GLOBAL TASK FORCE ON
CHOLERA CONTROL

REPORT OF THE

8TH MEETING OF THE GLOBAL TASK FORCE ON CHOLERA CONTROL WORKING GROUP ON ORAL CHOLERA VACCINE

6-8 December 2021 | Online & Les Pensières Conference Centre, Annecy, France

Contents

List of participants on site

Kate Alberti
Adidja Amani
Andrew Azman
Philippe Barboza
Marc Bonneville
Malika Bouhenia
Lucy Breakwell
Morgane Dominguez
Maryse Dugué
Georges Alain Etoundi Mballa
Nollascus Ganda
Annick-Berthie Gnakri
Marianne Gojon-Gerbelot
Justine Haag
Lee Hampton
Md Iqbal Hossain
Anna-Lea Kahn
Catherine Kiama
Melissa Ko
Martins Livinus
Francisco Javier Luquero Alcalde
Therese Nicole Mbarga Essim
Thomas Mollet
Francis Mulemba
Francine Neyroud
Terna Nomhwange
Placide Welo Okitayemba
Emmanuel Okunga
David Olson
Jayanthi Palani
Valentina Picot
Allyson Russell
David Sack
Tanya Shewchuk
Vincent Dossou Sodjinou
Carol Tevi Benissan
Dwamo Philip Zorto

Acronyms and abbreviations

AEFI	adverse events following immunization
AMR	antimicrobial resistance
BBIL	Bharat Biotech International Limited
CATI	case-area targeted intervention
CCV	cholera conjugate vaccine
CE	community engagement
CFE	contingency fund for emergencies
CFR	case fatality rate
CHISPIN	Community-Led Health Improvement Through Sanitation And Hygiene In Nigeria)
CIDRZ	Centre for Infectious Disease research in Zambia
CoP	correlate of protection
CSP	GTFCC Country Support Platform
CTC	controlled temperature chain
DFID	UK Department for International Development
DGCI	Drug Controller General of India
DRC	Democratic Republic of Congo
ECCP	Ethiopia Cholera Control and Prevention
ECHO	Enhancing Cholera Control
EPHI	Ethiopian Public Health Institute
EPI	WHO Expanded Programme on Immunization
GAVI	Global Alliance for Vaccines and Immunization
GMP	good manufacturing practice
GTFCC	Global Task Force on Cholera Control
GTM	Mozambican Multisectoral Cholera Elimination Plan Group
icddr'b	International Centre for Diarrhoeal Disease Research, Bangladesh
ICG	International Coordinating Group
IDP	internally displaced people
IEC	information, education and communication
IFRC	International Federation of Red Cross and Red Crescent societies
IPC	infection prevention and control
IRP	Independent Review Panel
IVI	International Vaccine Institute
IVR	WHO Initiative for Vaccine Research
KAP	knowledge, attitudes and practices
LGA	local government authorities
LSHTM	London School of Hygiene and Tropical Medicine
M&E	monitoring and evaluation
MEFA	Multi-Epitope Fusion Antigen
MGH	Massachusetts General Hospital
MSF	Médécins Sans Frontières
NCP	national cholera plan
NFI	Non-food items
NMCEP	Kenya national multisectoral cholera elimination plan
OCV	oral cholera vaccine
PCR	polymerase chain reaction
PPC	Preferred Product Characteristics
R&D	research and development

RCCE	risk communication and community engagement
RDT	rapid diagnostic test
RUSHPIN	Rural Sanitation And Hygiene Promotion In Nigeria)
SAM	severe acute malnutrition
SDGs	Sustainable Development Goals
SHAWN	Sanitation, Hygiene And Water In Nigeria
SOPs	standard operating procedures
US CDC	US Centers for Disease Control and Prevention
US NIH	US National Institutes of Health
VIS	Gavi Vaccines Investment Strategy
WASH	water, sanitation and hygiene
WASHCOM	WASH committee
WSSCC	Water Supply and Sanitation Collaborative Council
ZACCEP	Zanzibar Cholera elimination plan
ZNPHI	Zambia National Public Health Institute

Executive summary

The eighth annual meeting of the Global Task Force on Cholera Control (GTFCC) working group on oral cholera vaccine (OCV) took place on 6-8 December 2021. Because of the continued travel difficulties imposed by the COVID-19 pandemic, the meeting was held in a "hybrid" format, with some attendees meeting in person in Les Pensières, Annecy, and others attending virtually for part of the programme. Although everyone in the GTFCC community has been affected by the pandemic, members have remained committed to cholera control and elimination throughout the pandemic period, and the meeting was well-attended and productive – despite the great disruption caused by pandemic-related events that immediately preceded the meeting.

The objectives of the meeting were to:

- share updates on outbreaks and emergency oral cholera vaccine campaigns conducted in 2021;
- address specific issues in those campaigns and recommend solutions that will accelerate implementation of future emergency campaigns;
- share updates on the 2021 OCV stockpile;
- share updates on preventive campaigns;
- share updates on current production of vaccines and discuss production needs for the coming years;
- provide updates on partner activities;
- share updates on OCV-related research conducted in 2021 and discuss research priorities for 2022; and
- define tracks for the group's 2022 workplan.

On the morning of the first day, countries who were present on site presented their preliminary OCV dose requirements for the next one to three years, with a total of 57 million doses predicted to be needed for planned OCV campaigns in 2022 and 2023.

On the morning of the third day, those participants who were physically present at the conference split into three breakout groups that gave them the opportunity to exchange ideas about prioritization of hotspots for preventive OCV campaigns; OCV training issues and needs; and required improvements to the GTFCC application process. Each group identified some key recommendations that were presented to the wider online audience later in the day. Progress towards the implementation of these recommendations will be assessed and presented in the next annual meeting.

Elsewhere in the meeting, the GTFCC and participants provided each other with updates on work since the previous annual meeting, with breakdowns of activities and lessons in a number of OCV campaigns, both reactive and planned; information on OCV supply and procurement and OCV integration with WASH; updates on vaccine production and planned production; information on Gavi's vaccine investments, strategic planning and long term forecasting; and updates on a range of research projects including but not limited to projects on new vaccine development, new testing models, implementation of controlled temperature chain and the effect of case area targeted interventions (CATI).

Certain issues and requests emerged and re-emerged as prominent themes in the discussions that should shape the GTFCC's work in the coming months and years. These included the following:

- The need to improved forms and processes for requesting vaccines
- Streamlining GTFCC processes generally
- The need for more and better global communications and advocacy from the OCV working group
- The need for ideas and experiences around using or adapting to the COVID pandemic to advance the cholera elimination cause

- Finding and maximizing opportunities to improve regional collaboration and collaboration within governments
- How the working group can facilitate cooperation with other disease control programmes, like the WHO Expanded Programme on Immunization (EPI)
- The need to continue research and improve guidance on timing of second round vaccinations
- Clarifying OCV funding processes
- Supporting resource mobilization
- Increasing vaccine production and supply
- Increasing efforts to implement preventive and planned campaigns.

The meeting closed with a round of thanks to participants, donors and partners for their continued support of work to achieve the goals of the GTFCC core document, *Ending cholera: a global roadmap to 2030.*

Day 1: reactive campaigns in 2021; stockpile

Update from the chair of the working group

Frank Mahoney, US Centers for Disease Control and Prevention (US CDC)

Dr Mahoney summarized the working group's progress against its strategic priorities for 2020-2021. The group has updated plans to complete OCV hotspot prioritization guidance and an accompanying tool by June 2022. Integration of OCV with national cholera plans (NCP) is on track: in 2021, seven countries implemented planned campaigns, and more will be done in this area. Collaboration with the GTFCC Country Support Platform (CSP) and Gavi is ongoing, and the CSP is supporting Mozambique, Democratic Republic of Congo (DRC) with work to identify hotspots. It is anticipated that OCV requests will be ready by early 2022.

Work with other GTFCC working groups is going well. There is ongoing collaboration with the surveillance group on OCV hotspot prioritization guidance, and a subgroup has been established within the working group on water, sanitation and hygiene (WASH) to work on OCV materials. In the quest to strengthen monitoring and evaluation (M&E), plans have been updated to include monitoring tools in the work of the team looking at GTFCC processes by the second quarter of 2022. Work to further research according to the priorities of the Cholera Research Agenda continues, with the launch of research tracker on GTFCC website.

For 2022, the new priorities of the working group will be structured around three technical areas: (1) implementation; (2) technical guidance; (3) and improvements to working group structure and communication. On implementation, planned campaigns in priority countries (Bangladesh, DRC, Ethiopia, Mozambique, Nigeria and Sudan) will be conducted, two consultants will be hired to strengthen OCV emergency response, and Gavi funds will be used for OCV implementation and outbreak assessments. On the technical guidance front, an OCV training package will be developed along with technical documents to help ministries of health in endemic countries prepare, organize, monitor and evaluate campaigns. Guidance will also be developed on the allocation of OCV for planned use in cholera hotspots. To improve the working group, its composition will be expanded; three subteams will be created to develop technical guidance; topic-specific meetings will be held throughout the year; a public dashboard on OCV implementation will be launched; and a review will be carried out of the use of OCV from 2013-21.

Overview of the OCV working group

***Malika Bouhenia**, GTFCC Secretariat*

Ms Bouhenia started by presenting preliminary data on cholera outbreaks in 2021. Cases reported to WHO stood at 160 000 overall, approximately 130 000 of which were in Africa and 6 400 in Asia (Yemen excluded). None had been reported in the Americas. Excluding the anomalous situation in Yemen, more deaths (4000 in total) have already been reported in 2021 than in 2017, the year the Global Roadmap to End Cholera by 2030 ("the Roadmap") was launched. The last year in which a similar number of deaths was reported was 2011. Preliminary data suggest a global case fatality rate (CFR) of 2.5% and an African CFR of 3.1%. This represents a significant rise over last year and a dramatic change to a falling trend over the last 20 years. Multiple factors have contributed to this, including the size of the 2021 outbreaks, conflict and humanitarian crises and the effects of the COVID pandemic (including inaccessibility of health care).

Ms Bouhenia also highlighted the fact that an increase of the number of doses requested in the third quarter of 2021 coincided with an increase in the number of cases over the same period.

In this context there have been 10 requests for OCV in 2021, a total of 35 million doses. Two of these (for Yemen and Ethiopia, a total of 9.7 million doses) have come through the GTFCC mechanism. The other eight requests came through the mechanism of the International Coordinating Group on Vaccine Provision (ICG), and were for vaccination in Bangladesh, Ethiopia (three times), Nepal, Niger and Nigeria (twice). 30 million of these doses were approved, 8.4m through the GTFCC and 22.4m through the ICG.

Ms Bouhenia gave an overview of the total number of doses shipped per country since 2013, then outlined the countries reporting cases in 2021 and the reactive and preventive campaigns that had been or were taking place.

Key issues affecting work in 2021 can again be split into three main areas: (1) the impact of COVID; (2) the need to improve the processes of applying for and implementing OCV; and (3) the difficulty of balancing supply and demand.

On the first point, travel restrictions and the redeployment or reprioritization of staff to assist COVID responses have hampered work, and COVID vaccination campaigns have sometimes hindered OCV campaigns. On the second point, while the quality of OCV requests continues to improve, challenges remain. Late submissions and implementations are problematic, and the quality of campaigns needs better monitoring. On the final point, emergency requests in 2021 have threatened to exceed stockpiles and many countries remain on alert and/or are requesting preventive campaigns.

The next steps for the working group will be to encourage multisectoral collaboration to increase the quality of preventive requests; address the issue of funds for deployments and staff; develop further training; continue work to improve the quality of requests; and help countries implement and report campaigns more quickly.

