stated from these options described above.

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[5] Age for oral cholera vaccination is ≥12 months for Shanchol and Euvichaol and ≥24 months for Dukoral.

[6] Calculation of community coverage may be important when estimating the role of herd protection. By contrast, vaccine coverage may be a better gauge of the success of the program in reaching the intended target group.

Vaccine efficacy, effectiveness, and impact

a) Efficacy (also called protective efficacy (PE)) of a vaccine is the reduction in the rate of disease due to the biological effect of the vaccine when given to a population at risk of cholera. This is typically measured by conducting an individually randomized, double-blind clinical trial in which some people receive vaccine and others receive a placebo (or another non-protective vaccine product). For example, if the rate of cholera in those receiving vaccine was 1 per 1,000 and the rate in those receiving placebo was 4 per 1,000, the efficacy would be calculated as 75%, or (1-(1/1000)/(4/1000)) x 100%.

b) Effectiveness of a vaccine is the reduction in rates of disease due to a vaccine program as it is delivered to a population at risk of cholera. Since effectiveness refers to reduction due to the program rather than to the vaccine itself, effectiveness may be different from efficacy. Effectiveness may be lower than efficacy if there is low coverage or if there is very high level of environmental contamination (e.g. high force of infection). Alternatively, it may be higher if there is significant herd protection. Some computer models suggest that if over 50% of the population is immunized, there will be a major reduction in transmission. An ideal method to estimate effectiveness is through a cluster-randomized trial in which some geographic areas are included in a vaccine program and other, but comparable, areas are not included. The percent reduction in rates between the two groups is an estimate of the effectiveness. Alternatively, a vaccine program can be implemented and the rates of disease among those receiving or not receiving vaccine can be determined, after adjusting for other key variables that affect risk. This latter type of evaluation typically uses a case-control method.

c) The impact of a program is a more general term, which reflects the reduced burden of disease as a result of an integrated program for cholera control that includes vaccine as well as other preventive interventions. Impact can also refer to the improvements (or negative effects) on other non-cholera indicators, such as changes to water sanitation programs, EPI programs, or even the economy.

Herd protection (indirect protection) and herd immunity

OCV protects those who receive it because of the protective immune responses it induces. In addition to this direct protection, the effectiveness of the vaccine can increase through herd protection (indirect protection) if a large proportion of the population receives vaccine.

a) *Indirect protection of those who are not immunized* is one of the benefits of OCV. Persons who do not receive vaccine but whose neighbors are immunized may have a lower rate of cholera because the immunized persons are less likely to be excreting *V. cholerae* into the environment. This lowers the level of environmental contamination in the area and lowers the rate of cholera, even among those who do not receive the vaccine.

b) *Indirect protection of those who do receive vaccine* is another benefit of OCV. Persons who receive vaccine may have even higher protection if their neighbors are also immunized. This is because the level of immune protection is related to the inoculum size. Even an immunized person can develop cholera if the inoculum dose is very high. If the contamination level is lowered because a high proportion of the population has received vaccine, those who are immunized will have higher protection.

c) Herd protection and herd immunity are not synonymous. The difference can be illustrated by examining immunization between oral polio vaccine (OPV) and oral cholera vaccine (OCV). With OPV, the live attenuated virus is shed in the feces of immunized persons for several days and/or weeks. In areas with poor sanitation, the attenuated vaccine virus can be ingested through fecal-oral transmission. Thus the vaccine can immunize persons who were not given the vaccine directly. When these persons who inadvertently consume live vaccine develop an immune response, this is referred to as "herd immunity." By contrast, OCV is a killed vaccine and cannot directly immunize others through a similar secondary immunization. In the case of OCV, herd protection occurs because of decreased environmental contamination resulting from less *V. cholerae* being excreted into the environment.

Booster dose

A booster dose of a vaccine is a dose given after a long interval (usually several months to years) to boost the immune response following an initial immunization.

a) From an immunological perspective, a booster response is said to occur if the immune system responds more quickly or more vigorously as a result of an initial vaccination. That is, the immune system has immune memory and responds robustly when presented with the antigen again. The very rapid, vigorous immune response associated with a booster dose of a conjugated Hib vaccine represents an example of a true booster response.

b) As commonly used, however, the term booster dose is often used simply to refer to a follow-up dose of vaccine long after the first immunization. This immune response after such a follow-up immunization may or may not be different from the initial immunization. For example, an unconjugated Hib vaccine does not induce a true booster response since there is no immunological memory to this polysaccharide vaccine. Research continues as to whether oral killed whole cell cholera mounts a true immune booster response if a dose is given long after the first immunization."

