



## **Global Task Force on Cholera Control (GT FCC) Working Group on Oral Cholera Vaccine**

**OCV vaccine production update and vaccine use in hotspots**

Webinar 02, 3 December 2020

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## Acronyms and abbreviations

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

## Note to the reader

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

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

## Participants

(Total : 72)

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## Introduction

### ***Malika Bouhenia, WHO***

At the time of the meeting, 13 million doses of oral cholera vaccine (OCV) had been shipped in 2020, with five million doses shipping in Q4. Successful preventive and reactive campaigns had been implemented despite the COVID-19 pandemic, and countries were resuming preventive vaccination planning. While around 30.2 million doses were produced in 2019, in 2020 that figure was only 14 million.

Further doses are approved to be shipped in 2021, with an estimated demand for the year of 28 million doses (GAVI/WHO).

Overall, countries are becoming more engaged with national cholera control plans (NCPs) and preventive requests through the Global Task Force for Cholera Control (GTFCC). The GTFCC country support platform (CSP) will contribute further to developing requests and implementing campaigns.

## Update on vaccine production

*Amit Kumar, Shantha Biotec*

22.4 million doses of the Shanchol vaccine have been shipped since it was prequalified in September 2011. Due to the COVID-19 pandemic, vaccination campaigns in 2020 have been greatly reduced in number and volume, so Shanchol shipping volumes have been far lower than expected this year. There were purchase orders in 2020 from Cameroon, Bangladesh and Zambia, and one additional order from Bangladesh that was later cancelled, with fast turnaround between orders and shipments. In total, 2.07 million doses were shipped in 2020 and 3.7 million remain in stock at the time of the meeting. These will go to UNICEF in 2021.

Sanofi Pasteur will discontinue Shanchol production in 2023.

The International Vaccine Institute holds the equivalent of a patent for this vaccine, and once production is discontinued there is nothing to return and the licence for production cannot be transferred by Sanofi Pasteur to anyone else. Work will continue with other manufacturers to ensure supply. There are ongoing projects to create national supply for Bangladesh and India, and work with Eubiologics on reformulation in order to expand production with them. More information on the latter project will be provided in the next OCV webinar.

## 2021 OCV production plan

*Rachel Park, EuBiologics*

After providing a corporate overview of South Korea-based EuBiologics, Dr Park outlined the company's shipment history. EuBiologics has supplied around 53 million doses of Euvichol and Euvichol-Plus to cholera endemic or outbreak countries through UNICEF since its first shipment to Haiti in 2016. Of those, around 7 million were Euvichol and 46 million were Euvichol-Plus, which has now phased out the former version. Democratic Republic of Congo (DRC), Nigeria and Yemen account for the majority of these doses. COVID-19 has caused a large gap between awards and shipments in 2020. In 2021, plans are to produce 29 million doses of Euvichol-Plus, and the company is working on expansion to double its production capacity. COVID-19 has caused delays to this plan, but production is expected to commence in October 2022.

Dr Park outlined national registration status in different countries. EuBiologics is working to register in endemic countries, but this takes time—more than was initially expected. The company nonetheless remains committed to do this in order to facilitate shipments. Asked about specific countries, Dr Park clarified that a local agent is in place in India, and that a package has been submitted to the Indian regulatory body for clinical study; and in Cameroon, there is no local agent in place. EuBiologics is willing to register there, but the lack of private market potential in Cameroon means that to date local agents have been unwilling to register, and an agent is a requirement.

The next step with conjugate vaccines will be discussed at the next working group webinar.

## Hillchol® Next-Gen Oral Cholera Vaccine

*Mohan Krishna, Bharat Biotech*

This new Bharat Biotech product, Hillchol<sup>®</sup>, will be a single strain two-dose vaccine with no preservative. Doses will be given 14 days apart for three years' protection.

Key development stages have already been completed, including animal proof of concept; manufacturing process at research and development (R&D) scale; a pre-clinical toxicology study; a phase I/II study at the International Centre for Diarrhoeal Disease Research, Bangladesh (icDDR'b); technology transfer to Bharat Biotech International Limited (BBIL); and the commissioning of a new production facility for Hillchol at BBIL.

Ongoing further processes at the time of the meeting include production of commercial scale, good manufacturing practice (GMP) validation batches of the drug substance at BBIL (in November 2020), with commercial scale GMP batches of the drug product itself to be produced in December 2020.

Planned future processes include quality control studies on the drug substance and drug product; a meeting with the Drug Controller General of India and consultation with WHO to determine the course for prequalification of Hillchol; and a phase III non-inferiority immunogenicity study. BBIL is exploring human challenge study options but these are not yet confirmed. The pre-IND meeting will establish whether this is acceptable or not. India is targeted for the product's first registration.

If all goes to plan, the product will be available in 2022. Initial production capacity is not yet certain, but a large facility has been built, with large volume reactors, so a minimum of 50 million and up to 75 million doses per year could be possible.