Reactive campaign: Ethiopia (pre-emptive and reactive)

***Martin Livinus**, WHO Ethiopia, presenting on behalf of **Mesfin Wossen**, Ethiopia Public Health Institute*

Dr Livinus gave the first campaign-specific presentation, outlining Ethiopia's efforts over the last two years. In 2021 the country saw a total of 866 cases with a CFR of 1.05% in three regions over two outbreak seasons. At the time of the meeting active outbreaks had been ongoing in the Oromia and Somali regions since August 9, 2021.

Ethiopia's NCP has selected 118 hotspots for 2021-28, and Ethiopia has conducted reactive campaigns since 2019. The average coverage of these campaigns is 97%. In 2021, two campaigns were conducted: a pre-emptive campaign in Tigray (first round only), targeting people displaced by conflict, achieved 56.4% coverage; and a reactive two-round campaign in the SNNP and Oromia regions achieved 98% coverage. Impact surveys were ongoing at the time of the meeting. No adverse events following immunization (AEFI) had occurred.

The impact of OCV in Ethiopia has been dramatic: no outbreaks have happened in areas with vaccinated populations.

Ethiopia has worked to integrate WASH activities before, during and after these campaigns. These have included testing residual chlorine at different outlets and storage sites; increasing the chlorine

concentration of the water supply in SNNP; treating trucked water supplies in Somali region; trucking safe water into health care facilities and cholera-affected areas with water scarcity in Oromia region; improving institutional, private and common toilets and toilet utilization coverage; and reducing open defecation.

Challenges have included conflict in Northern Ethiopia that has held back planned campaigns; a shortage of funding to implement WASH, surveillance, risk communication and community engagement (RCCE) and surveys; shortages of OCV supply and a non-existent national stockpile; and delays releasing funds for OCV operational costs even after doses were released. Despite all this, the impact of OCV campaigns is clear: cholera outbreaks have not occurred in areas where campaigns have been conducted any time in the previous three years. OCV is a game changer for permanent outbreak prevention strategies in Ethiopia.

Given all this, the country's way forward is to ask the GTFCC to continue its support, especially with requests, and approve Ethiopia's NCP for implementation. A preventive campaign among conflict-displaced people in affected regions is national priority once the relevant request is approved, and further reactive campaigns are ongoing in outbreak-affected areas. Finally, an operational cost for impact study of OCV will be done in collaboration with the GTFCC, ICG, WHO, UNICEF and other partners.

Reactive campaign: Nigeria (outbreak in endemic context)

***James Onah**, Nigeria*

Between 1972 and 1990, Nigeria reported very few cases of cholera, but more than 20 000 cases were reported each year in 1991, 1999, 2010, 2011, 2014, 2018 and 2021. Over these seven years, cases reported in Nigeria have disproportionately represented over 10% of the global cholera burden.

By week 46 of 2021, a total of 103 589 suspected cases of cholera had been reported in Nigeria for the year, including 3566 deaths for a CFR of 3.4%.

With cholera endemic in Nigeria, the driving factors for spread include poor WASH conditions (worsened seasonal flooding) and armed conflict and humanitarian emergencies, especially in the Northeast, which have led to massive humanitarian emergencies and displacements of large numbers of people. The mainstays of cholera control have been WASH interventions, community and laboratory surveillance, risk communication and case management, all strengthened by strong stakeholder coordination.

In September 2017 an OCV campaign in Northeast Nigeria quickly contained an outbreak among internally displaced people (IDP). Since then, OCV been adopted as an integral part of multisectoral strategies to prevent and contain outbreaks, and the same outcome has been achieved every time they have been implemented for that purpose.

Preventive campaigns were carried out in November 2018 and September 2019, following a 2018 national hotspot survey that identified a total of 105 local government areas (LGA) as hotspots (this mapping exercise was done before the introduction of the new GTFCC hotspot mapping tool in 2019). An urgent outbreak in late 2018 necessitated the selection of 10 of the 105 LGAs for "Phase 0" of GTFCC-supported emergency OCV. These campaigns saw massive turnout and a high acceptability level for OCV among community members. Two rounds saw a total of 5 244 305 doses administered to a target population of 5 189 692 for a coverage of 101%. The aggregated weighted coverage for two LGAs in a survey in Borno State was 87%. AEFI was of negligible significance in any campaign.

Reactive campaigns in 2021 began with the response to a massive outbreak with over 100 000 suspected cases, for which the ICG approved a total of 5 132 186 OCV doses for reactive vaccination in seven high-

burden LGAs across four states (Benue, Bauchi, Zobe and Jigawa) targeting a total population of 2 566 093. Of over five million doses approved, 3 348 872 have been received and 2 783 484 administered since March 2021. Based on campaign reports, 1 783 150 outstanding doses are needed to complete the campaigns with a second round. Coverage of campaigns so far is 98.4%; an aggregated weighted average for a survey in Bauchi LGA showed 87.8% coverage. AEFI were of negligible significance in any of the campaigns. National impact evaluation is yet to happen, but Nigeria is open to collaborative research initiatives on OCV impact.

Prior to these campaigns, in March 2021 about 40 658 unused doses from the 2019 preventive campaigns were used to support containment in outbreaks in Agatu LGA, Benue State.

WASH integration in the short term is being implemented by WASH sector partners and community health volunteers in affected LGAs and communities, and consists of safe water provision, water chlorination, household disinfection and hygiene promotion; intensive risk communication (mainly sensitization on the dangers of open defecation) through radio and television; and distribution of information, education and communication (IEC) materials, an ongoing activity in high-risk communities. Identified cholera hotspots are being prioritized for construction of motorized solar-powered boreholes and the provision of other WASH facilities.

In the medium and long term, a number of major WASH projects are being implemented by different development partners, including the SHAWN (sanitation, hygiene and water in Nigeria) project with UNICEF and the UK Department for International Development (DFID); RUSHPIN (rural sanitation and hygiene promotion in Nigeria) with the WSSCC (Water Supply and Sanitation Collaborative Council); and CHISPIN (community-led health improvement through sanitation and hygiene in Nigeria) with United Purpose and DFID. Among other theories of change for the WASH programme being promoted in Nigeria, communities are being supported to form WASH committees (WASHCOMs) and empowered to recover operational costs, maintain their facilities and demand improved services. This is intended to ensure the sustainability and scale-up of investments in the WASH programme.

OCV is widely accepted in Nigerian communities. Efforts have been made to ensure that targeted hotspots are vaccinated before the onset of outbreak seasons, but due to the limited global availability of OCV, achievement of this outcome has been a major challenge. Cholera epidemics tend to occur in Nigeria in waves every two to three years, and the timing of preparedness and response planning for seasonal outbreaks must align with these trends.

Other challenges have included inadequate investment in WASH; security concerns; a crowded programme calendar due to other disease outbreaks; and a range of smaller issues generally associated with mass vaccination campaigns.

Reactive campaign: Niger (outbreak context)

***Tassiou Elhadji Ibrahim**, Niger*

Resurgence of cholera in Niger is due mainly to the country's immediate proximity to other regularly affected countries and the movement of people back and forth across the borders. Factors affecting amplification and spread are varied and include poor hygienic conditions and insufficient drinking water; the proximity of markets to borders; rain, floods and activities around temporary ponds; the movement of fishermen and traders along the Niger River; a lack of adequate support in areas experiencing outbreaks; and a range of sociocultural factors. At the time of the meeting, Niger had seen 5590 cases in 2021 leading to 166 deaths for a CFR of 3%.

OCV use in 2021 was planned for four regions, targeting around 2 million people, and implemented in one (the Maradi region), between 22 November and 1 December, covering three districts - Guidan Roumdji

(98% coverage), Madarounfa (87%) and Maradi (95%). Only the first round has taken place, with a total of 1 066 160 doses administered (93% coverage).

WASH integration has consisted of distribution of soap and Aquatabs to support good hygiene practices, including handwashing. Demonstration sessions have been held on use of Aquatab and PUR and home drinking water treatment. Awareness campaigns have been run on cholera prevention through handwashing with soap and water and treating water. Latrines have been built and chlorination points installed, along with disinfection of institutions, public places (health facilities, stations, etc.) and households of cases, contacts and neighbours. There has been follow up with free residual chlorine with households having benefited from PUR and Aquatab. All these activities are supported by a programme of RCCE activities.

Challenges have included insecurity in some areas, affecting seven health centres; campaign periods clashing with harvesting work; low vaccine storage capacity; and funding delays. Challenges expected for the second round will include the difficulties of catching up with all the people vaccinated on the first visit and the replacement of temporary vaccination cards with permanent ones. Observation of the cholera reduction impact will be carried out next season.

OCV supply and procurement update

***Antonia Naydenov**, UNICEF*

The supply market for WHO pre-qualified oral cholera vaccines is expected to remain unchanged through to 2023. Suppliers have offered their maximum capacity to UNICEF – around 37 million doses in 2022 and around 39 million in 2023 – and contract extensions are close to completion. With this level of supply the revolving Emergency Stockpile can be maintained, with the timeline for replenishing the stockpile adjusted as production plans permit. Availability will depend on demand, as suppliers will adjust production and availability to the most realistic demand forecasts.

Between 2017 and 2021 to date, OCV procurement through UNICEF has shown a trend of increased supply enabling larger and more frequent deliveries. 90 million doses have been supplied to 20 countries in the past five years, 46 million of which were for preventive campaigns.

Deliveries for outbreak response exceeded deliveries for preventive campaigns in both 2019 and 2021. Outbreak response procurement is based on the ICG requirement for the Emergency Stockpile to always hold three million doses of OCV available in a revolving stockpile maintained by two suppliers. This was achieved throughout 2021, except for a seven-day period during March (with the lowest supply during this period being 2.9 million doses); a longer, 20-day period in May (with a low of 1.3 million doses); 20 days during September including five days in which the stockpile was fully depleted; and a 14-day period in November when the lowest level was 1.8 million doses. Over the last five years, 44 million doses have been supplied to outbreak responses. In 2021, 10.5 million doses were supplied to Ethiopia and Nigeria.

Operational feedback and key takeaways from these experiences group into three areas: emergency orders; OCV campaigns; and logistics. Planning for 2nd dose shipment requests in emergencies could be assisted by better availability of commercial air cargo capacity and improvements in countries' operational readiness to receive shipments at short notice. For campaigns, longer term planning is needed to enable increased availability, especially when countries have programmatic preferences for specific vaccines. A limited supplier base means that lead times for delivery are lengthy. On the logistics front, COVID-19 continues to make its presence felt, including by impacting commercial air cargo capacity. Close co-ordination is required for campaign shipments to avoid delays.

Integration of WASH and OCV

***Justine Hagg**, GTFCC Secretariat*

Vaccination campaigns for OCV can be used as entry points and catalysts for implementing WASH; community engagement (CE); and advocacy for longer term WASH investments in cholera hotspots. The GTFCC has therefore defined a minimum package of WASH and CE to be delivered alongside emergency OCV campaigns. This package targets households in the area where an emergency OCV campaign is planned and provides chlorinated water at community or household level; containers for safe water storage; water quality monitoring; hygiene items (handwashing facilities and soap); mass communication campaigns; and post-intervention monitoring. The total costs for WASH and CE work out to around USD 200 000 per 200 000 people, i.e. USD1 per person. In the context of the wider campaign this makes up 20% of the total costs required to support two rounds of vaccination (i.e. USD 1 million per 200 000 people, or USD5 per capita for two rounds of vaccination with OCV, WASH and CE). WASH and CE interventions are carried out during the first round of vaccination. Post-intervention monitoring takes place during the second round, and the WASH assessment happens alongside the OCV coverage survey.

Operational considerations include the availability of funding for implementation of WASH and CE activities; whether there is adequate time to plan all the interventions properly in the emergency response; the availability of WASH and CE staff to be deployed in the vaccination teams; and the vital need for both national and local coordination.