Cost-effectiveness and cost-benefit

Economists express the benefits of a vaccine program by determining whether the vaccine is cost-effective or cost-beneficial.

a) Cost-effectiveness of a vaccine program can be expressed as cost-per-case averted, cost-per-death averted, and/or cost-per-DALY (disability-adjusted life year) averted. The major determinants of cost-effectiveness are the rates of disease, rates of cholera deaths, and the cost of the vaccine. Clearly, a vaccine will have improved cost-effectiveness if the disease burden is very high and if the vaccine is very inexpensive. If the rate of disease is very low (say <1 per 10,000) and/or if the cost of the vaccine is high (say >5 USD per dose), the vaccine will be less cost-effective.

b) When considering cost-effectiveness, one needs to consider the cost of the disease burden without a vaccine. In an area with a high burden of cholera, there are significant costs to the health system as well as personal costs for the patients to treat the disease. Furthermore, when cholera patients die, there are long-term costs due to the loss of lifetime productivity.

c) Cost-benefit is related to cost-effectiveness, but is calculated by considering both the costs and the benefits in monetary terms. Such an evaluation of cost-benefit may determine the cost-per-dollar invested in the program. For example, if a government decides to invest 1 million dollars for cholera control, they may save 2 million dollars in costs related to the disease. Such an intervention would obviously be cost saving, not simply cost-effective.

Integrated cholera control program

An integrated cholera control program has several coordinated preventive and treatment elements.

a) Examples of preventive elements include oral cholera vaccine, water and sanitation, health education, and surveillance.

b) Examples of treatment elements include excellent and available case management, including facilities for intravenous and oral rehydration, antibiotics, zinc, pregnancy delivery, and health education.

c) The different elements need to complement each other in an integrated, synergistic manner. For example, vaccine teams need to reinforce messages concerning water, sanitation, and hygiene (WASH) and availability of treatment. Families of cholera patients are at higher risk, so safe water interventions should target these families. Similarly, WASH staff should reinforce the need for treatment and vaccine, etc. Methods for integration will need to be adapted to each situation, and the lessons from this integration need to be documented and disseminated.

Cholera control, elimination, and eradication

a) The term control means reducing the risk of cholera death to a very low level (with a CFR less than 0.5%) and reducing the rate of cholera to a very low level (say 0.1/1,000). These numbers are obviously arbitrary and will probably depend on the individual area. For example, a country with a history of annual cholera outbreaks may consider it to be controlled when rates have been reduced by 90% relative to pre-intervention rates.

b) The term elimination is generally used to mean that the rates of cholera are so low that it is no longer a public health threat to the population. With an integrated program, elimination is possible for many of the countries where cholera is currently endemic.

c) The term eradication is generally used to mean that the pathogen is no longer present on Earth. Since *V. cholerae* normally inhabits environmental waters, it is not possible to achieve eradication given our current state of knowledge.

Annex

This annex is a commentary that expands on the use of the terms listed in the glossary above. It is designed to provide additional insight into conceptualization of the definitions used here and points the way toward additional research needed for certain concepts.

Annex A. Definition of acute diarrhea

The official definition is an illness characterized by > 3 loose or watery (non-bloody) stools in a 24-hour period generally associated with other symptoms, such as nausea, vomiting, fever, abdominal cramps, fatigue, or weakness. However, this definition includes many events which are rather trivial and do not constitute a serious threat to health. If one is attempting to carry out surveillance for illnesses that are a greater threat, one may wish to categorize the illness in a way that restricts the definition to those that are moderate or severe. A moderate or severe illness may restrict the cases to those seeking medical care, those with a certain degree of dehydration, those with a larger number of stools (say >5 in 24 hours), or those episodes associated with decreased daily activities. An example is the finding that the attack rate for acute diarrhea for groups of travelers to Guatemala was about 30%; however, when restricted to those episodes that were associated with a reduction in daily activities, the attack rate was about 10%. The others were mild cases and the individuals were able to continue with their normal activities.

