Global Task Force on Cholera Control (GTFCC) Working Group on Oral Cholera Vaccine

Research update

Webinar 03, 10 December 2020

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Acronyms and abbreviations

BBIL	Bharat Biotech International Limited
CSP	GTFCC Country Support Platform
DRC	Democratic Republic of Congo
GMP	good manufacturing practice
GTFCC	Global Task Force on Cholera Control
icddr,b	International Centre for Diarrhoeal Disease Research, Bangladesh
ICG	International Coordinating Group on Vaccine Provision
IND	investigational new drug
IPC	infection prevention and control
MAI	mean annual incidence
M&E	monitoring and evaluation
NCP	national cholera control plan
NGO	non-governmental organization
OCV	oral cholera vaccine
VIS	Gavi Vaccine Investment Strategy
WASH	water, sanitation and hygiene
WHO	World Health Organization

Note to the reader

This report condenses discussions according to the subjects addressed, including the discussions after each presentation, rather than attempting to provide a chronological summary. Summaries of discussions address the themes emerging from wide-ranging discussions, and do not necessarily imply consensus.

Summaries of presentations and of points made in discussion are presented as the opinions expressed; no judgement is implied as to their veracity or otherwise.

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(Total : 61)

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The Impact of Mass Oral Cholera Vaccination in Uvira, Democratic Republic of Congo

***Andrew Azman**, Johns Hopkins University*

Dr Azman described a new joint project, with participation from a range of bodies across the world, that is attempting to ascertain whether mass oral cholera vaccination in a cholera endemic area can lead to sustained reductions in cholera incidence.

Oral cholera vaccine (OCV) confers good levels of individual protection from cholera; but the Global Task Force for Cholera Control (GTFCC) Roadmap to Ending Cholera 2030 also includes the use of tools like OCV to control cholera hotspots. There are many tools to show what is theoretically possible in this regard, but so far little evidence that helps understand how vaccinating a population

changes incidence over time. Some evidence from Bangladesh showed a 37% reduction in risk over two years in vaccinated populations; but in terms of impact, that evidence is currently all we have.

To study this further requires a unique setting. Outbreak-prone locations are to be avoided, but it is necessary to choose an area where cholera is known to circulate regularly. Uvira, in Eastern Democratic Republic of Congo (DRC), fits these criteria, and previous research allows a basic understanding of how cholera behaves there.

The objectives of this study are as follows:

1. To estimate the impact of mass oral cholera vaccination on laboratory-confirmed, medically-attended cholera incidence and mortality in Uvira
2. To conduct serial cross-sectional serosurveys after vaccination to estimate the seroincidence of V. cholerae infection in Uvira over time and contextualise the primary results based on clinical cholera
3. To use phenotypic and molecular methods to describe the changes in the V. cholerae population after vaccination in both human and environmental samples in Uvira.

This will involve clinical surveys at two cholera treatment centres (CTCs), and follow-up for six years. Three rounds of serosurveys will capture infection history for 6-12 months in an attempt to picture unobserved infections in the community. Protocol development is currently in progress, with enhanced clinical surveillance, the first coverage and serology survey and environmental sampling set to begin in the first quarter of 2021.

Questioned about the water, sanitation and hygiene (WASH) component of the project, Dr Azman clarified that the past few years have seen major investments in upgrading the piped water network in Uvira. A specific evaluation of that project is ongoing; but this planned study is observational, not an intervention study. Separating the impact of OCV versus the WASH upgrade can be done with reference to detailed data on how things have changed. While the aforementioned evaluation is not yet complete, there is to date no strong obvious change to the cholera epi curve (though this may change once detailed analysis is done). WASH should be followed by reductions in all diarrhoeal diseases while cholera interventions should impact cholera alone, so it should be possible to extrapolate answers to this question from differences we in the future incidence of diarrhoeal diseases other than cholera.