This package was piloted in Tigray, Northern Ethiopia, where conflict starting in late 2020 caused a humanitarian crisis in the northern part of the region and an active cholera outbreak in the south. Thirty percent of the population has been displaced and 87% of healthcare facilities damaged as of mid 2021. A rapid risk assessment in May 2021 showed a very high cholera risk at national level. The WASH situation in IDP settings is very poor, with only one litre of water available per person per day and 6600 people using each water source (as opposed to the recommended 250-500 people). The availability of latrine toilets ranged from 638 to 2659 people per latrine (versus a recommended maximum of 50). In May 2021, 4 million OCV doses were requested through the ICG for a pre-emptive campaign targeting IDPs, refugees and host communities. A first round in June 2021 vaccinated 1.4m people, but finding the IDP was challenging, and escalation of conflict in June made monitoring and evaluation difficult. The second round is still pending, and over 500 000 doses remain from the first round.

Planned distribution of WASH non-food items (NFI) had to be scaled down from the initial target of 1 million people, mainly due to the poor availability of NFIs on the national and local market; storage, transport and access issues; and ad hoc planning. Tigray is a difficult operational context. Active conflict in rural areas makes assessing storage and cold chain capacity extremely challenging without access or telecommunications and with frequent power shortages. Continuous movement of IDP makes targeting OCV/WASH NFIs difficult, a problem exacerbated by the fact that procurement for distribution was not finalized when the OCV request was made. Additionally, transport into and within Tigray was difficult, with frequent roadblocks and blockades. Lessons from this pilot are based on experience, not formal evaluation.

Recommendations for future joint OCV-WASH interventions therefore include the prepositioning and/or stockpiling of the necessary WASH items. The items procured (e.g. purification products, water quality monitoring equipment, jerricans etc.) should be those most suitable for the context. Dedicated staff will be needed for WASH logistics.

Forecasting would make it possible to identify in advance those countries with a high risk of outbreaks where this intervention might need to be replicated. A contingency fund for emergencies (CFE) proved effective in the pilot.

The approach should be tested further in a smaller, more manageable situation (perhaps a non-emergency setting) and combined with a subsequent WASH baseline assessment for further evaluation.

Discussion

The panel was chaired by Vincent Sodjinou.

In Dr Sodjinou's introduction, he underlined the fact that cholera remains an emergency across Africa, with outbreaks in many countries, particularly in West Africa. As of the end of November 2021, 177 000 cases had been reported for the year across Africa, 110 000 of which were in West Africa, a concerning situation that calls for measured action. Nigeria and Niger were most affected with high numbers of deaths. DRC, Cameroon, Burundi, Mozambique, Ethiopia and Uganda also affected – though DRC represents a positive trend, with 2021 likely to be the first time the country remains below 10 000 cases in a year. Countries are requesting OCV as a component of their responses, but issues affect the response across the continent. Countries have been unable to make timely OCV requests in outbreak situations. This has led to campaigns taking place after outbreaks have peaked, causing issues for communities and health professionals and placing unnecessary pressure on the stockpile.

Panellists were asked a range of questions, including what difficulties and issues they had seen in implementing emergency campaigns; things that often prevent timely use of OVC; and the underlying reasons they had observed for delays in countries' vaccination responses. They gave a range of answers.

Common problems

- Due to misunderstandings on the part of communities and technical colleagues, responses are often implemented after the peak of the outbreak.
- Pressure on vaccine supply has been problematic in 2021.
- The tendency in a high pressure, technically complex outbreak situation is often to try to cover everything OCV-related rather than dealing with acute problems first and getting them out of the way before scaling up.
- Outbreaks are often relatively short – only a few last longer than three months. There is very little time to get ICG vaccine campaigns in place.
- When combining OCV with WASH and community engagement, it can be very difficult to isolate the effects of OCV in order to measure impact accurately.
- Better management is required within ministries. Ministry level responses are often incoherent because people are afraid of losing power, and vaccines are often wrongly seen as separate and siloed from other issues. Overarching coordination is required, because siloed approaches cause mistrust and result in a great deal of wasted energy.
- Delays in receiving and distributing funds are often problematic. Even between central and grassroots level it can take many days to distribute funds, making a seven-day vaccine turnaround impossible; and trying to vaccinate before the funds arrive can causes all sorts of problems.
- Taking **Cameroon** as an example, for the past three years the main issue has been the difficulty in gathering all the necessary information required to make an OCV request. As in many other countries, information does not flow easily from operational to central level, and there are not many people capable of understanding and filling the form.
- In **Nigeria**, as in other countries with challenging conflict and/or security situations, many of these problems are exacerbated by displacement and demographic change that affects both planning and implementation. Plans for vaccination in one community are out of date a week later when that community is displaced; situation reports change weekly; patients are hard or impossible to track.
- In **Kenya**, the principal challenge is the scarcity of resources for subnational implementation.

Possible solutions

- Using Gavi funds, the WHO country office for Cameroon recruited a consultant who greatly eased and accelerated Cameroon's OCV request process, accelerating different stages, facilitating communication between ministries, WHO and other partners, and eventually ensuring timely submission. In Cameroon, the national programme for cholera control and the national vaccination programme share a single coordinator, an arrangement that can facilitate OCV campaigns.
- When requests are done, a long and complex series of emails is used to exchange information. A centralized platform for submitting information would be a great help.
- It is important also to understand that a request "is not a PhD thesis:" if some information is unavailable, rather than spending time trying to find it or mask its absence, countries should feel comfortable to say that this it is not available.
- Cholera reveals all the weaknesses in health systems – and in surveillance in particular. Ultimately, there is a need for long term strengthening of health systems to ensure that they work properly.
- Given all the problems and the time sensitive nature not just of responses but of the outbreaks themselves, which naturally tend to end relatively quickly, there is a need to evaluate how many emergency requests end up with vaccines implemented in time to impact the outbreak. This is important missing information: it may be that preventive campaigns are in fact more useful than responding to outbreaks with vaccines.
- Predictive modelling should be done to avoid stockouts.
- Community intervention is at the root of success of all these activities. It requires a great deal of advocacy and mobilizing leaders to get communities on board with specific interventions, but it means that results are possible in an emergency even with basic activities.
- It is important to investigate local availability of products for the response. Local organizations are increasingly able to make the required products, but too often ministries assume the need to import without checking.

Suggestions to improve the work of the GTFCC

- The use of consultants to help with preparing requests should be increased.
- The GTFCC should accelerate training and adapt it to country contexts. The current level of training is not high enough – better tools are needed to help people understand the data and information they need in a health crisis.
- The GTFCC should establish an official collaboration mechanism for joint cholera responses between different Member States. There is a need for regional and/or state-implemented mechanisms that do not depend on WHO.
- More and deeper engagement is needed between the ICG, GTFCC and countries, and not just at request time or when information is being demanded. More ongoing collaboration is required, including formal platforms for more ongoing discussion, so that countries see the ICG and GTFCC as colleagues working together to solve problems, not just demanding information.

Day 2: Implemented preventive campaigns; supply & demand

NCPs, planned campaigns and coverage surveys: country plans

Malika Bouhenia, *GTFCC Secretariat*

To date, cholera hotspots have been identified using the GTFCC tool in Burundi, Ethiopia, South Sudan, Sudan, Yemen, Zambia, Zanzibar, Zimbabwe and Nigeria. The hotspot identification process is in progress in Cameroon, Mozambique, Togo, DRC, Niger and Kenya.

National cholera control plans have been launched in Bangladesh, Zambia, Somalia and Zanzibar. Further plans have been submitted for Independent Review Panel (IRP) approval from Ethiopia, Kenya and Zimbabwe, and the planning process is in progress in Cameroon, DRC, Mozambique, South Sudan, Sudan and mainland Tanzania.

Nine countries have presented their progress and challenges in Roadmap implementation: Bangladesh, Cameroon, DRC, Ethiopia, Kenya, Mozambique, Nigeria, South Sudan and The Sudan. These countries have already made significant progress with NCP development and hotspot analyses following GTFCC guidance, following which the next step will be hotspot identification. As above, this is already in progress in some countries.

After hotspots are finalized per GTFCC guidance, countries move into multi-year OCV implementation plans. Leadership and engagement of government officials has played an integral role in this activity to date: this leadership is crucial to success and needs to be developed and nurtured continually.

On day one of the meeting, countries presented their OCV plans for 2022-2023. All countries outlined their preliminary OCV dose requirements for the next 1-3 years, with a total of 57 million doses predicted to be needed for planned campaigns in 2022 and 2023. It is likely that this number of doses is an overestimate, as it was based on the total number of hotspots identified so far.

Challenges that countries have faced have included COVID-19, which has stretched resources and made it harder to raise cholera awareness, meaning better communication is now needed to improve understanding of cholera versus COVID. Data is still an issue – data quality is still improving, but gaps remain. Collection and access can be very challenging in cholera affected countries. In addition, WASH data presents further problems as it is not in “real time” and may not be at the right level for accurate analysis versus other interventions. Engagement with different sectors also remains hard: while governments are committed, multisectoral approaches are difficult to implement, and more clarity around the “rules of engagement” is needed. In addition, engagement of cholera vaccination programmes with the WHO Expanded Programme on immunization (EPI) engagement has been ad hoc in most contexts and needs more structure and better integration. Linking planned OCV campaigns with the Incident Management System could improve coordination between departments, including EPI teams. Finally, on the logistical side, vaccinating in insecure or hard-to-reach areas is always difficult; and campaigns have been hindered by delays in shipping second round vaccines.

Local political engagement is improving, but the world needs to stress the importance of cholera prevention: it is not efficient or effective to be dealing with cholera only at the last minute and/or in emergency situations. To make it genuinely effective, regional/cross-border coordination and

synchronization are needed. Finally, more and better data is needed to make planning and implementation of future campaigns effective enough to reach the Roadmap goals.

Vaccine availability and investment

EuBiologics/Euvichol

***Rachel Park**, EuBiologics*

To date, EuBiologics has supplied around 73 million doses of Euvichol and Euvichol-Plus vaccines to cholera endemic and outbreak countries through UNICEF. Of these, 19.6 million were doses of Euvichol-Plus shipped in 2021. The company had 5.8 further million doses ready for shipment at the time of the meeting and remains committed to produce at full capacity, with the expectation of having 8 million doses ready for shipment by the end of 2021.

EuBiologics would appreciate a purchase order to relieve current pressures on cold storage, which was at full capacity at the time of the meeting. In the short term, the company can continue to produce using capacity in the packaging room and additional cold storage capacity for at least 3-4 million doses will be available from March 2022. EuBiologics is considering hiring additional cold storage capacity in January and February 2022 if needed. The total quantity available for shipment in 2022 is 31.1 million doses; the quantity for 2023 is 36 million doses.

EuBiologics has expanded its OCV facility to double production capacity to up to 50 million doses. Good Manufacturing Practice (GMP) production at this level is expected in October 2023. EuBiologics is also considering building an additional fill/finish line to raise capacity to up to 65 million doses (based on the current formulation) from 2024 onwards. But private market potential for OCV is not dependable; forecasts and assurances of demand by 2030 are needed to make these expansion decisions. To establish a new fill/finish line, the decision must be taken by end 2022 at the latest (though earlier would be better). Demand forecast of 50m or more doses would make the new line feasible.

A new vaccine, Euvichol-S, is in preparation. This is a simplified formulation containing only two current components, O1 Inaba and O1 Ogawa, inactivated by a single method (formalin). Use of this approach is expected to lead to a 20% reduction in costs and a 38% increase in production capacity. A clinical trial of Euvichol-S started in Nepal in October 2021 (run by the International Vaccine Institute (IVI) and sponsored by the Bill and Melinda Gates Foundation). Regulatory submission for WHO prequalification is expected in early 2023, after which EuBiologics intends to switch production from Euvichol-Plus to Euvichol-S. The current controlled temperature chain (CTC) licensing process for Euvichol-Plus is suspended pending the expected change, but EuBiologics will start CTC licensing for the new formulation.