Annex B. Case definitions for cholera

A case generally refers to a person who has acute watery diarrhea rather than a person from whom the bacterium can be isolated. This distinction is important when reading about the proportion of cholera infections that are asymptomatic, mild, moderate, or severe. Health-care providers will not generally see the persons with asymptomatic infections, thus, to say that 80% of infections are mild or asymptomatic is relevant to the epidemiologist but not to the physician who is only seeing the persons with more severe symptoms. Among these ill patients, most will be moderate or severe.

The definition used by the World Health Organization recognizes that most health facilities will not be able to carry out fecal cultures and will have to make a diagnosis based on clinical signs and symptoms. The WHO definition is thus a compromise intended to include cases that are most likely to be cholera without including those illnesses due to other etiologies. Children under the age of 5 years often have diarrhea due to other bacteria or viruses, but by excluding severe diarrheal illnesses in young children, one will miss many cholera cases. In fact, children generally have the highest rates of cholera, but they have the highest rates of other illnesses as well.

Annex C. Cholera: endemic, epidemic, or outbreak

The words *endemic*, *epidemic* and *outbreak* are often used to describe certain patterns of cholera. Importantly, the World Health Organization made recommendations on the use of oral cholera vaccine using these terms. Generally they indicate whether cases are being detected at some regular frequency (endemic), whether there are many cases occurring in an unexpected manner (epidemic), or whether the cases are not exactly unexpected but the numbers have suddenly increased so that large numbers of persons are being affected (outbreak).

For many infections, the term epidemic implies that rates are more than normal. For example, there may be an influenza epidemic when the numbers of cases exceed the numbers seen during an average year in a given place. This definition does not work well for cholera since it is rare for an average number to be known.

Some countries' regions clearly are endemic. An example is Dhaka, Bangladesh, where cholera patients are treated every month of the year, but there are seasonal increases before and after the rainy season (April–May and September–October). In the southern districts of Bangladesh, cases are detected only in March–April but not during other times of the year. By contrast, cases are detected only in October–November in the northern part of the country. This country thus shows distinct, but regular, patterns of either continuous cholera or annual, but predictable, peaks. The rates of the disease vary from year to year, but the pattern

is fairly constant. Clearly, Dhaka has endemic cholera, but the other parts of the country are also endemic, though with strong seasonality such that for most of the year there are no cases.

Most countries with cholera have patterns which are less predictable. In these countries cholera cases may be detected from time to time, but not every year and/or not everywhere. It is unclear whether this pattern of skip years represents a true picture of cholera in these areas, or whether the surveillance system only detects cases when an outbreak with many cases is occurring. It may be that sporadic or occasional cases are not detected except when they occur in clusters.

Because of the need for simple and practical definitions, it was recently proposed that an endemic area is one with confirmed cholera cases recognized during 3 out of the last 5 years. Using this definition, it would seem that nearly all of the countries in sub-Saharan Africa have areas endemic for cholera. Within the countries, national authorities may be able to identify specific regions of the country that are endemic, while other regions are not. Thus, local knowledge is crucial when defining control strategies.

Annex D. Mechanisms of endemicity

The words endemic and outbreak refer to cases detected through clinical surveillance at health facilities. From detection of these clinical cases, it may appear that cholera transmission occurs exclusively through a fecal-oral route (person-to-feces-to-person (PFP)). This understanding of cholera's transmission is mostly, but not entirely, correct since *V. cholerae* can also live in environmental waters for months or even years. [1] From time to time, due to reasons that are poorly understood, the environmental vibrios can infect humans and begin a PFP transmission. However, in a given situation it is not always known whether an outbreak occurs because of emergence of *V. cholerae* from the environment or whether it is spread from one geographic region to another. Direct infection from the environment is sometimes referred to as slow transmission while direct fecal-oral transmission is referred to as fast transmission. [2]

An example of the difference between the two mechanisms is illustrated by the occurrence of sequential outbreaks in Kenya. [3] Initially, these outbreaks were thought to represent the spread of a strain of *V. cholerae* from people traveling on roads between three sites. Upon reanalysis of the strains, using additional molecular markers, these three outbreaks actually represented three separate outbreaks, each arising from a local (or at least a different) source. [3] Though cholera can originate from an environmentally acquired infection, during an outbreak, most cases are in fact a result of fecal-oral, or fast, transmission. Nevertheless, the outbreak may actually have originated from an infection from the environment.

