Global Task Force on Cholera Control (GTFCC) Working Group on Surveillance

Surveillance & Global Monitoring sub-group and Outbreak sub-group

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Acronyms and abbreviations

AWD	acute watery diarrhoea
CATI	case-area targeted intervention
GTFCC	Global Task Force on Cholera Control
NCP	national cholera control plan
OCV	oral cholera vaccine
PCR	polymerase chain reaction
RDT	rapid diagnostic test
SOP	standard operating procedure
WASH	water, sanitation and hygiene
WHO	World Health Organization

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Surveillance and Monitoring Subgroup update

Andrew Azman and Nick Thomson (sub-group leads)

The workplan of the surveillance and monitoring subgroup includes three main areas: establishing minimum indicator-based surveillance standards; the GTFCC global cholera database; and cholera elimination.

The presentation focussed on work to review and revise current GTFCC cholera case definitions.

Cholera surveillance has four goals: outbreak detection/early warning; outbreak monitoring; targeting prevention and control interventions; and routine monitoring of trends. All of these rely on correct and systematic application of case definitions, which are also necessary for sustained control and/or elimination of cholera.

The sub-group applied a stepwise approach to review the existing cholera case definitions. First, the components of different case definitions were identified; evidence was gathered from publications, guidelines, book chapters and expert opinions (though most was limited to what was available electronically). Based on this, the evidence was used to review and document the rationale for different components of case definitions (e.g., duration of illness, age, severity) and their impact on sensitivity and specificity. Potential adjustments and additions were then discussed through meetings, surveys and written feedback with the guiding principle of keeping definitions simple. In addition, knowledge and research gaps were identified.

Definition of acute watery diarrhoea (AWD)

The current GTFCC definition of AWD is: "*an illness characterized by three or more loose or watery (non-bloody) stools within a 24-hour period."* This is missing a definition of "acute," which would be useful to exclude persistent diarrhoeas likely due to other aetiologies, and for retrospective case finding. "Watery" might also benefit from more detailed description. To address this, the following new definition has been proposed:

Acute watery diarrhoea (AWD) is an illness where:

- *"Acute" is defined as lasting seven days or less*
- *"Watery" is defined as non-bloody liquid stools that may contain mucous**
- *Diarrhoea is defined as three or more loose stools within a 24-hour period*

(*NB rice water stool was discussed, but seen as too specific).

Ideally, the overall minimum surveillance standards guidance document under development will include recommendations on differential diagnoses of AWD.

Suspected cholera case definition

Detection of suspected cholera cases is the entry point for cholera case identification. Monitoring of these cases is part of routine surveillance and an important component for trends monitoring and early outbreak detection. The suspected cholera case definition is by design very sensitive, aiming to capture the largest possible number of cholera cases. As the suspected case definition is based on clinical criteria, it is not specific to cholera only. In this context, and especially in low cholera prevalence settings, the positive predictive value of the suspected case definition is low, meaning that many suspected cases are not true cholera cases. The primary aim of revising the suspected cholera case definition was to ensure to maintain high sensitivity of the case definition in order to avoid missing cases. The secondary aim was to have as high a specificity as possible without compromising sensitivity, to reduce overreporting

Suspected cases are also used in monitoring ongoing outbreaks in order to target interventions. The suspected case definition during outbreaks is broadened to include all age groups and remove severity as a criterion. Due to an increase in cholera prevalence during an outbreak, the positive predictive value also increases, and so to some extent compensates for lower sensitivity in the case definition. Suspected cases monitoring allows insight into whether control interventions are effective. Suspected cases are also the target population for confirmatory testing.

The current suspected case definition in areas where a cholera outbreak has not been declared is "*any patient aged 2 years and older presenting with acute watery diarrhoea and severe dehydration or dying from acute watery diarrhoea*." In areas where a cholera outbreak has been declared, it is "*any person presenting with or dying from acute watery diarrhoea*." Several potential challenges with these definitions were identified, including but not limited to the political dimension of declaring outbreaks, the definition of severe dehydration, the rationale for the age cut-off. To address these, the following new definition has been proposed:

> In areas where there is currently no known cholera outbreak, a suspected cholera case is defined as: *Any person aged two years and older presenting with acute watery diarrhoea AND Severe dehydration* OR dying from acute watery diarrhoea.*

In areas where a cholera outbreak has currently been detected, a suspected cholera case is defined as: *Any person presenting with or dying from AWD*

** Reference to GTFCC outbreak response field manual 2019, p.60*

The possible need for a community specific suspected cholera definition was discussed and it was concluded that the wording would be context/ country specific. The overall minimum surveillance standards guidance document under development should include a recommendation to adapt the suspect case definition as required, if surveillance at the community level is implemented.