Finding local agents for registration will be challenging. EuBiologics is working to identify local agents, but this is not easy: the private market potential of cholera vaccine is not enough to interest most agents. Euvichol-Plus is currently shipped through UNICEF to countries in need, but EuBiologics is doing its best to register its products in as many countries as possible. On the question of whether an independent market can be expected to emerge, Dr Park pointed out that while most Euvichol-Plus is currently purchased by UNICEF, the company does have local agents in place in a number of middle-income countries including Saudi Arabia, Malaysia and the Philippines.

Shanchol: update

***Amit Kumar**, Shanta biotechnics*

To date, 27.5 million doses of Shanchol have been supplied to the international and national public funded market and to NGOs, with very small additional amounts sold to private markets. In 2021, 5.16 million doses were supplied via UNICEF in five shipments, the most recent of which was to Bangladesh in mid-November. Around 600 000 doses were available at the time of the meeting. The supply plan for 2022 and 2023 is to supply four million doses in each year.

2023 will be the final year in which Shanchol is available.

The 2022 and 2023 doses are not yet produced. Bulk production will take place in July 2022 and be finished in December 22-January 2023.

Lead times between vaccine orders and shipping cannot be accurately predicted: they depend on the campaign and on whether the filling line is occupied with other products. Generally the filling line is planned for the year depending on supply capacity and demand.

Hillchol® (BBV131): next-gen OCV

***Krishna Mohan**, Bharat Biotech*

The current WHO-prequalified cholera vaccines, Dukoral, Shanchol and Euvichol, are effective but complex to manufacture because they require the use of three or four different strains, two different inactivation methods and five separate fermenter runs to produce drug substance. Bharat Biotech is therefore developing a new vaccine, Hillchol, based on a different approach designed to avoid these difficulties. It uses a single vaccine strain (stable Hikojima) incorporating desirable characteristics of the current Cholera vaccine, with dual (Ogawa and Inaba) expression, just one inactivation method and a simpler manufacturing process. This should lead to optimum costs and higher production.

A phase I/II study has been done by Hilleman Laboratories in partnership with EuBiologics to evaluate the safety, tolerability and immunogenicity of Hillchol in a sequentially age descending population in Bangladesh with two different doses. No serious adverse events were observed throughout the study period and the safety profile of both formulations of Hillchol was found to be similar to that of the comparator vaccine. Solicited and unsolicited adverse events observed were mostly mild to moderate in severity. Immunogenicity was measured by vibriocidal assay, and showed that single strain Hillchol induced vibriocidal antibodies against both Ogawa and Inaba serotypes. The ratio of geometric mean titers of vibriocidal antibodies for Hillchol® vs comparator vaccine was 0.88 (0.68,1.12) for Ogawa and 1.11 (0.87,1.43) for Inaba. Hillchol was found to be non-inferior to the comparator vaccine by seroconversion rate, based on the prespecified criterion of non-inferiority.

Completion of this study means full completion of the animal proof of concept; establishment of the manufacturing process at research and development (R&D) scale; a pre-clinical toxicology study; and now the necessary the Phase I/II study.

For production, technology transfer to Bharat Biotech International Limited (BBIL) is complete and a new facility for production of Hillchol has been commissioned. BBIL has now completed three commercial scale, GMP process validation batches of the drug substance and subsequently drug product batches at two different potency levels. The quality control studies on the drug substance and the drug product have been completed. Stability studies on the drug substance and drug product are ongoing.

A Phase III non-inferiority clinical trial protocol was drafted in August 2021 and an application for the trial was made to the Drug Controller General of India (DCGI) in September. A protocol review meeting with the DCGI has taken place and regulatory responses have been submitted for batch release and clinical trial. The phase III trial is being planned and should start in February 2022.

Consultation would soon begin begun with WHO to determine the prequalification approach for Hillchol. A leachables and extractables studies of the drug product is planned. After the Phase III trial, licensure and product availability are expected in the fourth quarter of 2022 or the beginning of 2023.

Gavi: vaccine investments, 5.0 strategy, and long-term forecasting update

***Marta Tufet, Samya Mandal & Allyson Russell**, Gavi*

Gavi investment in OCV & links to 5.0 strategy

Gavi has supported the global OCV stockpile since 2014 as part of its Vaccines Investment Strategy (VIS). This has been done to break the current cycle of low demand and low supply, reduce outbreaks and strengthen the evidence base for pre-emptive OCV campaigns. In November 2018 this support was extended to 2020 and – subject to availability of funds – support for the OCV programme will be expanded to include planned, preventive immunization.

The VIS is an evidence-based, consultative process in which every five years Gavi re-evaluates the immunization landscape to identify and evaluate new opportunities for investment; assess options, trade-offs and synergy opportunities; and update information to aid planning by partners, countries and manufacturers. Gavi reviews the evidence for each possible investment along criteria including but not limited to health and economic impact, value for money and equity. Partners and external stakeholders play essential parts in developing the VIS recommendations.

In 2018, expanded investment in cholera was considered an intervention with medium health impact, but which makes an important contribution to equity, social protection, and global health security – especially considering the high risk of large-scale sociopolitical and economic consequences of outbreaks and the probable underestimation of the global cholera burden. A recommendation was made for investment in planned, preventive vaccination.

OCV should be a part of a comprehensive disease control strategy that comes with complementary support from WASH interventions, and future support for OCV will emphasize WASH integration and the shift towards a life course approach of vaccination (a theme across several Gavi vaccine programmes). The goal is to establish immunization as a critical platform for primary health care and look for synergies across different components of health service delivery. OCV thereby complements the SDG objectives of leaving no child behind and using primary health care to achieve universal health coverage. Gavi's role in market-shaping is expected to continue, with the task of making sure OCV supply can meet increasing demand, building on gains made through Gavi's initial stockpile investment in 2013.

Long term forecast – strategic demand scenarios

Strategic demand scenarios are long-term forecasts (i.e. 10-15 years) for given antigens that model multiple scenarios of long-term demand trends. They inform different strategic areas of work, including vaccine roadmaps, tender strategies and communications with partners and suppliers. They are developed and updated every few years, when events mean that sufficient shifts are expected in long-term demand levels. The last SDS was done in late 2017 and used to inform the VIS 2018 strategy, which recommended investment in the preventive OCV programme. The next SDS update is planned for the first half of 2022. The process includes several rounds of consultations on inputs, partners' assumptions, a draft review and finalization.

Preventive OCV programme design

The VIS is designed to pave the way for long-term investment in a strengthened and expanded preventive OCV programme. While the operationalization of new VIS investments has been on pause since COVID-19, Gavi nonetheless intends to move ahead over the coming year with the design of a preventive OCV programme within the Gavi portfolio. This will build on the existing programme while broadening the use and impact of preventive vaccination.

The programme's guiding principles and goals are based on feedback from the current OCV programme. Health impact is the top priority, through targeted subnational campaigns to maximize impact; differentiated strategies based on context; campaigns to integrate WASH activities and identify and vaccinate under-immunized children and provide life course vaccines; and generation of evidence to improve future programme delivery strategies. All this means developing a process and mechanism that supports countries with what they need to have the greatest possible health impact with the funding and tools provided.

The second priority is improving coordination – both between global, regional and country actors and between the ICG, GTFCC, and Gavi to ensure equitable allocation and rapid deployment of vaccines between preventive and emergency programmes. For the OCV programme to remain successful this will need to include engagement of disease control divisions, EPI programmes, and teams focused on broader disease control measures such as WASH and health systems strengthening. At the global level, it will require more coordinated guidance to countries, and vaccine allocation.

The third priority is equity, principally through prioritizing and reaching those most in need, who are missed by existing cholera control interventions and/or at risk because they live in outbreak-prone areas or humanitarian crises. This requires ensuring the use of existing resources to reach those most in need at the best possible time: while the global availability of OCV should increase, it will still be necessary to balance vaccine allocation between responses to urgent needs and anticipation and prevention of the next outbreaks.

Updated application process

As this redesign takes place Gavi wants to create an interactive, holistic review to ensure campaigns are well-planned, drawing on local expertise and based on best practices around the world. This is a particular focus in the time of COVID, where innovation in implementation is increasingly important. Increased focus on prevention planning should also improve the predictability of campaigns over longer time periods, thereby providing much needed demand stability to the market, encouraging manufacturers to increase production, and prompting new manufacturers to join the market. There will also be opportunities to integrate OCV better with other prevention activities like WASH and EPI programmes, as some countries are already doing.

Finally, Gavi sees this investment as an opportunity to focus on prevention and reduce cholera's impact around the world.

Gavi still sees the GTFCC and its members as the right body to guide global cholera control activities. Routing OCV applications through the Gavi mechanism will strengthen monitoring systems and allow countries to access funding for OCV activities beyond just the operational cost – for example, by using health systems and other grant mechanisms to strengthen cholera-related activities. A call is imminent for new members to join the expert pool of the Independent Review Committee that will review OCV applications in the coming years.

Members should note that while this design process continues, the existing process remains in place until further notice and should be used. No timelines or application package are in place yet - this will take some time.

Planned campaign, Zanzibar

***Fadhil Abdalla**, MOH Zanzibar*

The Zanzibar Cholera elimination plan (ZACCEP) is a multisectoral plan under the leadership of the Vice President's Office. Its goal is to eliminate cholera from Zanzibar by 2028 strengthening WASH Infrastructure, providing adequate supplies of clean and safe water, deploying OCV and improving coordination and partnership.

Zanzibar's first OCV campaign was in 2009 and no cholera outbreak was reported in the five years that followed. The 2021 OCV campaign was in two rounds (6-10 July and 10-14 August) targeting 322 483 people across 33 hotspots. The objectives of the campaign were to vaccinate at least 90% of the eligible population, reduce incidence and the number of outbreaks, provide a "breather period" for strengthening WASH infrastructure, and raise awareness of cholera prevention. Two doses of Shanchol were given to people aged over one, excluding pregnant women. Nine out of 11 districts were involved and 1529 supervisors, vaccinators and community mobilizers deployed across 215 vaccination posts. A total of 586 589 doses were used: 295 849 were vaccinated in the first round and 188 354 received two doses(63.7%). 42% of vaccinated people were older than 16 and 64% were female. The post coverage survey was completed just prior to the meeting.

The campaign saw 29 cases of AEFI, 25 in the first round and four in the second. 22 cases displayed mild symptoms (vomiting, skin rashes and body fatigue); eight had moderate symptoms (dizziness, limb numbness and chest tightness) and one two-year-old child experienced severe vomiting followed by blood vomiting and anaemia, and was treated at a referral hospital before being discharged on the third day.

With regard to WASH implementation, Zanzibar has an ongoing project to renovate the urban water system and infrastructure and a complementary three-year project in partnership with UNICEF to enhance water quality and hygiene promotion. Health education on hygiene and sanitation is provided and religious and community leaders are engaged to support environmental sanitation. Water safety was monitored regularly.

Challenges to the campaign have included people confusing OCV with the COVID-19 vaccine, especially in the second round; low adherence to COVID control protocols by both the vaccinators and the public; poor internet connectivity affecting data collection; inadequate WASH facilities in hotspot areas; the long gap between the date the OCV request was made (2009) and the campaign (2021) meaning several contextual changes happened in the interim; insufficient storage capacity at district and health facility levels; and questions around vaccinating people beyond targeted areas.

The way forward from here will involve intensifying social mobilization work, especially during the COVID-19 pandemic and any other parallel events in future; continuing to document efforts and carry out research on OCV's impact on cholera elimination in Zanzibar; continued community engagement and work with government and partners on WASH; use of any remaining vaccine to vaccinate other at-risk populations; and work to strengthen the cholera detection and surveillance system at district and primary health care level.