The role of environmental vibrios suggests that an endemic area has two characteristics: a) *V. cholerae* has found a home in the environment and b) poor sanitation facilitates PFP transmission from the initial to secondary cases. The Gulf Coast of the US is potentially an endemic area because *V. cholerae* is resident in the offshore waters, but modern sanitation does not allow secondary transmission. Thus, in reality, the area is not endemic. By contrast, the waters of Bangladesh have both the resident environmental vibrios as well as poor sanitation which allows for secondary spread. By monitoring areas for environmental *V. cholerae*, we may be better able to identify those regions which are truly endemic and at higher risk for outbreaks.

Annex E. Cholera seasonality

Wherever cholera occurs, rates of cholera nearly always vary according to a seasonal pattern. In a given area, the seasonality tends to be fairly consistent, but within a country, the seasonality is not necessarily consistent. A high season in one part of the country may be a low season in another; thus, it is important to understand the seasonality of subnational areas. Historical data, where available, appears to be the best guide to future high seasons, but certain features may also be important, and characterizing these have led to different theories to explain seasonality. Some of the most common theories have included such factors as temperature, interaction with plankton, drought, floods, and waning immunity. Unfortunately, it has been difficult to develop a unifying explanation for cholera's seasonality that applies to all endemic areas.

One feature that does seem to be a consistently contributing factor is temperature. Cholera seasons often occur during times of the year with higher temperatures, though there may be a several-week lag between the high temperatures and increased rates. Cholera may also be associated with severe floods. Floods seem to be an obvious risk since they facilitate fecal contamination of drinking water. Even though severe outbreaks

may be associated with flooding rainy seasons, the initial cases often occur prior to the rainy season. It is possible that the season that initiates the outbreak may then be followed by other factors (e.g. flooding), which facilitate the spread of the outbreak. It may be then that floods, although important, are simply part of a seasonal cycle in which a perfect storm of events leads to a major outbreak.

Understanding seasonality is critical to understanding appropriate responses to a cholera threat. If cholera has been seen in an area during particular times of the year, measures can be targeted to this time period. Plans can be made to prepare for an outbreak, such as enhanced surveillance, refresher training of medical staff, communication to the public emphasizing safe water and sanitation during a high-risk period, pre-positioning supplies, and, when appropriate, vaccination.

The knowledge of seasonality is also important when attempting to evaluate different interventions to control cholera. Statements are frequently made about how the interventions have controlled the outbreak, when in fact, the season simply passed and the outbreak was following its normal course. This should not discourage efforts to reduce the cholera risk, but policy makers should understand that most outbreaks do follow a certain pattern and tend to decline after reaching a peak, and that an outbreak may last for a few months before it subsides.

While realizing that cholera does follow seasonal patterns, one must also be alert to unusually long outbreaks, such as one in Zimbabwe where cholera transmission continued for over a year. [4, 5] It is not clear if this type of unusually long outbreak pattern will occur more frequently or if the social situation in Zimbabwe at that time was sufficiently unique that such long-lasting outbreaks will be rare.

Annex F. Rates of cholera

Estimating the rate of cholera helps to determine appropriate control measures. The rate, in theory, is a simple calculation in which the numerator is the number of cholera cases and the denominator is the population at risk. Unfortunately, in practice, this calculation is not simple since the number of cases may not be known with precision and the population at risk is also not well defined. For most estimates, a case of cholera is a patient who has (severe) acute watery diarrhea and. These cases are normally counted among patients who come for treatment at a health facility.

An example of an area that has the ability to calculate accurate (gold standard) rates is the rural surveillance area in Matlab, Bangladesh, run by the International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b). Here, cholera rates have ranged from 5 to 50 per 10,000. In this example, the numerator is the number of cases identified among patients who live in this demographically defined study area of 220,000 people, who come to the icddr,b health facility when they have diarrhea, and who are documented by culture to have *V. cholerae* in their fecal sample. The Matlab field area is unique, however, because of the high quality demographic surveillance system which maintains a continuously accurate census, as well as readily accessible health facilities and a high quality microbiology laboratory able to culture fecal specimens on all such patients.

