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

Cholera Indicators

Webinar 02, 26 June 2020

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Acronyms and abbreviations

CFR	case fatality rate
GTFCC	Global Task Force on Cholera Control
IDP	internally displaced population
LGA	local government authority (Nigeria)
MAI	mean annual incidence
MSF	Médécins sans Frontières
NCCP	national cholera control plan
NCDC	Nigeria Centre for Disease Control
NGO	non-governmental organization
OCV	oral cholera vaccine
RDT	rapid diagnostic test
UN	United Nations
US CDC	US Centers for Disease Control and Prevention
WASH	water, sanitation and hygiene
WHO	World Health Organization

Note to the reader

This report condenses discussions according to the subjects addressed, rather than attempting to provide a chronological summary. It addresses the themes emerging from wide-ranging discussions among all speakers, and do not necessarily imply consensus. Summaries of presentations and points made in discussion are presented as the opinions expressed; no judgement is implied as to their veracity or otherwise.

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This webinar was moderated by **David Olson** (WHO) and **Fran Luquero** (Médécins Sans Frontières/MSF), whose introduction stressed the importance of choosing the correct surveillance indicators to identify areas to be prioritized for cholera control.

Cholera hotspots mapping in Nigeria

Iliya Cheshi, *Nigeria Centre for Disease Control (NCDC)*

Nigeria is a large, varied country with a population of around 160 million people spread over 36 states; over 250 ethnic groups speaking over 500 languages; and a rough 50/50 split between Christian and Muslim populations.

To align its cholera control strategies with the global road map of the Global Task Force on Cholera Control (GTFCC), the NCDC cholera team has published a preparedness and response plan in which assessing national cholera transmission dynamics and identifying cholera hotspots are immediate goals—both essential in order to guide rapid development of cholera prevention and control activities, and to catalyze design and implementation of solutions for long-term, cost-effective cholera elimination.

The NCDC defines cholera hotspots as geographically limited areas in which environmental, cultural and/or socioeconomic conditions facilitate transmission, and where cholera persists or re-appears regularly. Identification was based on standardized retrospective cholera case data from 2012 to 2017, aggregated by week at local government authority (LGA) level. Data were reformatted for statistical analysis and mapping using projected population figures 2012-2018 for each LGA. Factors for identifying and prioritizing hotspots for mid-to long-term control activities included burden of cholera (mean annual incidence or MAI); frequency of reporting (the number of years in which an

LGA reported cases); the severity of outbreaks (case fatality rate, or CFR), conditions for water, sanitation and hygiene (WASH); and the demographic nature of local settlements—i.e. the proportion of people living there who represent internally displaced populations (IDP).

Of the 774 LGAs in Nigeria, 310 (or 40% of the total) reported at least one case of cholera for the period under consideration. The NCDC calculated the mean annual incidence rate for each LGA and set an incidence threshold of one case per 10 000 per year as a definition of a "high risk" hotspot, meaning that 83 LGAs—home to an estimated 23 082 577 (or 11.6%) of the Nigerian population—were classified as hotspot areas to be prioritized for interventions. Between them, these LGAs accounted for 83.6% of the total cases recorded nationwide between 2012 and 2017.

The NCDC established six further indicators, or criteria, for more detailed assessment and prioritization of these 83 areas.

Criterion 1 is the frequency of reporting of cholera cases. A weight of 20 was assigned to this criterion and scores were assigned to the number of years of reporting:

- 1 to 2 years = 1
- 3 to 4 years = 2
- 5 to 6 years = 3

Criterion 2 is responsibility for the first 50% of all cholera cases reported. After arranging the total number of cases reported by each LGA in descending order, it became apparent that only 14 LGAs together recorded 50% of the total cases between 2012 and 2017. A weight of 20 was assigned to this criterion with the following scores assigned to each sub category:

- Responsible for first 50% (Yes)= 2
- Responsible for first 50% (No) =1

Criterion 3 was the severity of outbreaks, measured by CFR. Because data were gathered mainly by passive surveillance, this criterion was given the smallest weight, of 10, with the following scores:

- 0% CFR =1
- 0.1 to 10% CFR = 2
- >10% CFR = 3

While the second threshold appears high, it was based on aggregate data from 2012-17, during which period a total of 83 local governments had experienced this level of mortality.