Planned campaign, Zambia

***Abrahams Mwanamwenge**, WHO country Office for Zambia, presenting on behalf of **Princess Kayeye**, Zambia Ministry of Health*

In Zambia cholera is considered a major public health problem. The country has 11 hotspot districts, some along the DRC border, some central (Lusaka is the biggest) and some in fishing communities. Most

outbreaks occur during the rainy season. The last recorded outbreak was in 2018, when Euvichol was used for outbreak control. Zambia has an NCP (under the office of the Vice President) that covers plans for pre-emptive campaigns. These were done in December 2020 and December 2021 using Shanchol vaccines. No major AEFI were recorded in these campaigns. Eight hotspots have been vaccinated so far this year, with higher coverage in the first round than the second. Vaccine campaigns to date have had a positive effect, with no outbreaks reported since 2018.

The planning process works to find all the possible areas where there might be eligible people, rather than just concentrating on high density areas. The priority is to reach those who might really need the vaccines, even if they live in smaller populations in remote areas. Target areas are mapped and vaccinators sent to sometimes quite small communities. This is done in the hope of increasing equity and ensuring that the campaigns reach those underserved populations that most need them. Afterwards, independent monitors and some national monitors visit target areas to verify independently that these communities have been reached.

Community engagement has been done for WASH interventions. For example, new toilets have been built with communities co-funding: a sanitation programme ran an activity in which households came together and contributed cash that was supplemented by money from the Sanitation Committee. New water tanks have also been built in Lusaka, the country's biggest hotspot.

Challenges have included difficulties with timing: conducting campaigns during the rainy season is very difficult, with some areas becoming inaccessible to vehicles. Pockets of vaccine refusal have obstructed progress, especially when COVID-19 vaccination was introduced. Demographic data has also posed difficulties: official population figures are usually lower than the actual numbers on the ground. Growing populations have increased target populations, imposing a need for vaccines that has exceeded supply for hotspot districts. The sharp appreciation of the Zambian kwacha has directly affected the budget, which is usually in US dollars. A lack of resources directly affects the ability to implement WASH activities such as toilet construction or purchasing chlorine.

Zambia's cholera control efforts enjoy a high level of political engagement. A delegation from GTFCC visited the Minister of Water and other ministers to emphasize to the government and its partners the need for a multisectoral approach to cholera control and strong coordination of the management of the NCP.

Planned campaign: Democratic Republic of Congo

***Placide Okitayemba**, DRC Ministry of Health*

Democratic Republic of Congo's NCP is organized around seven strategic axes: strengthening surveillance; curative management; sustainable WASH interventions in hotspots; improving access to WASH in outbreak areas; preventive vaccination activities in hotspots and reactive vaccination in eligible epidemic areas (depending on context); operational research; and improved coordination and communication for behaviour change and advocacy.

Up to week 46 of 2021 DRC had seen 7736 cases of cholera for 148 deaths for a CFR of 1.9% - on track for an improvement over 2020, which saw 19 785 cases and 353 deaths (CFR of 1.8%). Response activities in 2021 included coordination, medical case management, communication and awareness-raising, community activities including case area targeted interventions (CATI); and preventive vaccination campaigns.

Preventive campaigns were previously carried out in DRC in 2018, over four provinces, targeting 1 235 972 people. In 2021, by the time of the meeting, preventive vaccination had been done in Haut Katanga, targeting a population of 1 433 064. The first round was in April, with coverage of 93%, and the second in July, with coverage of 105.4%. An impact study has not yet been carried out. Another campaign is planned before the end of 2021 in South Kivu (targeting an eligible population of 1 842 547), Tanganyika (364 527) and Haut- Lomami (219 607). The total number of doses planned to be distributed over two rounds is 4 013 918.

A range of WASH activities accompanies these campaigns. Before vaccination, awareness-raising is done around hygiene measures; during vaccination, this is repeated, along with distribution of water purifiers and soap. After the vaccination, the awareness raising is repeated.

The biggest challenge to this work is logistical: DRC is huge, and the majority of cholera hotspots are geographically inaccessible. Some are insecure, and others have no telephone network. These barriers have particularly affected WASH activities before and after the vaccination campaigns.

The next steps for DRC are to update its hotspot mapping (mapping consists of a combination of community activities, then campaign teams go door-to-door in the mapped zone to treat water, distribute soap and clean impacted households); develop the next NCP (for the period 2023-2027); develop a vaccination plan for the next five years; develop a plan of WASH activities to be implemented before, during and after vaccination; and conduct studies on vaccination coverage and the impact of vaccination on cholera incidence.

Discussion

The panel was chaired by Lucy Breakwell, who opened the session with a brief summary of the day's discussions.
Based on their experiences planning preventive OCV campaigns in different countries, panellists were asked for lessons they had identified, ideas to improve the planning process, what information they needed, and how planning can impact campaign activities.

The **DRC** situation has evolved positively, based on good interaction with the GTFCC, the ICG and others: requests have been examined and processed quickly. Acceptance of a single global request for 7m doses covering six districts really helped. The biggest challenge is logistics: the country has over 95m people spread over an enormous area (one health district can be the size of a country), much of which is very difficult to access. Transporting millions of doses from Kinshasa to the provinces is challenging, especially as the doses get closer to communities and trucks are deployed across terrible roads. This has to be planned seasonally: some provinces are inaccessible by vehicle when it rains.

The COVID pandemic has made things hard but has had some positive effects, such as the forced development and acceleration of videoconferencing capacity, something not habitually used before in DRC. Online preparatory meetings for health districts have allowed zone-by-zone discussion of implementation problems and solutions, and greatly helped with timely deployments. DRC teams have tried to react fast, beginning work with local WHO teams as soon as relevant contracts were signed. Community engagement has been a central strength: engaging chiefs and leaders helps win over local populations reluctant to accept vaccination. These combined approaches have allowed DRC to achieve good coverage despite COVID.

In **Zanzibar**, the main challenge this year came from COVID - not the disease, but the vaccination. Myths and rumours created a lot of hesitancy in people suspecting the OCV was in fact an oral COVID vaccine. This was exacerbated by a lack of coordination between COVID and OCV campaigns. The second round of the OCV campaigns was implemented just a few days after launching the COVID vaccine, and in retrospect

this was a mistake. The lesson is that internal coordination is hugely important. Zanzibar's next exercise will ensure better coordination and simplified ownership of the campaign.

In **Nigeria**, preventive campaigns are based on 12 months of preparation and planning. Having clear, committed vaccine supplies and multiyear plans done well in advance is crucial. Manufacturers' assurances are important: with commitments around supplies, countries can plan better, with a longer-term view, and engagement can be done ahead of time. This planning ability is crucial: for example, cold chain and logistics pose challenges, particularly for cholera, because of the vaccine volume. While macro planning can happen at national level, subnational micro planning must be done ahead of time to assess storage space and capacity and figure out how to fill any gaps. The government also has to provide resources, and these are easier to get for reactive campaigns where the need for vaccine is more obvious. Difficulties ensuring budgets are another reason why work must happen early.

Success is also dependent on communication: public health in Nigeria is busy, with many campaigns and activities happening at same time. This makes for robust environment in which teams can easily share.

A few general points were raised in a period of open discussion.

COVID-19 and community engagement

- Some countries are unavoidably not fully committed to cholera control because they are overwhelmed by the pandemic: but the data may show that in some of those countries, cholera has more of an impact than COVID. There is a need for more and better technical evidence on this issue to guide policy decisions – and, more generally, for improvements in data analysis and funding of evidence to support political decision-making. Politics relies on technical teams, and those teams need to be supported.
- COVID-19 has interrupted not just OCV but other campaigns too, including mass drug administration for neglected diseases, basic vaccinations, vitamin A campaigns and more. All these campaigns are now struggling to figure out how to restart and regain lost ground. This risks making it even more difficult to coordinate and integrate activities unless they are acknowledged and planned for.
- COVID is unlikely to go away soon: planning for continuation alongside the pandemic is crucial. Communities get vaccination fatigue, and this must be taken into account so that they can be shown exactly what is happening and why.
- Community engagement is hard: the GTFCC is relying on the collective experiences of its members – positive and negative, failures and successes – to build a body of knowledge about what works and what does not.
- The ability to do all these things comes with planning. Planning preventive campaigns well in advance, and identifying, anticipating and planning for the likely challenges, is crucial.

OCV integration with other campaigns

- Given that OCV is not part of EPI, and looking at the impact on OCV of COVID-19 vaccination campaigns, countries could consider systems-level design of the vaccine supply system to reduce or eliminate delivery interruptions in the field. Leveraging other campaigns can be helpful – for example, Nigeria has found that integrating OCV with different vaccine campaigns (measles, for example) has increased efficiency. Future emphasis on integration will help deliver better.
- This is a best practice – but OCV imposes the additional issue of space. One of the main benefits of preventive campaigns is that long lead times allow for these issues to be addressed if planning is properly prioritized.
- There is a clear need to improve administrative processes around OCV implementation, mainly at country level. Many recent campaigns have been delayed because administrative processes meant that the necessary funds were not received in time. All countries need to improve this so the worldwide OCV effort can be more organized.

Equity

- There is a need for greater focus on equity and vaccine access for neglected populations, which miss out not only on routine vaccines but also on other necessities like access to WASH and education.
- Nigeria has done risk assessments of districts with high numbers of unvaccinated children. As part of mass campaigns the country has identified 64 districts for a ”Zero Drop Operational Plan” that develops separate plans to address the specific challenges faced in these areas. The project is based on data, and has a dashboard fed with geolocation data by teams that submit numbers of vaccinated children so the central authority can monitor the situation and help deal with challenges. The use of geospatial data also helps identify and reach out to remote communities and reduce the distance between health centres and those communities, increasing efficiency and reaching more people.

WASH integration

- It is a mark of progress that this meeting is discussing examples of combined provision of WASH and OCV in both preventive and reactive campaigns.
- Effective WASH integration relies on effective partnerships – with sanitation partners and with communities – and effective lobbying of governments for the necessary funds to make infrastructure improvements. A huge amount of coordination and advocacy is needed between the public and private sectors and other partners.
- Funding is a significant challenge in many contexts. WASH is expensive, and in some resource-limited settings meeting all WASH needs would exhaust funds and leave no money for outbreak response.
- Outbreaks can be useful as triggers for governments to react. Politicians are often reluctant to invest in cholera or WASH until an outbreak happens – at which point leverage is possible. Countries with outbreaks this year: “seize the opportunity and GTFCC will supply you!”

Day 3: Partner OCV updates

The GTFCC Research Agenda: OCV research priorities

Jan Holmgren

Launched in early 2021, the GTFCC Research Agenda is a prioritized list of research questions that could have a significant impact on achieving the goals of the Roadmap. Its objective is to accelerate progress toward those goals: a 90% reduction in cholera deaths and cholera elimination in 20 countries by 2030. Research will be critical in achieving these targets by helping control cholera faster, better, and at lower cost.

Filling important evidence gaps will also attract donor funds, encourage links between research and implementation, and increase the effectiveness with which research and evidence address the needs of patients and the people implementing the Roadmap. The Agenda can also align efforts and resources to encourage and facilitate discovery and innovation. The work it guides will result in more effective tools and strategies and a stronger evidence base to accelerate progress towards a cholera-free world.

The top five overall priorities for OCV research all concern the "best use" of OCV.