Case-area targeted interventions for cholera outbreaks: protocol for an analytical observational evaluation

***Flavio Finger**, Epicentre*

Case-area targeted interventions (CATIs) against cholera are conducted by rapid response teams attempting to exploit the fact that cholera cases tend to appear in clusters by quickly targeting households within a short radius, or “ring,” around a primary case. Current evidence to support their use includes a 2015-7 retrospective analysis of data from Haiti looking at the reduction in size and duration of small-scale outbreaks when CATIs using WASH and antibiotic chemoprophylaxis were deployed; a 2013 randomized trial of culture-confirmed cases in Bangladesh that showed a reduction in intra-household transmission when household contacts were targeted with hygiene promotion and WASH versus standard messaging; and a scoping review of current evidence done earlier this year. Major gaps include the fact that most studies are retrospective; no CATIs include OCV; and CATIs are based on suspected rather than confirmed cholera.

If OCV were to be included in a CATI it would be reasonable to expect increased effectiveness from the intervention and a longer duration of protection. On the other hand, protection from OCV ramps up over time, and OCV would have to be combined with other, faster interventions such as WASH and chemoprophylaxis. A single dose might be given for reactivity, and second dose can be given subsequently. There is very little experience and evidence with this approach so far—just a small amount from South Sudan and very recently in Cameroon.

Médécins Sans Frontières (MSF) is interested in the concept of CATIs using OCV as an additional tool for cholera outbreak response, combined with household WASH and possibly chemoprophylaxis as well. Different MSF Operational Centres are developing strategies to this effect, and discussions are taking place with ministries of health in DRC, Zimbabwe and Cameroon about first implementations.

This evaluation will use a research protocol developed in collaboration with Epicentre and the London School of Hygiene and Tropical Medicine (LSHTM) in order to evaluate the effectiveness of CATI in the rapid containment of case-clusters at the start of a cholera outbreak. Its primary objective is to evaluate the effectiveness of CATI in reducing incidence of enriched rapid diagnostic test (RDT)-positive cholera within targeted rings. The secondary objectives will be to examine population-based coverage, spatiotemporal transmission patterns of the outbreak, effectiveness in reducing household transmission, antimicrobial resistance related to chemoprophylaxis (if used), and the resources and costs required.

A generic protocol has been developed and is currently undergoing ethical review. Evaluation principles are as follows: this will be an observational study of CATIs performed by MSF with a study design appropriate for outbreaks (i.e. with no control group) and will use real-time data (CTC linelist data and the locations of primary cases) to evaluate a CATI strategy prospectively. It will compare immediately-implemented CATIs with naturally delayed CATIs as regards incidence of enriched RDT-positive cholera in order to improve understanding of the pathway to impact.

OCV use under CTC conditions: pilot study

***Francis Dien Mwansa**, MOH*

Dr Mwansa described an ongoing (December 2020) study of the performance of a vaccination campaign using oral cholera vaccine with and without a controlled-temperature chain (CTC). CTC use of vaccines allows for a planned removal of the vaccine from the standard 2-8°C cold chain into ambient temperatures (typically up to +40°C) for a limited period of time, under monitored and controlled conditions. Heat-stable vaccines differ in the length of time they can be stored in a CTC and the maximum temperature they can endure while remaining stable and potent. CTC qualification involves regulatory approval and prequalification by WHO. The expected benefits include greater efficiency in vaccine delivery, reduced burdens on health care workers, reduced delivery costs, and increased vaccination coverage and equity. This study is using Shanchol™, which is labelled for storage and transport at up to 40ºC for a single period of time of up to 14 days immediately prior to administration. Key time/temperature monitoring tools for the study include vaccine vial monitors (VVM) and peak threshold temperature indicators (PTTI).