In manufacturing terms the advantage versus against existing vaccines is the scale advantage of a single strain-based vaccine. There is a capacity shortage in the cholera vaccine arena, and this is a driving point for BBIL. Until further data is available, it is impossible to comment on the relative merits of different vaccine candidates.

## **Update from Gavi**

***Adam Soble, Gavi***

Mr Soble gave a brief history of key board decisions and developments for Gavi's OCV support since 2018, when, as part of its Vaccine Investment Strategy (VIS), the Gavi Board approved transition of the OCV to include a preventive immunization programme beginning in 2021. Extension of Gavi support for use of the global cholera stockpile for preventive campaigns in cholera hotspots for 2020 was approved, as was funding for cholera learning agenda activities. In 2019, the Gavi 5.0 approach assumed inclusion of VIS vaccine candidates in Gavi's portfolio to evaluate the potential impact of different strategic options for the 2021-2025 period, and the board approved the Gavi 5.0 strategy, which included transition of cholera support to a preventive immunization programme as part of new vaccine programme support recommended through VIS. In 2020, due to the COVID-19 pandemic, the Gavi Board approved delaying the implementation of VIS programmes until after the acute phase of the pandemic, and the Board was asked to approve extension of Gavi support for use of the stockpile in endemic settings through to 2022. Implementation and support for the Gavi preventive cholera immunization programme will start no later than January 2023.

Mr Soble emphasized that Gavi's OCV support will continue for the next two years without any changes to the design of that support, and the aim is to roll out the full programme in 2023 at the latest.

While planning back in 2018 required countries to co-fund vaccines under certain circumstances, Gavi is currently leading a review of all policies related to vaccine financing from countries, and "there is consideration that that requirement may be removed." This remains to be seen: the requirements when the programme rolls out in 2023 are still to be determined.

Regarding market shipping, Gavi is continuing to engage with existing and new manufacturers and remains open to discussing support needs and finding common ways to provide support and ensure that projects remain on track.

Questioned on possible COVID-related costs related to IPC requirements, Mr Soble pointed out that at the start of the pandemic, policies were introduced allowing for procurement of IPC and related materials to support continuation of immunization programming. At this time, Gavi is not considering increases in cost for OCV or other mass campaigns. Current OCV campaigns seem to show that budgets within current policy have more than adequate funds available to support implementation and procurement of relevant protective materials. There has been no need to date for additional funding.

## **Prioritization of preventive OCV use in hotspots**

*Elizabeth C. Lee, Johns Hopkins Bloomberg School of Public Health*

Dr Lee's team is working to develop standardized global guidance for the preventive use of OCV. Cholera-affected countries and GTFCC partners are in need of guiding principles for the allocation of vaccines and other support for preventive campaigns, and to clarify what epidemiological criteria will be used to determine target populations eligible to receive preventive vaccines. This requires balancing a number of competing priorities, including equity of vaccine access across countries, maximization of vaccine impact and cost-effectiveness, allowing for flexibility so that countries can adapt OCV plans to local contexts, and providing support for those countries nearing cholera elimination.

In the last year, guiding principles were discussed at the 2019 annual GTFCC meeting, after which the members of the OCV working group drafted an initial proposal, which was piloted as preliminary guidance in Ethiopia in January 2020. Revisions to this guidance are ongoing.

Following the initial proposal, countries would submit a phase 1 preventive OCV request for no more than 10% of the country population with proposed campaign targets according to two categories:

- Populations with automatic eligibility (i.e. with high mean annual incidence (MAI) or moderate MAI and high persistence)
- Populations requiring additional justification (i.e. those with known surveillance gaps, poor access to WASH and/or high importation risk despite low incidence).

Feedback to date has centred on a number of issues. OCV request guidance needs to be better integrated with hotspot identification guidance; metrics and standards should be aligned across all guidance; there is confusion about why "hotspots" needed to be selected twice; and strict thresholds for MAI may cause equity problems between countries.

Once agreement has been reached on the priorities for balancing the four competing priorities listed above, the GTFCC will draft a document with the guiding principles and interim guidance on policy

for preventive OCV and circulate it to the OCV working group by March 2021. The hotspot subgroup in the surveillance working group will work with the OCV group to generate a more permanent and data-driven guidance document.

A period of discussion followed.

Hotspots are not constant, and in countries where the surveillance system is working regularly, hotspot analysis should be reapplied every few years. Among other factors, such an approach allows for response to changing external pressures such as climate change.

There are constraints with current methods of identifying hotspots through MAI and persistence data: generally, this information is available in countries based on district level data, whereas targeting of OCV is at sub-district level. Further methods are required for more accurate identification of more specific areas. Furthermore, while some hotspots are consistent in location year to year, others are variable and move around, and methods are needed to adapt to such situations. A phased approach is under consideration whereby it is assumed that surveillance systems might not initially be collecting data at the required scale, but more detailed information can be requested over time. Work is ongoing to develop guidance for the initial context, but better information can be integrated over time. Countries will know their own territories better, so keeping flexibility to adapt plans is important.