Probable case definition

Discussion of the merits of a probable case definition have not yet achieved consensus. Many other diseases have this, and in the context of cholera the motivation behind arguing for it is to have a label for people who test positive using rapid diagnostic tests (RDTs). Arguments for such a definition include its use to prioritize interventions where resources are limited; to increase visibility of RDTs and their use in cholera surveillance; to improve outbreak detection and monitoring; and to provide continuity from case reporting to outbreak detection. Arguments against include the potential difficulty for interpretation and potential for misuse of such a definition unless denominators (e.g. number of suspected cases tested by RDT) are systematically provided; the fact that focusing on systematic reporting of testing results could achieve the same goals; and the fact that in low prevalence settings, the likelihood of positive RDT being cholera is lower. In addition to this, no RDT has yet been prequalified by WHO.

Discussions on this point are still going on, with the following possible definitions presented for discussion:

A suspected cholera case AND (the following options are being discussed)*:*

- *a reactive (positive) rapid diagnostic test (RDT), where the reported RDT performance is at least equivalent to the WHO prequalification target product profile (sensitivity = XX% ; specificity = XX%)*
- *a reactive (positive) rapid diagnostic test (RDT), where the reported RDT performance has a sensitivity ≥ XX% and specificity ≥ XX%*
- *a reactive (positive) rapid diagnostic test (RDT) in the process of prequalification by WHO*
- *a reactive (positive) rapid diagnostic test (RDT) that is prequalified by WHO.*

Confirmed case definition

The current definition of a confirmed case is "*a suspected case with Vibrio cholerae O1 or O139 confirmed by culture or PCR (polymerase chain reaction) test and, in countries where cholera is not present or has been eliminated, the Vibrio cholerae O1or O139 strain is demonstrated to be toxigenic*." The following new definition has been proposed:

A confirmed cholera case is a suspected case infected with Vibrio cholerae identified by:

Culture followed by serogroup testing for O1 or O139 by agglutination tests with specific antisera

OR

PCR targeting genes specific for V. cholerae species AND O1 or O139 antigens

AND in countries where cholera has not been detected for 3 years or more, PCR targeting gene(s) specific for cholera toxin.*

(*3 years relates to current definition of elimination, this may be reviewed/ updated).

Next steps

The next steps in this process will be to anchor these proposed case definitions within a defined testing strategy; to apply them practically in order to trigger public health action (such as by reviewing and updating existing guidance working alongside the outbreak subgroup); to prepare job aids that can be printed and displayed at health facilities, including recommended public health actions; to define different transmission settings and recommend surveillance approaches for each; to develop and agree a minimum core dataset that can meet surveillance goals and support the goals of the Global Roadmap to 2030 (Roadmap); and, beyond the definitions themselves, to work continuously towards accurate implementation, clear guidance, continuous training and further important investments in sustained control and elimination of cholera.

Discussion

A period of open discussion raised several points and themes.

The impact of the case definitions on the rapid deployment of response interventions was discussed. There may be a risk that complete distinction between suspect, probable and confirmed cases may be used politically in a manner that could be detrimental to outbreak response. To mitigate this risk, definitions should be as simple as possible in order to improve their application in the field. These definitions will often be implemented in areas where facilities are scarce and responses depend more on suspected cases . If definitions are simple, their implementation in the field is easier.

There are concerns regarding confirmation of cases in places where there has not been an outbreak for a long time – for example, Somalia reported an outbreak in 2020 in an area free from cholera for over three years, and this needed to be confirmed in order to direct prevention and control measures. This raises challenges if confirmation requires often inaccessible technologies like PCR testing. Serogroup testing coupled with culture is also not going to be an approach that helps countries to test more systematically. The minimum surveillance standards guidance document on surveillance should include information for countries on follow up and response actions to be taken even upon identification of clusters of suspected cases (suspected outbreaks) to prevent such situations.