The primary objective is to evaluate the superiority of the CTC strategy in terms of the average number of people vaccinated per day by a vaccination team as compared with the standard cold

chain strategy, holding all other resources constant. Secondary objectives are to compare CTC versus standard cold chain for vaccine wastage, cost per dose delivered and coverage achieved in areas vaccinated; to assess perceptions of the CTC strategy among vaccination teams; to assess knowledge, attitudes and practices towards vaccination among vaccinators and vaccine supervisors; and to compare cost, coverage and average number of individuals vaccinated between outreach and fixed site strategies if both strategies are used to implement the campaign. It is an open-label, cluster randomized controlled superiority trial comparing the number of people vaccinated per day, supplemented with a knowledge, attitudes and practices (KAP) sub-study. The sample size is 30 clusters (sub-districts) per group. Data being collected include the average number of people vaccinated per team per day (with working time per day fixed and constant between study teams); the proportion of vaccine wasted; the average operational cost per dose delivered; appreciation of the CTC strategy among vaccination teams; knowledge, attitudes and practices towards vaccination and CTC strategy among vaccination teams; the proportion of individuals reporting adverse events following immunisation (via passive surveillance and through active screening among the population-based coverage survey participants); and vaccination coverage in the target population.

It was noted in discussion that WHO encourages taking up CTC for cholera vaccine activities, given the benefits and ease it brings to campaigns, but it was emphasized that to date only Shanchol is prequalified for this approach. CTC can only be done with a properly licensed product and should be planned for. It is not an approach that should be done by accident or at the last minute; rather it should be integrated deliberately into a strategy using the correct tools.

Vibriocidal serum responses to oral cholera vaccine (Shanchol) when the second dose is delayed six months

***Amanda Debes**, Johns Hopkins University*

The rationale for delaying second doses of OCV is that single doses have been shown to stimulate protection for months and even years. A 2015 study in Kolkata, India that compared immune responses after 14 days and 28 days showed that seroconversion rates and geometric mean titer (GMT) vibriocidal responses were similar between the two groups. Outbreak response campaigns in the past have had delayed second dose schedules—for example, a 2016 campaign in Zambia had six to eight months between doses. The purpose of this study was to compare vibriocidal responses if a second dose of OCV is given after six months rather than the current standard of two weeks.

The study site was a community of floating reed islands in the Lukanga Swamps in Zambia, a community affected by lack of access to proper WASH; often, drinking water is taken from one side of the floating island while defecation is done at the other, making for problematic situations in hygiene terms. In the first study group, the first OCV dose was given at baseline (day 0), and the second six months later. 157 people were included in the analysis; 100% of subjects in group 1 received both doses, while for group 2 the figure was 94%.

The study showed that vibriocidal titers two weeks after the second dose of OCV were similar whether the second dose was administered two weeks or six months after the first. A second dose given two weeks after the first maintained higher titer briefly, but by three months there was no difference between the groups. All follow-up GMTs were higher than baseline through nine months.

Additional ongoing analyses of the same question includes a similar study in different setting: Douala, Cameroon, a large urban area and major trade centre. It has had no cholera since 2012, so there will be no confounding with intercurrent infections. Analysis will include groups receiving second doses

at two weeks, six months and 11.5 months. Preliminary analyses suggest that the first may be inferior to the others.

In discussion, the question was raised of whether recommendations and/or restrictions in current guidance should be changed concerning how far apart OCV doses should be administered—especially given the challenges faced in many contexts that make swift, regular dosing more difficult. The evidence for this is strong already, and once it is possible to incorporate the Cameroon study it will be stronger yet. That said, this Lukanga study does not evaluate protection (though there is good protection data regarding the two-week interval), though it provides some assurance of protection if second doses are delayed.

There could be other factors that improve protection—for example, after a six month gap between rounds there will be some people in the population who receive either the first or the second dose but not both, such that more people are ultimately vaccinated than would be the case with a two-week interval, effectively improving coverage. Such other factors must feed into any decisions about changing policy.