Criterion 4 was current WASH conditions, which were classified as satisfactory if at least 50% of the population can access potable water and/or the presence of active WASH partners or government agencies is verified. "Unsatisfactory" refers to LGAs where less than 50% of the population can access potable water and/or there are no active WASH partners or government agencies present in the LGA. A weight of 25 was assigned to this category with the following score breakdown:

- Satisfactory = 1
- Unsatisfactory = 2

Criterion 5 was "nature of settlement," assigned a weight of 25, with each hotspot LGA demographically classified into three settlement types with the following scores:

- Predominantly host = 1
- Mixture of host and IDP = 2
- Predominantly IDP = 3

Criterion 6 was ongoing transmission. On week 24 of the exercise, which fell in June 2018, 13 009 cases of cholera had been reported with a CFR of 0.89%, and 57 LGAs had been affected across 12 states. Of these, four LGAs had received oral cholera vaccine (OCV) or been approved for OCV in 2018 (the vaccine was introduced in Nigeria in 2017).

To prioritize hotspots for OCV intervention, the NCDC factored in LGAs with ongoing or active transmission. LGAs with at least one case confirmed by stool culture or minimum of 30 cases confirmed by RDT were considered as having confirmed outbreaks and were prioritized over those not confirmed; and LGAs not yet vaccinated or approved for vaccination were prioritized over those vaccinated in 2017 and 2018 and those approved for vaccination in 2018. Based on these considerations, all 83 hotspot LGAs were assigned 3 main groups:

- Group 1 (active transmission with confirmed outbreak but not yet vaccinated)
- Group 2 (active transmission without confirmed outbreak and not yet vaccinated)
- Group 3 (all other LGAs not belonging to Group 1 or 2).

An LGA's score for each criterion assessed was multiplied by the weight assigned to the criterion to determine the composite risk score, allowing prioritization as follows:

- **Group 1, priority 1**: Hotspots with active transmission, with a minimum of one case confirmed by stool culture or 30% of all suspected cases positive for V. cholerae by RDT and not yet vaccinated or approved for vaccination in 2018
- **Group 2**: Hotspots with active transmission, but without a minimum of one case confirmed
    - **Priority 2**: LGAs within Group 2 with population density ≥ 1000 inhabitants/km^2 (score: 4).
    - **Priority 3**: LGAs within Group 2 with population density ranging from 500 to 1000 inhabitants/km^2 (score: 3).
    - **Priority 4**: LGAs within Group 2 with population density ranging from 100 to < 500 inhabitants/km^2 (score: 2) and those less than 100 inhabitants/km^2 (score: 1).
- **Group 3**: Hotspot LGAs without active transmission
    - **Priority 5**: LGAs within Group 3 with population density ≥ 1000 inhabitants/km2 (score: 4)
    - **Priority 6**: LGAs within Group 3 with population density ranging from 500 to 1000 inhabitants/km^2 (score: 3)
    - **Priority 7**: LGAs within Group 3 with population density ranging from 100 to < 500 inhabitants/km^2 (score: 2)
    - **Priority 8**: LGAs within Group 3 with population density <100 inhabitants/km^2 (score: 1).

This hotspot mapping was able to help lessen cases in 2018-20, which fell from 50 719 in the second half of 2018 (with 1 136 deaths) to 3 513 in the second half of 2019 (with 71 deaths) to 956 (with 55 deaths) in the first half of 2020.

In conclusion, mapping cholera hotspots in Nigeria has been an important step towards attaining the strategic goals of the Global Roadmap to end cholera.

Cholera hotspot analysis: experiences from Yemen

***Amna Haider**, Epicentre, Médécins Sans Frontières (MSF)*

Dr Haider presented a country hotspot analysis analysing the last three years of surveillance data to help MSF prioritize areas for cholera response in Yemen. Results will be shared with other stakeholders and parties working on cholera control.