Arguments for a probable case definition include the position that simple-as-possible case definitions are required at same time as the need for countries to have realistic ways of prioritizing investigations, support, testing and other measures. High incidence of other diarrhoeal diseases than cholera in some areas make it impossible or unlikely that all cases of severe diarrhoea will be properly investigated, especially when resources are scarce. To detect outbreaks and/or reintroduction of *V. cholerae* in such settings it is important not to generate too many false alerts, and to be able to focus on the most important cases when the system is overwhelmed which would be facilitated by probable case definitions.

Cholera RDTs are less specific or sensitive compared to RDTs for malaria, HIV and other diseases for which RDTs have proven very helpful. Some people feel that the technology of current RDTs and the policy framework through which WHO is in the process of identifying RDTs that meet the desired performance characteristics (prequalification) have not yet reached the point where the benefits of including RDTs in an official probable case definition for surveillance purposes outweigh the risks. That

said, currently, while there are no WHO-prequalified RDTs, tests are nonetheless in use, there remains a role for RDTs, and the GTFCC has a role in setting parameters to define it. The use of RDTs should be accompanied by appropriate training and monitoring. If the use of RDTs is monitored according to parameters that are clearly defined and disseminated, and if the GTFCC works to encourage progress on the technology and the development of a more robust policy framework, then in the next few years the GTFCC, frontline health care providers and public health officials in cholera-affected countries will learn a lot more about the challenges and benefits of RDT use in different contexts – at which point the world will be better prepared to evaluate and consider their inclusion in probable case definitions to increase the likelihood that a signal that is generated is truly cholera. Overall, the strategy promoted by the GTFCC is therefore to encourage manufacturers to submit their products for prequalification, and to support accessibility and availability of RDTs, especially in countries with low resources. Looking ahead, beyond initial difficulties to establish how, with the necessary support, RDTs can be more broadly used for surveillance.

Work around patterns of disease has involved lots of discussions around how to incorporate new diagnostics, including in-the-field approaches like RDTs. These discussions also have value in setting a trajectory for how RDTs might be used in context of implementing the Roadmap.

Update from the Outbreak subgroup

Raoul Kamadjeu *(sub-group lead)*

The workplan of the outbreak subgroup includes three main areas: outbreak detection; investigation; and case-area targeted interventions.

This presentation focussed on work to review and revise cholera outbreak definitions.

The purpose of a suspected outbreak definition is as a trigger for investigation of (and early response to) an outbreak. The purpose of a confirmed outbreak definition is as a trigger for comprehensive response, including *V. cholerae*-specific response (e.g. reactive vaccination). The purpose of defining the end of an outbreak is to provide a means of returning to routine surveillance activities. In some countries, an end of outbreak declaration also has policy implications.

The process of refining these definitions began with a broader discussion on current definitions and options for their modification. As a first step, the group agreed to propose outbreak definitions by non-persistent and persistent transmission settings, where a persistent transmission setting refers to places with year-round cholera transmission, and a non-persistent setting to places where cholera transmission is interrupted for a specified period of time (to be defined). The rationale for this was that investigation and response thresholds between those settings should differ. Currently, there are no clear separate definitions of those two separate settings. The outbreak definitions were then reviewed in detail by persistent and non-persistent transmission settings.

Several other themes were discussed, including whether the humanitarian setting requires its own set of definitions. As this type of setting would be highly contextual and therefore too complex to allow a blanket recommendation, the group agreed to include a note to the effect that these settings require special considerations and may warrant different (more sensitive) thresholds. The end of an outbreak – currently mentioned in the testing strategy section of the GTFCC interim surveillance guidance – requires a reviewed definition. Finally, certain terminology (such as geographical area for an outbreak detection and local transmission) need to be considered and a decision made as to whether improved definitions are needed.

Suspected outbreak definition – non persistent transmission setting

The current definition of a suspected outbreak, or cholera alert, is defined by the detection of: "*Two or more people aged 2 years and older (linked by time and place) with acute watery diarrhoea and severe dehydration or dying from acute watery diarrhoea from the same areas within one week of one another; OR; One death from severe acute watery diarrhoea in a person at least 5 years old; OR One case of acute watery diarrhoea testing positive for cholera by rapid diagnostic test (RDT) in an area (including those at risk for extension from a current outbreak) that has not yet detected a confirmed case of cholera*". This requires adjustment of terminology from "alert" to "suspected outbreak" to align with other WHO early warning terminology; some refinement of the wording; the addition of the definition of a confirmed case with no evidence of local transmission, to align with the definition of a confirmed outbreak.