One study by icddr,b (International Centre for Diarrhoeal Disease Research, Bangladesh) suggested that a second dose may improve protection in children under five. This was a randomized control trial with a clinical end point that showed that children under five given a single dose had no protection after six or 12 years despite having antibody responses comparable to adults. It is important not to overinterpret immunological data, which does not correlate fully with protection.

International Vaccine Institute Research Updates 2020

***Julia Lynch**, Cholera Program Director, International Vaccine Institute*

Dr Lynch presented an update on the International Vaccine Institute (IVI) cholera programme strategy and projects, which are organized according to three goals. The first is to ensure OCV supply Ωby supporting manufacturers. Current projects in this regard include work on critical reagents; new technology transfer to India for the BIBCOL vaccine; and work on reformulation of OCV. The second is to improve the cholera vaccine by improving its efficacy—especially in under-fives—and flexibility of use. Current projects include work on the Euvichol CTC label, and the pre-clinical development of cholera conjugate vaccine (CCV). The third goal is to support OCV use and introduction by generating evidence for introduction in endemic countries and use of OCV in support of the global roadmap. Projects in this area are ongoing in Malawi, Mozambique, Ethiopia, Nepal and Mozambique.

Due to time constraints, Dr Lynch provided detailed updates on just a couple of projects.

The reformulation of OCV is being done to ascertain whether a simplified formulation containing only two current components (O1 Inaba (El Tor) and O1 Ogawa (classical)), and inactivated by a single method (formalin), could be equally effective. If so, such a formula could be produced with an anticipated 20% reduction in cost and 38% increase in production capacity. Done in partnership with EuBiologics, the project commenced with a technical expert group meeting in January 2020 which reached consensus that the two-component vaccine should achieve an equivalent protective immune response to O1 serotypes of V. cholerae, and that the O139 component provides no cross-protection to O1 and little public health value. Regulatory consultations confirmed an acceptable rationale for change and an acceptable clinical development plan, and test formulations have shown that production is feasible. Process validation is ongoing at EuBiologics, with a view to clinical trials in May-June 2021 and regulatory submission in 2023.

Work on the CCV is being done because conjugate vaccines elicit long lasting T-cell dependent immune responses in young children, often with a single dose. An injected vaccine with a long duration of protection can be incorporated into the expanded programme on immunization (EPI) in a cost effective manner, reducing the burden of repeated vaccination campaigns and building population immunity from infancy in endemic populations. Work on CCV at Harvard University has purified OSP (Immune responses to O-specific polysaccharide) from V. cholerae O1 Inaba El Tor strain PIC018 conjugated to a recombinant tetanus toxoid heavy chain fragment. This has been protectively immunogenic in preclinical animal models. Analysis suggests a cost of USD 0.42 per dose. The manufacturing process has been transferred to EuBiologics and a pre-clinical toxicology study is underway. IND (investigational new drug) filing is expected in June 2021.

OCV effectiveness research and challenges

***Se Eun Park**, International Vaccine Institute*

Dr Park described a baseline household survey in Cuamba District, Mozambique, where a cholera outbreak in 2014-2015 caused over 8 835 cholera cases and 65 deaths. Cuamba sees 100-200 suspected cholera cases and 2 000 diarrheal cases almost every year.

The survey showed that 80% of surveyed households had traditional latrines, while 10% had no toilet facilities. 49% had no garbage disposal system; 38% disposed of their garbage in pits, and 5% burned it. 5.2% of households had never heard of cholera. 70% of households had hand washing facilities, 59% of which were in the kitchen or near the toilet. 75% used soap or ash to wash hands; 78% washed raw food before cooking or eating; 78% cleaned utensils before serving food; and 66% used a covered container to store drinking water.