Yemen does not have a long cholera history, but the disease has been highly present since late 2016, with different presentations across the years and a total of 2.4 million cases and 3 800 associated deaths.

Analysis was done using the GTFCC tool, complemented by spatial mapping of districts based on epidemiological indicators as well as priority levels, and exploration of additional indicators involving cholera mortality and testing positivity. Advantages of the tool in the Yemeni context include its simplicity and replicability, the use of standard indicators and the fact that it does not require laboratory confirmations. Using these results, districts were classified into high, medium and low priority, with medium priority districts the most common. Spatial analysis produced the observation that most cholera occurred in the western half of the country, with incidence concentrated in certain districts and clusters.

There was an increase in persistence in high priority districts between the two year subsets, but changes in priority levels were based more on fluctuation than on incidence per se. Data from this study should be read with a few caveats: Yemen has a short history of cholera, and only three years of data were used; only surveillance data was available and cholera presentation was not consistent in space or time; and issues of data quality and completeness meant that aggregate data were used.

To offset these challenges somewhat, additional indicators were used: CFR, RDT positivity and RDT coverage.

First, a sensitivity analysis was done to measure the robustness of observations, comparing the two-year subsets from 2017-18 and 2018-19. Districts were ranked by product of mean annual incidence (MAI) and persistence, and order imposed in order to create a single indicator that allowed better comparisons between low, medium and high priority districts. In this ranking the majority of hotspot districts kept their original priority status, but with some changes in the rank order based on annual data (primarily incidence). Mapping districts based on priority level made for easier visualization than mapping of MAI, but provided no additional insight on the difference between observations from each priority level.

CFR was also plotted against rank order based on additional cutoffs, using a CFR cutoff of 1% and a rank order of 5000, revealing that many of the highest CFRs were in the lowest priority districts. This requires further examination to assess surveillance quality.

RDT positivity followed the epicurve roughly, but with positivity increasing as cases increased. It remained consistently higher than 30% from end-2018 until week 19 of 2019. RDT coverage among cases was measured using the number of tests conducted versus the number of cases, reported as a percentage. Overall positivity across the three years was over 40% in all districts in the study. Plotting this suggested that it could be possible that in some districts only severe cases are being tested, resulting in underreporting of incidence, and that in those districts increased availability of PCR and culture confirmation could be helpful.

Integration of RDT and CFR results into the selection of hotspots is a work in evolution, and MSF has

not yet shared the final results of this study. It is, however, already possible to say that the results produced by these additional methods should be counted within analysis and decision-making processes.

While incidence and persistence remain a good way to characterize hotspots, it would be good to replicate this work in other countries to understand how CFR risk and RDT positivity rates relate to incidence. Yemen is interesting, but it should be noted that it is a very large outbreak with disparities in surveillance. Before big conclusions are drawn, other approaches should be considered. Outliers should also be investigated—areas of high CFR with low incidence, or high positivity rates with low incidence for example. In this study the list of such outliers is short—only around 20 districts—and is mainly made up of areas of high incidence with low RDT positivity rates.

These are important indicators to explore. This work is in evolution and needs to be repeated over years to see how it evolves and explore the observations. It allows us to order districts within categories, and allocate resources and target responses accordingly. Suggestions are needed on how to proceed in those directions.

Cholera epidemiologic indicators

***David Olson**, WHO*

Dr Olson gave a brief overview of the various additional types epidemiological indicators that could be used to classify cholera hotspots along with current methods; the types of indicators these approaches could yield; and issues to consider in deciding whether or not to use them.

The current GTFCC tool identifies hotspots using MAI and the proportion of weeks with ≥ 1 case reported (not confirmed) over the previous five years (3-7 years for sensitivity analysis). This could be improved by the addition of further epidemiological indicators, including for mortality (CFR, cholera mortality and/or absolute number of deaths); laboratory data (such as proportion of cases confirmed by culture/PCR, persistence defined by >1 confirmed case and/or proportion positive on RDT screen); differing durations of historic data analysed; current active transmission; the hotspot's role as centre of spread to other areas; analysis of the proportion of cases in children under five and the expected differences versus endemic and epidemic contexts; and the proportion of the population with severe dehydration versus the expected proportion.