Since obtaining gold standard rates is not practical for most countries, rates of cholera will need to be based on estimates of the catchment population while counting the numbers of patients who meet a case definition of cholera, but often without bacteriological confirmation. While these estimates are important to make, there are several reasons that these rates are imprecise, including the following:

1. Cases that are less severe may not be recognized as cholera even though they were severe enough that medical care was sought.
2. Cases may not be counted because the patients did not come for treatment, or were not able to come. They may have received treatment from other providers or they may have received no treatment. These missed cases importantly include some who died.
3. Sporadic cases may not be counted if they occur outside of an outbreak.
4. The numbers of cases may be overestimated because other pathogens may also cause diarrhea and be counted as cholera cases during an outbreak.

5. The catchment population may not be known with precision and is imprecise because of a variable distance that patients travel for treatment. Persons living close to the facility are more likely to come for treatment, but those living farther away may not be able to reach the facility, or reach it in time.

6. The case definition may change during a declared cholera outbreak and the numbers of patients able to avail free medical care may also change during the declared outbreak.

Annex G. Addressing the limitations of estimating rates

Since routinely collected data have many limitations when attempting to calculate rates, countries need to identify methods for providing sufficiently reliable information for decision-making. There is a need for testing innovative epidemiological/lab methods to better define the cholera disease burden. An example of such a system is the selection of sentinel sites where cholera has historically occurred and detecting cases using rapid diagnostic tests. These will hopefully improve knowledge of rates of cholera, as well as assist in defining the seasonality and risk factors for cholera. (A manual for using the rapid diagnostic test is included in the toolkit at www.stopcholera.org.)

Annex H. Case fatality rate (CFR) and cholera-specific mortality rate

Case fatality rates (CFRs) provide an estimate of cholera deaths among patients coming to a health facility. If treatment is high quality, all cholera patients who come for treatment should survive. Unfortunately, not all patients do survive. The rate of these deaths is calculated using the number of cholera cases who arrive alive at a health facility as the denominator and the number of patients who die as the numerator. Thus, this rate is used to express the percentage of cholera cases who die after reaching the treatment facility. However, there may be inconsistencies in the way that this rate is calculated. Some inconsistencies have included whether or not to include the deaths of patients who died:

a) Prior to arrival at the facility but were still brought to the facility,

b) Upon arrival at the facility or very soon after arrival (say within 5 minutes),

c) Without coming to a health facility but whose death was detected through a retrospective survey or active case finding or community based surveillance.

Calculation of the CFR is an important indicator of quality of health care and is frequently reported in the national and WHO reports, but generally these rates are not explained. That is, the reasons for the deaths are not generally categorized as to what actions might best improve survival.

Borrowing from the system developed for maternal emergencies, cholera deaths might be categorized into 3 "delays." According to this model, "If prompt, adequate treatment is provided, the outcome will usually be satisfactory; therefore, the outcome is most adversely affected by delayed treatment. We examine research on the factors that: (1) delay the decision to seek care; (2) delay arrival at a health facility; and (3) delay the provision of adequate care."[6]

This model could then be extended to further characterize the third delay: 3a) deaths that occur within the first critical hour after reaching the facility, and 3b) those that occur later, presumably after the patient should have stabilized.

Clearly the CFR should provide an estimate of the deaths related to the 3rd delay, but it will not provide an estimate of the deaths that occur prior to arrival at a facility. Thus, other methods will be needed to detect these additional deaths, which often far exceed the deaths at the facility. [7] The total number of cholera deaths would then best be expressed as a cholera-specific mortality rate in the population, and this rate should include all cholera-related deaths whether or not they were treated at a facility. Unfortunately, cholera deaths most often occur in areas without death registers that would identify cholera deaths occurring in the community, but hopefully better methods for detecting these deaths can be developed.