A pre-emptive mass vaccination campaign took place in August 2018, using a two-dose regime of Euvichol-Plus, with each round conducted over 5-6 days and a 15-day dose interval. A mixed vaccination strategy was used to improve accessibility and coverage, with OCV given both at fixed posts and by mobile teams. In the first round 194 581 people were vaccinated, with administrative coverage of 99%; in the second, 194 325 people were vaccinated, again with coverage of 99%. 60.4% of households were estimated to have received the full two doses of OCV . Throughout the surveillance period, no cholera cases were detected post vaccination apart from two imported cases. Diarrhoeal case numbers showed an overall reduction in cases when comparing 2018 to 2020.

In summary, it is probably not possible to conclude that the observed reduction of incidence is only due to OCV; it may also be attributable to other ongoing WASH interventions. Another important factor is the cholera outbreak pattern in Mozambique, where cholera is endemic and outbreaks occur periodically.

The challenges for vaccine effectiveness studies include the minimum sample size requirement for cholera cases post-vaccination with OCV; natural cholera outbreak patterns, as noted above; the challenges of setting up prospective surveillance systems in research naïve and/or remote settings; and factoring in WASH interventions (for which reason, comprehensive integrated approaches are recommended). Considerations for the impact of vaccination include cholera incidence with and without vaccination; reviewing the same population pre- and post-vaccination; data comparability when looking at cholera case detection and reporting; and interpretation of confounding and biases.

Discussion

A short period of discussion followed.

One of the core basic values with regard to cholera and other diarrhoeal diseases is the need for water quality testing and monitoring, especially when looking for foecal choliform content in water supply. The goal is to get to the point where none are evident; but, if it still exists, then diarrhoeal diseases including cholera are likely to be transferred through the water supply. We need to focus on this, and it should be included both in studies and in relation to OCV campaigns.

It is motivating to see the extent of study work being done and the widespread commitment and institutional activity to combat cholera. As the Country Support Platform begins its induction period, this is encouraging, and everybody's commitment should be acknowledged.

A process is required for understanding when and how to include antibiotics in CATIs. They could be very effective, but this requires input from the clinical working group, given concerns about issues of antimicrobial resistance.

Advice and strategies are required on how to overcome availability challenges for CATI interventions in humanitarian contexts, where there is always concern about vaccine availability once an outbreak has started. Outbreaks are not constant or regular, so to use in CATIs in outbreak response it is necessary to know that sufficient quantities of vaccine will be available with very short lead times. In a recent MSF-run CATI in Cameroon it was possible to use OCV doses left over from a mass campaign, which were about to expire, but that was a small amount of vaccine in a one-off situation. In other places (e.g. DRC) MSF is making an effort to maintain its own small stock of OCV in country for cholera response activities, potentially including CATIs.

There was some discussion of whether CATIs are necessary or useful in areas that have just had OCV campaigns. After a mass campaign it could conceivably be good to do CATIs in areas where there are still cases appearing, or in pockets where campaign coverage was too low. Such areas would, however, remain lower priority than known unvaccinated areas where transmission risk is higher.

Closing comments

***Kashmira Date**, US CDC*

Dr Date announced the imminent end of her stint as Chair of the OCV working group, prior to a transfer to work on COVID-19. She expressed sincere thanks to all for all the efforts of the group and for the opportunities to learn that it has provided.

***Philippe Barboza**, GTFCC*

Dr Barboza thanked Dr Date on behalf of the WHO team and the GTFCC, for all the great work she has done in this group and in others.

It is reassuring to see how much effort, time, energy and money has gone into addressing key questions around OCV use and how to improve vaccination—especially during a time in which production remains constrained but demand is expected to continue to rise. We do not yet have all

the answers, but the work presented today is moving us towards a light at the end of the current tunnel.

By working collectively we can continue to improve our understanding of what can be done with those resources we have available, adapting new strategies and more targeted interventions. There is a great and increasing need for more operational research to complement this work, and of course there are a number of ongoing projects in this area that were not presented today.

Thanks are due to all the presenters, and all of the working group. More discussions will take place starting in February 2021; in the meantime, happy new year to all.