Rank	Research Question
1	What are the **optimal** OCV**schedules** (number of doses and dosing intervals) to enhance immune response and clinical effectiveness in **children 1 to 5 years** of age?
2	What are potential delivery strategies to optimize OCV coverage in hard-to-reach populations (including during humanitarian emergencies and areas of insecurity)?
3	Is there additional benefit of **adding WASH** packages, for example household WASH kits, to an OCV campaign?
4	What is the optimal number of doses of OCV to be used for **follow-up campaigns** in communities previously vaccinated with a two-dose schedule?
5	Can the **impact** of OCV on disease transmission, morbidity and mortality be maximized by **targeting specific populations** and/or targeted delivery strategies?

Professor Holmgren outlined a few examples of current research projects that align with the Agenda priorities, and demonstrated the Agenda's companion tool, the Cholera Research Tracker. This is an online platform and living database that allows an oversight of cholera research, and facilitates monitoring of progress against priorities. The value of this tool is dependent on the working group adding research projects to the Tracker database and providing examples of research for policy or implementation. Thank are due to the researchers and others who have already contributed project information to the Tracker.

This presentation ended with a personal view inspired by Research Question five: "can the impact of OCV be maximized by targeting specific populations?". Professor Holmgren argued that successful, massive, sustained use of OCV and other interventions in India and Bangladesh may be critical to the ultimate success of the Roadmap, because only this will specifically target and interrupt the primary *Vibrio cholerae* "incubator" for cholera pandemics. Achieving this would require dedicated advocacy, political commitment and innovative strategic operational research.

US Centers of Disease Control and prevention (US CDC)

***Lucy Breakwell**, US CDC*

US CDC's cholera vaccination pillar activities in 2021 have been split between the Division of Global Health Protection (which has run an OCV & WASH baseline coverage survey in Zanzibar) and the Global Immunization Division, which has provided technical assistance for a cholera hotspot review in DRC; run training to improve OCV campaigns; described impact of COVID on OCV campaign implementation; and supported the International Federation of Red Cross and Red Crescent Societies (IFRC) with an OCV social mobilization program across Africa.

The Zanzibar survey and WASH baseline exercise was an initial attempt to integrate OCV and WASH in a post-coverage vaccination survey. Involving collaboration between the Zanzibar Ministry of Health, US CDC and WHO, it set out to estimate OCV coverage and create baseline WASH coverage estimates for three districts. Coverage results are pending.

Technical assistance for DRC's cholera hotspot review was provided as part of US CDC's multi-centre approach to controlling cholera. The national team was helped to identify cholera hotspots using the GTFCC method and space-time analysis, and assisted with identification and review of other data sources (such as line lists, laboratory data and provincial surveillance data) to inform the review. A descriptive analysis of "old" hotspots and reported cases was also carried out.

US CDC is also working on the broader question of how to improve the effectiveness and timeliness of OCV campaigns. An increased number of delayed and lower-quality requests for reactive OCV campaigns have meant that campaigns have been poor quality and the use of a limited number OCV doses has been inefficient. Working with a range of partners, US CDC has developed and implemented training curricula for OCV requests and campaign implementation. Two five-day in-person trainings are planned for the first quarter of 2022, including theoretical and practical components. This combined in-person and virtual training has been designed for individuals likely to lead or be part of decision making on the inclusion of OCV in cholera control activities, or those who may coordinate OCV campaigns. It is intended to increase capacity to conduct risk assessments to inform OCV inclusion in prevention and control activities in emergency contexts; to develop requests for emergency and planned campaigns; to help prepare and implement OCV campaigns; to define M&E strategies for OCV campaigns; and to introduce OCV into NCPs.

In 2022, US CDC will continue ongoing activities, including OCV training workshops, and finish an in-progress manuscript on OCV campaigns; continue supporting activity in DRC and the work of the IFRC; support work on prioritizing hotspots for OCV use; monitor and evaluate OCV campaigns, including WASH and OCV integration, vaccine safety, coverage, cost effectiveness and impact; and expand country-specific support for OCV as part of the CDC multi-centre initiative.

International Vaccine Institute (IVI)

***Julia Lynch**, IVI*

The IVI Cholera Programme strategy and projects are organised around three pillars. In the first, ensuring OCV supply by supporting manufacturers, there are ongoing projects around critical reagents, BIBCOL and the reformulation of OCV. In the second, improving cholera vaccine efficacy (especially for children under five) and flexibility of use, there are projects around CTC labelling for Euvichol-P and the pre-clinical development of a new cholera conjugate vaccine (CCV). In the third, OCV use and introduction, IVI is generating evidence to support introduction in endemic countries through work in Nepal, Mozambique and Ethiopia and an extended analysis project.

The OCV reformulation project was outlined the previous day in the EuBiologics presentation, and if successful is expected to lead to around a 20% reduction in costs and a 38% increase in production capacity.

The CCV project is funded by RIGHT Fund and the Wellcome Trust and conducted in collaboration with Massachusetts General Hospital (MGH) and EuBiologics. It follows a call from a 2017 Stakeholder Consultation convened by the WHO Initiative for Vaccine Research (IVR) to outline Preferred Product Characteristics (PPCs) for next generation cholera vaccines that would support a new sustainable implementation paradigm for cholera control. These PPCs were: higher efficacy in infants and children under five; longer duration of protection; lower cost; and single dose administration. The rationale for CCV as a solution to these needs is that conjugate vaccines elicit long lasting T-cell dependent immune responses in young children, often with a single dose; and an injected vaccine with a long duration of protection can be incorporated efficiently into EPI, thereby reducing the burden of repeated vaccination campaigns and building population immunity from infancy.

A candidate vaccine was developed by collaborators at MGH-Harvard, icddr,b and the US National Institutes of Health (US NIH). It is protectively immunogenic in preclinical animal models, and a cost of goods analysis suggests a cost of USD 0.42 per dose. Preclinical development of this vaccine is complete, including toxicology studies, and an IND application is under review. A grant application for a Phase I trial is conditionally approved by the RIGHT Fund, pending cofunding.

The Enhancing Cholera Control (ECHO) project in Nepal is conducting a nationally representative serosurvey in 2021; looking at cost effectiveness of CATIs; carrying out surveillance capacity enhancement and a 2023-2024 mass vaccination campaign; and supporting NCP development. The ECHO project in Mozambique is supporting a range of activities including mass vaccination campaigns and impact studies, sentinel-based surveillance, community health utilization and risk factor surveys, cost effectiveness analysis, strengthening outbreak preparedness and rapid response capacity, and supporting NCP development.

In Ethiopia, the Ethiopia Cholera Control and Prevention (ECCP) is providing support in several areas, including specialized laboratory support, cold chain vaccine storage, sentinel healthcare facilities, surveillance in high priority areas, community health utilization and risk factor surveys, mass vaccination interventions and surveillance, vaccine effectiveness and impact assessment, and government stakeholder engagement for cholera control.

Epicentre

Anaïs Broban

Epicentre is running two main studies of OCV's impact on cholera control: an impact evaluation of preventive OCV campaigns in endemic areas in DRC; and an impact evaluation of CATI that include OCV.

The main objective of the DRC study is to evaluate whether a large OCV vaccination campaign in a cholera endemic hotspot in Africa might allow efficient control of the disease for at least two years. It is using three pillars – clinical surveillance, repeated seroprevalence surveys and home follow-up – in two sites, one urban and one rural.

Clinical surveillance is set up in active cholera treatment centres/units, taking a baseline of permanent activity, conducting systematic rapid diagnostic tests (RDT), culture, antibiograms and quantitative PCR, and implementing a questionnaire. All of these are intended to determine the real cholera epidemic curve over the years, and to monitor changes following vaccination.

The seroprevalence surveys are being run over two years, three in the rural site and six in the urban site. Blood samples and some stool samples are collected and a full questionnaire conducted. Supported by a lab strategy combining vibriocidal analysis, ELISA and Luminex, this monitors population-level immunity over years and seasons to improve estimates of levels of asymptomatic infections. Follow-up is done for households with a positive case and includes household visits and testing of the whole family for V. cholerae shedding. This is accompanied by a questionnaire, environmental sampling of water, latrines and food, and follow-up up to six months. This part of the study aims to determine vibrio shedding duration and the extent and patterns of bacteria circulation in the household, and according to vaccination status. In the urban site surveillance started in May 2021 and the first seroprevalence survey is expected in January 2022. In the rural site the first seroprevalence survey was done in October 2021 (before OCV vaccination) and surveillance started the same month.

The other Epicentre study is on CATI that include OCV. Médécins Sans Frontières (MSF) is planning to implement these in several countries, combining single-dose OCV with household WASH and selective chemoprophylaxis (the possibility remains of completing the second dose of the vaccine course after the CATI is done). It is an observational study of CATI effectiveness using a research protocol developed by Epicentre in collaboration with the London School of Hygiene and Tropical Medicine (LSHTM) in DRC. Ethical and administrative approvals have been obtained, MSF has obtained 100 000 doses of OCV for CATI, and preparations are ongoing in different provinces. Discussions and ethical approval processes for further studies are ongoing with ministries of health in Cameroon, Zimbabwe and Niger.

Johns Hopkins University

Andrew Azman and David Sacks

This presentation outlined the progress and outcomes of a range of different cholera research projects at Johns Hopkins University.

The first examines flexibility in OCV dose intervals to see how vibriocidal serum response differs if the second dose is significantly delayed. Current recommendations are for two doses 2-4 weeks apart, but the second is often delayed. Previous knowledge from a study in Kolkata suggests that two-week and four-week intervals show no difference in vibriocidal responses two weeks after the second dose and both result in a single peak antibody response. The duration of elevated titer was not defined in this study and nor was the response in young children (<5). The Johns Hopkins study has produced new findings on dose intervals from Zambia and Cameroon. In Zambia, second doses were given at two weeks or six months: the six-month interval was not inferior and resulted in two vibriocidal peaks. Titer fell by three months. In Cameroon, doses were given at two weeks, six months or 11.5 months, and the six-month and 11.5-month intervals appeared superior to the two-week interval, again resulting in two vibriocidal peaks. Titer fell by three months. The trade-offs when delaying the second dose appear to be that more people get at least one dose; more get only one; and there are more dropouts.

The next study, in collaboration with Harvard and the Centre for Infectious Disease research in Zambia (CIDRZ), is to develop new safe cholera challenge strains for a controlled human infection model (CHIM) trial. Other than field trials, CHIMs are the best approach for validating immune protection and are particularly useful when testing new vaccines, new vaccine schedules, duration of protection and efficacy of booster doses. However, current CHIMs require specialized inpatient units; they make volunteers ill; they are expensive to run; and they use an old (wave 1) cholera strain. The goal of this research is to develop a safe outpatient CHIM strain available for LMICs, using Zambia Ogawa (2016) to create isogenic, non-toxigenic Ogawa and Inaba strains. Non-toxigenic ZChol^{0} and ZChol^{I} are also useful for vibriocidal assay. The use of isogenic non-toxigenic strains may improve serotype specific vibriocidal assay and allow for distribution of these standard strains internationally.

The third study is working to develop a Multi-Epitope Fusion Antigen (MEFA) Cholera Vaccine. Current understanding is that protective immunity is based on Lipopolysaccharide (LPS) and is best measured by vibriocidal antibody; proteins play only a secondary role, if any. This study challenges these assumptions. Based on the development of a MEFA vaccine for ***Abrahams Mwanamwenge**, WHO country Office for Zambia, presenting on behalf of **Princess Kayeye**, Zambia Ministry of Health*

, a similar approach was used to prepare a cholera MEFA immunogen. Epitopes from many of the potential virulence proteins were fused to a FlaB backbone. When IM is injected it stimulates antibodies, including functional antibodies, to the proteins, but no antibodies to LPS and no vibriocidal response. This broadly protects rabbits (intestinal colonization in adults and disease in infant rabbits) without LPS immunity.