Current GTFCC guidance focuses on MAI and persistence mainly because those are currently the strongest indicators of future incidence; but other indicators are also incorporated, such as WASH coverage and importation risk. These are often less well supported by data, so are not primary indicators. Yet others, such as case fatality rate, are under consideration in an effort to expand and possibly redefine some of the existing indicators.

Mapping out sub-populations within hotspots could help reduce demand and bring down the cost of WASH interventions. It is also important to convince countries that existing administrative units are not necessarily homogeneous in terms of risk. Work is being done to detail adequate units that would make the most sense for better targeting and prioritization of different packages of interventions in every hotspot. One difficulty is not yet having sufficiently granular data. Work is done to encourage countries to gather better quality data because this will help them establish better targeted interventions. There is, however, a limit to scale – it is possible to target too small, and the right balance is always a challenge. This area could be chosen for more detailed discussion in a later topic-specific session.

## Discussion

A brief period of open discussion covered a number of themes.

- There must be some top down effort to enforce more equitable spread of the vaccine, and further discussion of how to balance impact with fair distribution.
- The intent in current allocation approaches not to make OCV requests more complicated, but to make the best use of available vaccine and be able to adjust that as production might increase in the future. This integrates bottom-up and top-down approaches in search of a global framework to define what is feasible for markets, and to set thresholds. It is important to find the right balance so that single countries do not claim too much vaccine to the detriment of others. Looking at hotspots in different ways is part of the solution, in that it may give countries the ability to adapt their requests to their actual situations. The clear constraint is of course the limited amount of vaccine, for which demand is likely to increase.

- Over time there have been many requests for OCV, and historically we can see that there have been fewer outbreaks; countries are learning and trying to adapt. But there is a danger that instead of trying to invest in WASH, they use vaccine to reduce incidence for a while, then repeat the strategy when it goes up again. Production and stockpiling are a constant challenge, and so this approach is not sustainable. It may be necessary to act more strongly to ensure that countries commit resources to WASH when they ask for vaccine, to strike the right balance. When vaccine requests are made, countries are asked about planned WASH interventions and how to link and integrate them better; but if this condition is insufficiently strict, the stockpile and operations costs increase, and these can be substantial over time. This approach has worked with other vaccines and can help mitigate the constant demand to increase vaccine production. The road map strategy and a focus on multisectoral national cholera control plans (NCPs) should partly address this issue.
- It is a challenge to make sure all different pillars of the roadmap are linked and everything is balanced. Cholera will not be eliminated by OCV alone; but OCV could be a trigger for the implementation of WASH, with innovative strategies for better targeting.
- There was some discussion of the benefits of vaccine registration in different countries and whether this was mainly for private markets or whether it also assists with campaigns and helps accelerate timelines. It facilitates vaccine shipments with UNICEF, which can be easier when registration is in place. Private market potential is often limited in cholera-endemic or outbreak countries, and so finding local agents for registration can be a big challenge.
- Registration is required by local authorities in all countries, but the specifics of a national vaccine registration process are subject to local legislation and regulation. In some countries registration is more or less a formality through WHO prequalification; in others, it is much more complex. Registration may require a local resident who is a designated formal agent of the vaccine company to hand in the dossier to the regulatory authority. In other countries, registration may even need to be renewed annually.

## Closing comments

*Philippe Barboza, GTFCC*

This has been a very particular year for everyone, with a lot of COVID-19-related challenges. It is encouraging that preventive campaigns are starting up again and the number of preventive requests is mounting; hopefully, these levels will be back to normal soon.

The discontinuation of Shanchol production is bad news. The GTFCC is grateful for the efforts elsewhere to increase vaccine production over the coming years: while the year has been complicated by unexpected reduction in demand, it is important to highlight the strong efforts of EuBiologics, and it is good news that a new vaccine will be available soon; this could be a game changer—though we have to be prudent and temper our expectations regarding deadlines and timetables; vaccine production is a complicated business.

In the coming years we will continue to struggle with a shortfall in capacity and availability. All the discussions in this meeting have highlighted to some extent the difficulty of finding the right balance between factors around long term surveillance, data, hotspot issues and sustainability. The GTFCC is



working on an interim solution that could provide a framework that still encourages countries—even those with poor surveillance—to continue to use OCV, and to find ways to ensure that vaccine distribution and allocation is not a “first come, first served” thing. This is a challenge we will need to address collectively in the coming months; there is much more discussion to come, and everybody’s input will be needed. The road will be long, but the journey will be interesting if we all take it together.

Thanks to everyone, and thanks for the large number of people attending: it is encouraging.