Annex I. Additional information about the microbiology of V. cholerae

a. There are many other serogroups of *V. cholerae* in addition to O1 and 0139. However, even though these bacteria may cause diarrheal illness, the resulting infections have not been associated with epidemic disease. The term used for these strains is non O1-non O139 *V. cholerae*. Previously, they were known as "NAG" (non-agglutinating vibrios).

b. Within the serogroup O1 *V. cholerae*, there are two serotypes, Ogawa and Inaba and these can be identified by agglutination with specific antisera. A third serotype, Hikojima agglutinates with both the Ogawa and the Inaba antisera. The serotype is useful as a marker of the epidemic strain, but the clinical disease is the same between the two.

c. The serogroup O1 can also be divided between two biotypes, classical and El Tor. Classical strains were the predominant biotype until the late 1960s when El Tor strains replaced classical strains.

d. The pathogenic mechanism of *V. cholerae* includes production of a toxin called cholera toxin. Strains of *V. cholerae* O1 generally produce the toxin, but not all strains do. In fact, strains from the environment frequently are non-toxigenic. Strains of other serotypes may produce the toxin, but generally they do not.

e. An epidemic strain is identified as one that is serogroup O1 or O139 and also produces cholera toxin. However, during outbreaks, one can generally assume the strains isolated are toxigenic.

f. Toxins of classical and El Tor strains can be differentiated genetically. Since the 1990s, El Tor strains expressing classical toxin have become predominant and are called hybrid strains. On average, these mutant strains appear to cause more severe disease.

g. Molecular markers of strains of *V. cholerae*. Different molecular methods are now available to identify specific strains of *V. cholerae*. These vary in their specificity ranging from PFGE (which is a useful starting method) to complete sequencing of the bacterial DNA). Another method, MLVA, is becoming more commonly used as a less expensive method to quickly assess differences between strains during an outbreak, or to observe the evolution of strains over time and space.

Annex J. Vaccine coverage rates

When implementing a cholera vaccine campaign, the implementing agency will define a target group and will attempt to reach everyone in that target group. That is, the campaign will attempt to have a coverage rate of 100%. Clearly, this never happens since there are always some people who will not receive the vaccine because they refuse, they may be ill, they may be away, etc. Furthermore, some may receive only one dose but may not receive the second dose, so the coverage rates will differ between first and second doses. To improve their campaigns, the agency will attempt strategies to increase coverage rates, and the indicator of the success of these strategies will be the coverage rate.

While the goal of the campaign is to attempt to reach a high percentage of the target group, the target group may represent only a certain proportion of the total population. For example, the campaign might decide to target all women and children between age 1 and 15 years. Assuming that this target group represents 60% of the entire population, coverage of the target population of 80% suggests that 48% of the total population has received vaccine. Overall coverage rate, not just target coverage rate, will be important to those who wish to evaluate the overall impact of the vaccine campaign.

Thus, calculation of coverage rates are needed to monitor efficiency of the campaign within the target group as well as to evaluate the overall impact of the vaccine campaign in the population, but a single coverage is not adequate to describe vaccine coverage.

Annex K. The goal of a vaccine program: reduced rates of disease or reduced mortality rates?

Oral cholera vaccine (OCV) is designed to protect against cases of cholera, and such a reduction will logically reduce the number of cholera deaths. However, there may be a differential effect on cholera mortality because of access to effective treatment. Persons living close to a cholera treatment center should never die from cholera, regardless of vaccinations, since treatment (if provided in time) should be 100% successful in

preventing death. However, if people do not have access for quick treatment, deaths are much more common. Thus, if vaccine supplies are limited, one needs to consider whether it is feasible to provide vaccine to persons at risk (especially those in remote areas) who may not have access to treatment.

Annex L. Booster doses of vaccine

a. There is limited research on the booster doses of OCV. Only one study has been carried out on the immunological characteristics to B subunit following a booster dose of Dukoral given to Swedish volunteers several years after the first dose. [8] It is not clear if this study is representative of persons living in cholera endemic areas, or if there is a true booster response to LPS antigens in the vaccine, but it does suggest that a true booster response may be possible with OCV, as do studies which have demonstrated that memory B cells are stimulated by OCV.

b. The package insert for Dukoral recommends a booster dose after 2 years for persons over 6 years and after 6 months for those 2 to 6 years using the same dose schedule as the original immunization. The inserts for Shanchol and Euvichol do not provide guidance for booster doses. The recommendation for Dukoral was based on the data from the 1985 trial in Bangladesh which showed a decline in protection among children after 6 months and after 3 years among older persons. Current studies with Shanchol have documented that immunization using current formulations of vaccine protects for 5 years in both children and adults.

c. Clearly, there is need to carry out studies on which to base recommendations for booster doses with both Dukoral, Euvichol and Shanchol. Specific questions relate to the number and optimal interval of doses needed for such a booster, how these factors relate to the age of the subject and how to integrate this information into national programs

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