Another study looked at targeting OCV to micro-hotspots. District level hotspots are too large and miss the true micro-hotspots within the “hot districts.” Micro-hotspots that exist within “cold districts” are completely missed by current methods. Studies in Nigeria and Kenya suggest that identifying micro-hotspots may more precisely identify true high-risk areas and may be important when identifying risk factors because district-level analysis does not identify WASH risks. This study recommends continuing to improve methods for identifying micro-hotspots to improve OCV focus.

The final study presented sets out to estimate the impact of mass OCV campaigns in the city of Uvira, DRC on the incidence of confirmed clinical cholera cases and deaths between 2021 and 2026. It will describe changes in vaccine coverage, care-seeking behaviour, and serologically derived V. cholerae infection rates in the city. It will also describe V. cholerae contamination patterns and genetic diversity in patients, households, and the broader environment through microbiological analyses of clinical and environmental samples.

Update on Zambia Controlled Temperature Control (CTC) study

***Fred Kapaya**, epidemiologist*

Timely use of OCV is essential, particularly in an outbreak response. A CTC strategy reduces the logistics burden of a cold chain and makes it possible to reach large populations in a shorter time. This increases the impact of vaccination by reducing morbidity and mortality. Building a strong evidence base for the advantages of CTC will help refine and restructure OCV programmes to improve coverage, and highlight and prioritize areas for further research.

The primary objective of this study was to demonstrate the superiority of the CTC approach in terms of the average number of people vaccinated per day by a vaccination team compared with the standard cold chain. The secondary objectives are to compare vaccine coverage achieved in areas vaccinated using CTC with the coverage achieved in areas using the standard cold chain; to assess perceptions of the CTC

strategy among vaccination teams; and to assess vaccinators' and vaccine supervisors' knowledge, attitudes and practices (KAP) towards vaccination.

The study was a simple randomized, multistage interventional trial comparing performance of the two approaches, with a sub-study administering a KAP survey to vaccinators and vaccine supervisors.

More people were vaccinated in the in CTC arm of the trial (65 365 people, 53.2%) than the standard cold chain arm (57 554, 46.8%).

The survey found that participants were general knowledgeable about CTC: over 90% of participants had adequate knowledge about CTC. Most participants expressed the desire to roll out the approach to other districts, and 100% expressed confidence in CTC and indicated that they would prefer CTC to standard cold chain in future campaigns. They felt its advantages included higher coverage, ease of implementation in rural areas that have challenges with cold chain, and lesser physical burden (reduced weight) of vaccines during outreach. The main challenge with CTC was felt to be managing the vaccines in very hot conditions.

Limitations of this study included the small sample size (it took place in only two of Zambia's 116 districts) and the fact that it took place during the COVID-19 pandemic, overstretching the workforce. Furthermore, the fact that it introduced a new strategy just before political elections increased rumours even among health workers. It is recommended that another, similar study be conducted with a larger sample size.

Serologic markers for Vibrio cholerae infection, vaccination and protection: work in progress

Jason Harris

There are two primary antigens or targets of the antibody response in cholera: the cholera toxin and the O polysaccharide. The function and structure of the antibody are also important. Thinking about the uses of different antibodies can help us understand the relationship between the host and pathogen in the infection, but also serve as practical markers of vaccination or infection or protection; and these markers may overlap. A marker seen after infection and vaccination might also be associated with protection, or might not.

Serum vibriocidal assay is the most accepted predictor of recent infection and the most accepted correlate of protection (CoP) following vaccination (as demonstrated in challenge studies in human volunteers and in household contacts of patients with cholera); but it is not an absolute or (likely) mechanistic CoP, and the question of this study is whether it is possible to do better.

With that background, Dr Harris briefly described some work in progress to conduct a systematic analysis of what antibodies are associated with protection against infection, and/or with past exposure to cholera or cholera vaccination. The objective is to compare multiple targets, isotypes, antibody structures and antibody functions. The expanded list of antigenic targets includes hemolysin, sialidase and toxin-co-regulated pilus; isotypes include IgG, IgA, IgM and subclasses; and functional profiles include complement binding and phagocytosis. The project is also trying to use "higher throughput" technologies that allow testing of multiple antigens and functions simultaneously with very low amounts of blood required, such as multiplex bead assays.

Dr Harris discussed the application of this sort of systematic approach to serology, looking at antibodies as markers of past infection and antibodies as correlates of protection in both challenge models and household contact models, and showed some graphs to illustrate what the results might look like.

Ultimately, even using the full combination of markers, there is only a limited ability to predict who will be protected following vaccination.

This work illustrates how much remains to be done in the quest to develop ideal correlates of protection for cholera vaccination; but this type of systematic approach to comparing different antigens and antibodies does shed light on the situation and is probably a good methodology by which to evaluate new markers of protection following vaccination.

Reports from working group sessions

Group 1: prioritization of preventive OCV

Francisco Luquero

After a session grounded in data and information from country partners, Dr Luquero presented the outcome of a discussion about the difficult topic of how best to prioritize vaccination.

Different settings impose different prioritization objectives. In high to moderate transmission settings, a realistic operational objective for cholera control is to mitigate cholera impact by reducing morbidity and mortality and bring incidence and persistence to low levels – "mitigation." In low transmission settings the objective is to contain transmission to bring incidence to a very low rate – "containment." In very low transmission settings, the objective is to interrupt local transmission – "elimination."

A subgroup of the surveillance working group has been reviewing the current hotspot identification tool and has incorporated this concept into a new version. This will provide different recommendations for countries with different burdens. This necessitates a global effort to benchmark these different settings and establish exactly what is meant by high, moderate or low transmission.

If a country has a high to moderate cholera burden, the task is to identify high burden hotspots. If a country has a low cholera burden or is nearing elimination, the task is to identify vulnerable areas. Criteria for hotspot burdens consist of mean annual incidence (MAI) and persistence (i.e. proportion of weeks with reported cases). Other criteria suggested for use include CFR and quality of evidence – i.e. whether laboratory confirmation is possible.

Criteria that establish vulnerability should be considered while evaluating all interventions, including OCV. Criteria for vulnerable areas or priority areas for interventions include any remaining geographic areas reporting cases, and any areas with risk factors for reintroduction and spread of cholera based on qualitative risk factors and a WASH assessment.

The group suggested that qualitative factors for introduction and spread might include adjacency to other cholera hotspots (including across borders); intensive movement of populations through the area (whether the population is substantially nomadic or highly mobile or whether the area contains roads or transportation hubs); high population density; the presence of displaced populations; whether the area serves as a locus for mass gatherings; whether the area would expect severe consequences from a cholera outbreak in mortality terms; and the risk of cholera introduction.

Moving from hotspots to OCV priority areas in high transmission settings should be doable based primarily on epidemiological indicators: high persistence and incidence should be prioritized. Countries with improved knowledge of how cholera circulates, such as DRC, could also use this knowledge to inform selection.

In lower transmission settings the question gets more complex. Analysis at district level might hide important smaller areas – micro hotspots – that can only be detected at subnational level. Countries with

low incidence therefore need to do sub district level analysis, and guidance should reflect that. They also need to consider other specific risk factors (such as displacement, slum areas etc.) and include a narrative of these different applicable factors in their hotspot analysis.

In very low transmission settings, the main criteria for vaccination would be the risk of reintroduction.

Preventive revaccination should be done when there is a persistent public health risk, when active transmission remains, or when the risk of introduction and amplification remains high.

Group 2: Training

Martin Livinus

This group considered the different training needs round vaccine evidence and data, preparation of OCV applications, implementation of campaigns; and monitoring.

Policymakers tend to assume that technical people have the necessary information to brief them. It is important to remember, however, that technical information is needed at all levels, down to individual vaccinators who must be able to answer questions from community members.

There is also a continued need to increase the integration of OCV into the EPI at all levels. At every level, there must be a clear message that OCV is part of the overall national vaccine response.

When preparing applications for OCV it is important to ensure that all relevant ministries and other stakeholders are included in the process of completing the forms. This group varies by country, and EPI and WASH representatives are not always included when they should be.

The WASH section of the GTFCC application is seen to be relatively weak, and is nationally-oriented rather than targeted at areas to be vaccinated. It could be that further guidance and training is needed in this area.

There is also a feeling that the form should be improved, including with the addition of checklists that clarify what is expected from countries. If the form could be made into an online tool, that would also be very useful.

When it comes to campaign implementation, from the very beginning it is important to integrate campaigns with the work of EPI and – where applicable – the Incident Management System (IMS) and any EOC activities operating in the country; the activity of logistics partners and stakeholders, particularly around cold chain issues; and WASH implementation. Standard operating procedures (SOPs) and/or guidance documents are needed to ensure that everyone knows their roles and responsibilities. Logistics is crucial, and it was suggested that OCV issues might be integrated into the traditionally strong logistics tools and training foundations of EOCs. WASH integration also has logistics implications. The group consensus was that adding OCV to existing national systems and processes is likely to be the best option in most contexts.

Monitoring campaigns should be included in cascade training once the highest level is trained. Vaccinators need to be aware of M&E; among other obligations, they have to let patients and communities know that surveyors will be coming.

First among the training challenges that the group identified was attrition: there is significant turnover of staff even at the highest levels. To mitigate this, more could be done to include partners such as WHO and UNICEF in training to ensure that knowledge stays in countries. OCV and general cholera training could also be incorporated into broader, more regular training programmes to create a knowledge base that runs through the whole of the health system. This approach is followed for surveillance in Cameroon and has been successful. Another challenge experienced in many countries is the fact that district-level

authorities are not always included in training, decision making and implementation, even though they are key to implementation.

The recommendations of the group are as follows: work is needed to identify and fill gaps in SOPs, checklists and field manuals so everyone has the same information and follows the same steps; cascade training should be used; checklists should be incorporated into ICG and GTFCC vaccine request processes; an analysis of barriers and lessons at country level should be done to improve future campaigns; and OCV should be integrated better into existing programmes such as EPI, EOCs and IMS, which has extensive logistics trainings and tools that do not currently benefit OCV, but could.

Training specific recommendations included the implementation of face-to-face training at the highest coordinating levels, involving all key coordinators (EPI, cholera focal points, partners, and others). This training should be all-encompassing, covering ICG and GTFCC applications, campaign planning, M&E and more. It should be supported by a resource package including field manuals, campaign tools, and other necessary documents and tools. Online training could be a prerequisite to participation in face-to-face training. Training should be designed considering the need to improve integration of OCV into existing programmes and their associated training approaches.

Other ideas and issues addressed by the group included the operational costs for cascade training and whether funding is available; the possibility of implementing an online data collection platform for vaccination and whether EPI might have online tools into which OCV can be integrated; and the possibility of an online OCV budgeting tool.

The next steps for the OCV subteam are as follows: in December 2021 training materials will be developed based on feedback from this meeting; in January 2022, those can be circulated to partners for feedback; in February 2022, two training sessions can be conducted in the African context; in March, feedback from that training can be used to carry out any necessary revision of the training materials; in April all relevant documents can be posted on the GTFCC website; and in May work can begin on developing training materials for the platform.

Group 3: GTFCC application process

Terna Nomhwange,

This group looked at challenges around preparing vaccine requests, and their potential solutions.

The first main challenge identified for preventive campaigns is the fact that historical data collection is very time consuming, and there is no standard database for historical data. Furthermore, no systemic information on cholera epidemiology is available for countries to apply. To help with this situation, the OCV working group should develop a standardized database open to all that provides easy access to historical incidence and OCV campaign data. The group can also consider standardizing situation analyses of cholera to increase data durability.

The next highlighted challenge is the poor availability of WASH data at level three. Countries are currently relying on national or level two data and collaborations are beginning via the CSP. The working group should clarify requirements for countries for which data is not available and encourage more and better collaboration at national and global levels – for example, with the WASH working group.