Use of CFR or other mortality indicators is supported by the fact that preventing death is primary goal of disease control, and the Cholera Roadmap calls for both a 90% reduction in deaths and a CFR of <1%. Factors affecting CFR include quality of and access to care and supplies and the prevalence and nature of vulnerable populations, as well as deaths occurring in relatively closed groups such as populations in facilities or small communities. Discussion around how this approach could be implemented include whether to use (incidence + CFR), (persistence + CFR), (incidence + CFR + persistence) or some other formulation; and whether to introduce secondary weighting factors for all or only for certain risk categories. Issues to consider include whether these indicators are predictive of public health risk; whether they are more pertinent to issues of case management and/or access or whether they are a useful part of global cholera prevention strategies; whether population-based mortality is more relevant than absolute number of deaths; whether mortality indicators are primary or secondary; and how these approaches could be included in the current tool.

Lab data allows improved targeting of national cholera control programmes, but lab results and/or rapid diagnostic tests are heavily dependent on availability of facilities, tests and reagents. In some contexts laboratory data are reported separately, or not at all. Laboratory and/or diagnostic

indicators could include number of weeks with positive cultures, and the proportion of positive RDTs or total RDTs over time. Issues to consider include whether or not laboratory capacity and test results are available in all relevant potential hotspot districts; whether indicators of incidence and persistence should be modified by culture confirmation results; whether and how to include RDT results; and whether laboratory data can be introduced as an additional weighting factor.

Use of historical data in a timeframe that can be adapted to context is useful because the conventional use of the last five years of cholera data does not work for all types of epidemiology. It is effective for heavily endemic countries, but too broad for countries or regions with episodic outbreaks or recurrent outbreaks in shorter timeframes. Data must be recent enough to provide estimate of future risk, and could be adapted in a number of ways: by expanding the five-year period to ten where suitable; using non-sequential years (i.e. only those in which cholera is reported); and/or by defining ad hoc timeframes that suite the cholera-specific context and epidemiology. Issues to consider include whether to standardize GTFCC guidance on a fixed new historic data timeframe or whether countries can adapt this to their epidemiology; whether there should be a maximum duration between last year of reported cholera and time of analysis; and whether to restrict data to that from years when cholera was reported.

Discussion

A short period of discussion covered a number of different themes.

Mortality

- The current standardized approach (use of indicators for incidence and persistence) has not itself necessarily been validated. It is important for the working group to consider the use of new indicators, and from previous seminars it is apparent that some countries are already using some of them. It is therefore possible to start looking at specific country examples to make comparisons and begin to assess whether the inclusion of—for example—some form of CFR results in different outputs compared to current guidance.
- We are seeing important variations in the indicators used. CFR and lab results could have important roles to play in refining the list and ranks that countries use to prioritise interventions, and it would be useful to have a more standardized approach to how these new dimensions are explored.
- CFR tells us a lot about the intensity of surveillance: when low numbers of cases are reported with a high CFR, this suggests issues around access to healthcare, but also could also suggest that those cases reported are just the tip of an iceberg, and that surveillance is only picking up severe cases. It is more difficult to interpret a low CFR than a high CFR. At the very least, a high CFR warrants investigation—perhaps with case management and access to healthcare as first interventions, making sure that these foundational aspects are in place before addressing other measures such as WASH and OCV.
- CFR is also not always reported accurately, sometimes due to the political considerations of governments that want to show how well they manage outbreaks.
- Total numbers of cholera deaths could be used instead of CFR, as the latter is highly variable and affected by other factors. Incidence rate and CFR are often negatively correlated, but total number of deaths is related to actual rather than relative risk. With reference to the NCDC presentation and the decision in Nigeria to rank LGAs according to the first 50% of cases, it could be possible to do a similar ranking of administrative areas by the proportion of total deaths occurring. If the global goal is a set reduction in deaths, then raw numbers matter.