To address these issues, the following new definition has been proposed:

> *Two or more suspected cholera cases (person) from the same geographical area (place) reported within one week of each other (time)*
>
> *OR*
>
> *One person aged 2 years or older dying from acute watery diarrhoea*
>
> *OR*
>
> *One probable case (or: One suspected cholera case testing positive by rapid diagnostic test)*
>
> *OR*
>
> *One single confirmed cholera case with no evidence of local transmission identified (yet)*

Confirmed outbreak definition – non persistent transmission setting

Currently, a cholera outbreak "*is defined by the occurrence of at least one confirmed case of cholera and evidence of local transmission. Outbreaks can also occur in areas with sustained (year-round) transmission and are defined as an unexpected increase (in magnitude or timing) of suspected cases over two consecutive weeks of which some are laboratory confirmed. Such increases should be investigated and responded to appropriately through additional outbreak response and control measures*." This does not specifically use the term "confirmed" as in "confirmed cholera outbreak." The first part applies to non-persistent cholera settings and the second to persistent ones, so "unexpected increase" is unclear. Separating the two settings could be an improvement. The discussion on defining "evidence of local transmission" concluded that this would be very context-dependent and so examples could be included in the guidance, but no strict definition developed. The following new definition has therefore been proposed for a confirmed outbreak:

> *The occurrence of at least one laboratory (culture or PCR) confirmed cholera case AND evidence of local transmission in a specified geographical area (cases reporting common risk exposure(s) or being linked by place and time).*
>
> **Outbreak start date: The start date of the outbreak is the date of onset of the first reported case (suspected, probable or confirmed)*

End of outbreak definition – non persistent transmission setting

The current definition of the end of an outbreak is: "*when the number of suspected cases in the epidemic area significantly declines and all samples from all AWD cases test negative by RDT, culture or PCR for a minimum period of two weeks, the outbreak can be considered ended*." There was discussion of whether an option should be provided for areas with limited testing capacities, and agreement that the aim should be to improve the capacity to test suspected cases during and at the end of outbreaks in all cholera affected areas. An option was proposed for situations where not all suspected cases can be sampled and tested. The following new definition has been proposed:

> *Complete interruption of cholera transmission evidenced by negative laboratory test results (culture or PCR) of all reported suspected cholera cases (supported by active case finding) in a specified geographical area, for a minimum of 2 consecutive weeks.*
>
> *Consideration for areas with limited laboratory capacity:*
> *Evidence of negative laboratory test results for all sampled suspected cases for a minimum of 2 consecutive weeks, with a minimum of x suspected cases sampled per week (remains to be defined).*
>
> **Outbreak end date: The end of the outbreak is 14 days after the date of recovery of the last confirmed case OR 14 days after the date of death of the last suspected, probable or confirmed case, whichever comes last.*

Suspected outbreak definitions - persistent transmission setting

There is currently no definition of a suspected outbreak in a persistent setting. Where possible and logical, any new definition should mirror that for non-persistent settings. Increase in deaths over baseline was not considered an appropriate metric as weekly baseline is unlikely to be meaningful (in that it is too variable), and any unexpected increase in deaths would be covered through event-based surveillance. For laboratory tests, an increase in positive tests on its own is not meaningful, as such an increase could be due purely to increased testing; instead it is more appropriate to look at increases in the proportion of positive tests. There is as yet no consensus on how to calculate the baseline and degree of deviation from baseline (threshold). The following new definition has been proposed:

> *An increase in reported suspected cholera cases for ≥1 week above the established baseline in a specified geographical area*
>
> *OR*
>
> *An increase in the positivity rate of RDT tested suspected cholera cases (probable cases) for ≥1 week above the established baseline in a specified geographical area*
>
> *OR*
>
> *An increase in the positivity rate of suspected cholera cases tested by PCR or culture (confirmed cases) for ≥1 week above the established baseline in a specified geographical area*

Confirmed outbreak definition - persistent transmission setting

The current definition of a confirmed outbreak is derived from p6 of the GTFCC interim guidance: "*Outbreaks can also occur in areas with sustained (year-round) transmission and are defined as an unexpected increase (in magnitude or timing) of suspected cases over two consecutive weeks of which some are laboratory confirmed. Such increases should be investigated and responded to appropriately through additional outbreak response and control measures*." In this text, "unexpected" may be too vague. The following new definition is therefore proposed in order to achieve greater clarity and a more logical following-on from the suspected definition:

An increase in the positivity rate of suspected cholera cases tested by PCR or culture (i.e., increase proportion confirmed cases of all cases tested) over ≥ 2 consecutive weeks above the established baseline in a specified geographical area

Considerations for areas with limited laboratory capacity (2 suggestions)

In the absence of adequate laboratory capacities, the confirmed outbreak definition for non-persistent transmission settings may be used.