It can be difficult to manage supply constraints and prioritize hotspots, and there is a need therefore for countries to ensure the allocation of doses to reflect hotspot population sizes. Here, the working group can develop communication materials on how doses are allocated between countries.

Responding to complaints that all forms and processes are currently conducted in English, the working group can translate the forms into French and conduct reviews in French.

Given that culture confirmation is not available in all areas, the GTFCC can clarify what level of confirmation is required where culture is not available.

Requests are often delayed. The working group can review timelines for the request process and identify any potential efficiencies. For this, a virtual follow-up meeting with the GTFCC and/or the working group will be necessary.

Applications for preventive OCV are long and it can be difficult for reviewers to understand and identify where to focus. It is also difficult for countries to get working group members to provide feedback on their applications. There is an obvious need to improve the assessment processes for each request. Here, the working group might consider using a core group of two or three people as main reviewers and segmenting certain parts of the request. This will require careful consideration of the burden for partners. Virtual meetings could be held to provide additional information to countries either before or after the review. Case studies of good OCV requests can be circulated to the working group for feedback then adapted for use as guidance for countries. It is also important for the working group to explore further how they can improve assessments – for example, by considering pre-screening requests or the use of checklists, and leveraging learning from the IRP.

Other implementation challenges include the physical volume of the vaccine – many countries are surprised by the size of the shipments and hence face logistical challenges – and the fact that M&E is not clearly described or budgeted for in current processes. Here, the working group can develop more training and communication materials on practical information including vaccine size and logistical implications, and guidance on good components of M&E activities.

Closing discussion

It is hugely encouraging to see how research has progressed in the past few years – especially given the pressures and challenges imposed by COVID-19. Compared to the big questions just a couple of years ago, amazing progress has been made.

A short period of discussion addressed the Research Agenda and any possible gaps or desires for future work.

CATIs and antibiotics

- There are some common questions about the types of research being done. One issue about the use of CATIs, for example, is the apparent contradiction between pushing for OCV and WASH in NCPs, but at the same time foregrounding CATIs and the use of antibiotics. More and more, vaccines are promoted to reduce antimicrobial resistance (AMR) - so why push for CATIs in a context where investment in preventive campaigns and WASH is important? The simple answer is that these approaches are not mutually exclusive. CATIs can be useful if implemented early to prevent outbreaks, especially if reintroduction is a risk. Better understanding is needed of the complementarity of different strategies. MSF's research is trying to understand whether CATIs should be used more systematically – and if so, where and how? The trial does not involve mass distribution of antibiotics – instead, antibiotic use is targeted at very small groups of households for containment.
- The context of elimination and the use of preventive vaccination also raises the question of how OCV can practically and rapidly be deployed in CATIs, and what role it can play in low transmission settings with poor vaccine availability. CATI is a potential tool for reactive use in areas that have had no OCV campaign, or incomplete campaign coverage, or which have cases continuing to pop up. It can also be deployed fast if there are vaccines in the country – and can be deployed more easily before there is time to set up a full-scale reactive campaign, with all the delays that implies. It is a complementary strategy that does not replace any of the other tools for outbreak response or prevention.

- The role and cost/benefit equation of antibiotic use generally is an important topic and should be addressed by the case management working group, with the aim of developing guidance.
- Many countries have experience of using antibiotics in response to outbreaks – officially and unofficially. It is important for those countries to summarize what they have learnt. Proposals have been made to evaluate this more scientifically, but learning from existing experiences is important. Some countries use antibiotics in treatment centres, for example, to reduce the length of illness and stool volume, but limit their use on household contacts. Others use them to treat severe cases. The elephant in the room is the critical issue of AMR. When antibiotics are used it is essential to have the laboratory capacity for proper monitoring of the potential effects of use.

New vaccines

- With all the discussion of different types of integration of OCV, conjugate vaccine should not be overlooked. Cholera conjugate is not an OCV replacement: like CATIs, it is an additional tool, especially in heavily endemic countries where elimination through repetitive OCV administration will be hard. It could also play a role in building population immunity from the youngest up, and may be implementable through EPI, targeting the EPI age range. It will have some delivery cost benefits.
- It could be possible to have vaccine that would cover most common causes of diarrhoea. As a standalone cholera vaccine this approach has less opportunity, but as a combined vaccine it could be very attractive.
- Another argument is that conjugate vaccines may not be as effective as hoped against cholera, for which protection is moderated by mucosal antibodies and long-term immunological memory to mount in-gut responses to exposure. There is a need for more testing in people to see if protection is possible in people not immunologically primed by natural routes.
- It is important to be sceptical about all new approaches, but it is equally important to test them. Cholera not being an invasive organism and protection being driven largely by what happens in the gut is important. Experience with parental vaccines is a difficult comparison to make - they were killed vaccines and had efficacy but were not durable. Polysaccharides can result in high levels of specific antibody.
- Local immunity is very important, but injectable vaccines work hand in hand with it in areas where there is natural exposure. If a vaccine could protect temporarily while natural exposure takes place that would be likely to provide combined protection.

Dose intervals

- The last few years have confirmed that delayed campaigns still work, and this is good news; but advocating spacing vaccine doses for longer than two weeks is arguably dangerous for small children. Circumstances often necessitate a wider dose interval, but it is known that children are unprotected in this scenario, and it is important to be careful about overinterpreting immunogenicity studies. Clinical studies show single dose in young children does not protect. However: there is not even a great deal of evidence that even two doses in children under five is very protective. Discussion of herd protection should also be treated with caution. Pragmatically, what is meant in the context of this discussion is really family immunity: a young child is surrounded with family members. The most pressing need is to ensure that the family is vaccinated and protected: they are the ones exposing the baby to infection.
- Duration is another concern: getting the same people vaccinated six months apart is hard.
- The mucosal immunological memory is fascinatingly long-lived – up to 12-14 years after immunization. This suggests that coming back years after a campaign and giving a booster dose would work (except, of course, in the younger population). In most endemic areas a single dose would probably work as a booster for most adults – though if it is mainly those who are immunologically weaker who are most susceptible, it would be problematic discerning who is immune and who is not for single dose regimen. This would be even more difficult in an outbreak

situation. If the intervention is early enough, two vaccines might be better; if it is late, one might work. It depends on whether the population is naturally primed.

- There was discussion of what remaining evidence is needed to provide clear guidelines on the ideal flexibility in dosing arrangements. We now know that a single dose is quite protective - at least one or two years – but hopefully there is surveillance taking place after campaigns, and some case control analyses to get field experience on whether the vaccine works in the field. This is an ambitious desire, given the difficulty of getting valid vaccination records in campaigns. The other possibility is the use of the CHIM model to provide direct evidence of protection from a different strategy and a new vaccine in for at-risk populations.
- It is important also to clarify whether the goal is to immunize individuals or populations. When there are long delays before the second round, the total number of people who get at least one dose expands – some are lost and some drop out between rounds. This could be better for the population than having a smaller number of people get two doses. Addressing this is an important task for modellers, hopefully supplemented by evidence from the field. It would also be interesting to see if the CHIM model answers some of these questions.
- The results of all these studies are very important. Current advice is to implement the second dose within 14 days and no longer than six months. A lot of second rounds have been cancelled when delays exceeded that window. These studies are questioning the fundamentals of a lot of what GTFCC currently recommends to countries.

Closing statements

It is always great to see such a wide spectrum of people in attendance at these meetings, and to have these groups together: people who design vaccines, people who do the clinical trials, people who use the vaccines in the field. Great progress has been and continues to be made. The GTFCC wants to learn lessons from field to design new vaccines and interventions, and design trials to allow the flexibility to deploy things in practical ways. It is hoped that these discussions will continue in the months to come, so there is even more to present next year.

It is clear from this year that the GTFCC has its work cut out it. Key themes have been noted as prominent in the discussions, including the following:

- issues with request forms;
- how the GTFCC can streamline its processes;
- the need for more and better global communications and advocacy from the working group;
- notions of how to use or work with the COVID pandemic to advance the cholera elimination cause;
- opportunities for improving regional collaboration and collaboration within governments;
- how the working group can facilitate cooperation with other disease control programmes like EPI;
- improving guidance on timing of second rounds;
- clarifying OCV funding;
- supporting resource mobilization;
- improving production and supply; and
- increasing efforts to implement preventive and planned campaigns.

Thanks are due to all who attended. Physical interaction is a privilege, and the last-minute impact of Omicron on the meeting has been regrettable. But there will be other opportunities: further meetings are planned on different topics throughout 2022. Options for attendance will be expanded, but it is very important to have human interaction once in a while.

Annex 1: Agenda

5 December -

Agenda

Monday, 6 December: Implemented reactive campaigns 2021, stockpile

Session	Content
14.00 – 14.10	Update from the Chair of the Working Group: ***Frank Mahoney*** *(CDC)*
14.10 – 14.30	Overview of the OCV: ***Malika Bouhenia*** *(GTFCC Secretariat)*
14.30 – 14.40	Reactive campaign**:** Ethiopia (pre-emptive and reactive): ***Mesfin Wossen*** (*Ethiopia Public Health Institute)*
14.40 – 14.50	Reactive campaign: Nigeria (outbreak in endemic context): ***James Onah*** *(Nigeria)*
14.50 – 15.00	Reactive campaign: Niger (outbreak): ***Tassiou Elhadji Ibrahim*** *(Niger)*
15.00 – 15.10	Oral Cholera Vaccine – supply and procurement update: ***Antonia Naydenov*** *(UNICEF)*
15.10 – 15.20	Integration of Wash and OCV during emergency campaign: ***Justine Hagg*** *(GTFCC Secretariat)*
15.30 – 16.00	**Coffee break**
16.00 – 17.00	**Discussion**

Tuesday, 7 December: Implemented preventive campaigns, supply and demand

Session	Content
14.00 – 14.10	Introduction: NCP, planned campaign, coverage surveys: ***Malika Bouhenia*** *(GTFCC Secretariat)*
14.10 –14.20	Euvichol: ***Rachel Park*** *(Eubiologics)*
14.20 – 14.30	Shanchol: ***Amit Kumar*** *(Shanta biotechnics)*
14.30 – 14.40	Hillchol: ***Krishna Mohan*** *(Bharat Biotech)*
14.40 – 14.50	GAVI: Vaccine investments, 5.0 strategy, and long-term forecasting update: ***Marta Tufet, Samya Mandal, Allyson Russel***
14.50 – 15.00	Planned campaign, Zanzibar: ***Fadhil Abdalla*** *(MOH Zanzibar)*
15.00 – 15.10	Planned campaign, Zambia: ***Princess Kayeye*** *(MOH Zambia)*
15.10 – 15.20	Planned campaign, DRC: ***Placide Okitayemba*** *(MOH DRC)*
15.30 – 16.00	**Coffee break**
16.00 – 17.00	**Discussion**

5 December -

Wednesday, 8 December: Partners update on OCV

Session	Content
14.00 – 14.10	Introduction: ***Jan Holmgren***
14.10 – 14.20	Center of Disease Control and prevention (CDC): ***Lucy Breakwell***
14.20 – 14.30	International Vaccine Institute (IVI): ***Julia Lynch***
14.30 – 14.40	International Center for Diarrhoeal Disease Bangladesh (icddr,b): ***Firdausi Qadri***
14.40 – 14.50	Epicentre /MSF: ***Anaïs Broban***
14.50 – 15.00	Johns Hopkins University: ***Andrew Azman, David Sacks***
15.00 – 15.10	Update on Controlled Temperature Control study in Zambia: ***Fred Kapaya***
15.10 – 15.20	Harvard university: ***Jason B Harris***
15.30 – 16.00	**Coffee break**
16.00 – 16.30	Feedback from subteam groups: chairs of groups
16.30 – 17.20	**Discussion**
17.20 –17.30	Closure: ***Malika Bouhenia, Frank Mahoney, Philippe Barboza***