Laboratory data

- There is currently very little data with which to make comparisons: countries with outbreaks are pressured, but many hotspot areas have low testing intensity or low reporting of testing, and there is a need for standard indicators.
- One important question when thinking about how to incorporate laboratory data (and establish guidelines for it) is that of how should it be handled given current infrastructure and data—considering the infrastructure and capacity used for decision making now versus the infrastructure and data that would ideally exist in the future. There are huge variations in laboratory capacity across regions, and it would be helpful—as a political and strategic measure to encourage the improvement of capacity—to articulate what would happen in currently underserved areas if the required laboratory data were to become available, clarifying exactly how improved data would affect decision making. This could be done by creating parallel scenarios postulating what decisions would be taken with an ideal laboratory network in place, helping lay the groundwork for investments in capacity.
- Consideration of the role of RDTs is also required. There tends to be a strategic focus on culture confirmation, but use of imperfect tests like RDT is fine if they are used correctly. Guidance is therefore required on how they can be applied systematically. While culture capacity is needed in some places, there is still a long way to go in controlling cholera, and real, usable improvements in surveillance will be more likely with improved guidance on the systematic use of RDTs. Stability in specification of rapid testing would also be helpful. Any form of laboratory information—whether from RDTs, culture, PCR or elsewhere—can be useful as long as it is clear how it fits into decision making processes.
- It would also be helpful to start reporting on intensity of testing in hotspots. In the Yemen study, for example, most districts were below 30% positivity rate, implying that many districts may be over reporting cholera. This could be supplemented with laboratory data, if not nationally then at least in hotspots.
- In the Nigerian example, laboratory confirmation was a big challenge. Most data used to access vaccines for OCV campaigns in the past has been based on RDT results: cholera is mostly rural in Nigeria, meaning cases tend to be reported in facilities with low capacity, and culture/PCR capacity is concentrated in a small handful of states. This suggests that the NCDC should continue to concentrate on using RDT results as indicators for incidence/persistence for now, but challenge the government to increase capacity on the basis that lack of confirmation means there are many undiagnosed cholera cases. In the meantime, “RDT will support us to move forward to getting cholera line listed.”
- There are new RDTs coming to market soon, some of which have been evaluated, with promising results, by the US Centers for Disease Control and Prevention (US CDC).
- A further session was proposed to discuss this issue with laboratory representatives to assess (a) where they stand on the topics discussed, and (b) how GTFCC partners can help in this area. The laboratory surveillance working group is already considering how to get diagnostics closer to patients, underlining the need to emphasize how best to do RDTs, interpret their results, and apply them collectively to make decisions about cholera epidemiology.
- The number of cases tested and the proportion of positive cases are important indicators: it is not acceptable to have no confirmations. It would be helpful to hold another specific session about that.

Concluding remarks

Philippe Barboza

- There is general agreement in principle that additional indicators are useful and required, but much discussion still to come on how to use them practically and pragmatically. The cases of Yemen and Nigeria illustrate the number and complexity of questions that still need to be addressed in order to improve the assessment of hotspots.
- A one-size-fits-all strategy is unlikely to be possible. Different settings appear to require diverse strategies and different ways of assessing hotspots.
- There is a clear need to clarify rules around the use of RDTs; a specific session on this is called for.
- Beyond hotspots, there is clearly still a critical role for cholera surveillance, and a lot of related concerns. At present, "we are not providing all the answers, but figuring out the questions."
- There are many elements for further investigation of how we can all benefit from the expertise and experience of countries in assessing their own hotspots and consider how best the GTFCC can feed into their processes, continuing to help countries refine their work over time. Targets are constantly moving, and we must facilitate the constant, agile evolution of tools to support assessment and determination of hotspots.
- The Stage 1 tool currently recommended by the GTFCC was conceived as a first step, not the ultimate answer. There is much more work and discussion to come on how we can improve it. This exercise not just about defining hotspots, but also about identifying places where more information is required in specific contexts.