OR

In areas where systematic laboratory testing of suspected cholera cases has not yet been implemented, a confirmed outbreak may be defined as an increase of suspected cases above the established baseline for two consecutive weeks, of which some (at least x?) are laboratory confirmed.

**Outbreak start date: The start date of the outbreak is the date on which the increase above baseline was first detected.*

End of an outbreak - persistent transmission setting

The current definition of the end of an outbreak is derived from GTFCC interim guidance: "*When the number of suspected cases in the epidemic area significantly declines and all samples from all AWD cases test negative by RDT, culture or PCR for a minimum period of two weeks, the outbreak can be considered ended*." Discussion on improving this included the suggestion to require the return of all available cholera indicators (incidence, positivity rate of tests) to their respective baseline values for two consecutive weeks, with the precise outbreak end date defined as the date on which indicators have returned to baseline for two weeks.

The following new definition has been proposed:

> *Return of all available cholera indicators (incidence, positivity rate of tests) to their respective baseline values for 2 consecutive weeks*

Next steps

These proposed adaptations have attempted to achieve clear separation of outbreak definitions for persistent and non-persistent settings, due to the different action thresholds required in each; and to specify a clear end to outbreak definitions for both types of settings. Pending items include a decision on how to calculate the baseline for persistent settings; defining action thresholds and guidance on which actions to take; development of a testing strategy and use of RDTs for outbreak detection and monitoring (a joint effort with the laboratory working group and the surveillance and monitoring subgroup); and the development of a case report and case investigation form (jointly with the surveillance and monitoring subgroup). For outbreak detection, the next steps will be to develop recommendations on minimum standards for event-based surveillance for outbreak detection and on community-based surveillance for outbreak detection and monitoring (further to indicator-based surveillance); to develop practical recommendations to support implementation of the recommended minimum surveillance standards for outbreak detection; to develop criteria for evaluating sensitivity of cholera surveillance for timely detection and notification of cholera outbreaks; and to foster innovation in cholera outbreak detection and forecasting. For outbreak investigation, the next steps are to review existing resources, assess the need to develop further GTFCC guidance on investigating cholera outbreaks, and develop standard operating procedures (SOPs) and case investigation forms if appropriate; and to integrate and track indicators for timeliness of cholera outbreak investigations.

Finally, in the area of case-area targeted interventions (CATI), a framework will be recommended for CATI implementation.

Discussion

A period of open discussion raised several points and themes.

“Persistent” versus “non-persistent” terminology is a placeholder, intended to distinguish between countries that report on occasion or which have outbreaks but not all year round versus those that report throughout most of the year. This is not equivalent to the current definition of ”endemic,” which encompasses any country that has had some transmission of cholera in the past three years.

There is discussion to be had around whether to include RDTs more in outbreak definitions: while they might be more problematic in case definitions for individual patients, in outbreaks they could be very important. Discussion of RDTs and the strategy of their use will be approached in partnership with both epidemiology and laboratory experts.

Establishment of baselines is a critical part of the conversation. There is an important need to clarify baselines in places with persistent regular transmission. Flexibility and simplicity are required to capture baselines, relying on local knowledge and local data to establish them. Many discussions are ongoing as to how such a process should work – i.e. with national teams calculating and applying it to areas, or through data being collected for areas (and if so by whom), or in some other way. Baselines are intuitively known by people on the ground with data and historical knowledge, who are able, when surveillance is working, to pick up on abnormal trends; making that process more systematic is a job to be approached with the help of the GTFCC secretariat. A preliminary examination of country data has been undertaken to see where year-round transmission settings are found and to look at possibilities on how to calculate baselines, but this requires further work and is likely to vary by country. This effort aims at least to provide examples of how such data can be collected and calculated.