WHO Technical Working Group on creation of an oral cholera vaccine stockpile

Meeting report

Geneva, 26–27 April 2012

Pandemic and Epidemic Diseases

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Acknowledgements

This meeting was a collaborative effort led by the Control of Epidemic Diseases (CED) Unit in the Department of Pandemic and Epidemic Diseases (PED), of the Health Security and Environment (HSE) cluster at World Health Organization (WHO) headquarters.

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Contents

Tables:

Executive summary

The global burden of cholera is unknown, however it is estimated that there are 1.4–4.3 million cholera cases and 28 000–142 000 cholera deaths each year. Two large national cholera epidemics in Zimbabwe and Haiti, which resulted in thousands of cases and deaths, have focused the world's attention in recent years on the need not only to control endemic disease but also to put in place improved epidemic cholera preparedness and response measures.

Effective cholera prevention and treatment regimens are well established, yet cholera remains poorly controlled in both outbreak and endemic contexts. The occurrence of cholera today reflects weaknesses of water and sanitation programmes, limitations of the surveillance systems for the early detection and monitoring of epidemics, and lack of access to timely health care for patients.

In view of this situation, the 64th World Health Assembly in 2011 called for an integrated, comprehensive strategy of cholera prevention and control. WHA Resolution 64.15 included the consideration of the use of oral cholera vaccines (OCV) "where appropriate, in conjunction with other recommended prevention and control methods and not as a substitute for such methods". This consideration was taken forward at a September 2011 consultation, which noted that an OCV stockpile for outbreak control could be initiated in the near future.

This Technical Working Group was convened to develop an OCV stockpile implementation framework. Participants advised on: the criteria for choice of stockpiled vaccine and its deployment; the appropriate size of an OCV stockpile; the managing partnership and evaluation processes required; the decision-making procedure and operational issues; and the financing mechanism.

Below are the key points that summarize the findings for each of the numbered sections of the report.

1.1: Vaccination has a role in prevention and control of cholera outbreaks together with timely treatment, access to potable water and adequate sanitation, and community involvement, all of which must be supported by effective epidemiological surveillance.

2.1: The focus of this Working Group was to advise the creation of an OCV stockpile specifically to respond to outbreaks, with the understanding that guidance on other cholera

outbreak prevention and control measures already exists and the introduction of cholera vaccines in routine immunization programmes should be dealt with separately.

2.2: Creation and use of the OCV stockpile should be guided by epidemiological, technical, and operational evidence, some of which remains incomplete and must be consolidated as experience is gained.

3.1: Establishment of an OCV stockpile should not detract attention from the key established responses to cholera outbreaks:

- Detection, diagnosis, and treatment of cases with oral rehydration and antibiotic treatment;
- Establishment of a safe water supply;
- Implementation of adequate waste disposal, sanitation, and hygiene; and
- Communication and social mobilization.

3.2: Creation of an initial, necessarily small, OCV stockpile and its use will not in itself constitute sufficient preparedness for a large and/or sustained cholera epidemic.

4.1: The Working Group agreed on a matrix of criteria to guide the choice of vaccine(s) to be stockpiled. OCV characteristics that should guide the development of new vaccines were also outlined.

5.1: The Working Group agreed a set of epidemiological criteria that should inform a decision to release stockpile vaccine in response to an outbreak.

5.2: The Working Group agreed that requests for use of OCV from the stockpile in humanitarian emergencies could be considered if vaccine supply from standard sources is not readily available. Emergency response funds should be used to replenish the vaccine used from the stockpile.

6.1: The International Coordinating Group (ICG) decision-making body comprising MSF, IFRC, UNICEF, and WHO that oversees the meningococcal and yellow fever vaccine stockpiles should extend its mandate to include OCV. This body is charged with developing its own terms of reference and will require funding to cover the added operational costs. Criteria for any additional members were defined. The OCV ICG should be nested within a

wider group of organizations (e.g. technical, commercial, civil society, funding) that can inform the partnership on their specific areas of expertise.

6.2: Submission of a vaccine request may be made by any national or international organization. On receipt of such a request, the ICG should make a decision within 48 hours.

6.3: The OCV stockpile vaccine should be targeted at epidemics in those countries where cholera is going to cause a significant burden. Participants agreed that the OCV stockpile vaccine should be targeted at epidemics in low-income countries.

7.1: The OCV stockpile should initially comprise two million doses per year.

7.2: Storage of stockpile vaccine should be the responsibility of the manufacturer. The stockpile should be maintained on a rotating stock basis.

7.3: Initial donor contributions should be sought to fund vaccine procurement, country preparedness, and planned operational costs for the first 2-3 years based on the extensive experience of the ICG. A revolving fund should be established to assure longer-term financial stability.

8.1: A Procurement Reference Group should be established by the UNICEF Supply Division (UNICEF/SD) to advise on technical issues regarding vaccine and stockpile specifications. A reserved rather than prepaid stockpile is preferred.

9.1: A rigorous system of short- and longer-term monitoring and evaluation should be embedded within the OCV stockpile mechanism. WHO should establish a stockpile evaluation group to define and implement the detailed monitoring required. As experience and data accrue, the results of this evaluation should enable continuous improvement in the structure and functioning of the stockpile.

The Working Group agreed next steps and a timeline for action during 2012, as outlined in section 10. These are summarized below.

WHO will:

- Recruit ICG focal points for cholera stockpile from partner institutions and agree on terms of reference (July).

- Advocate for and seek financial support and prepare and submit proposals to: the European Union, the Bill & Melinda Gates Foundation, GAVI, the United Kingdom Department for International Development, and the United States Agency for International Development (ongoing).

- Inform WHO Headquarters, Regional Offices, Member States, and partners about the planned availability of OCV stockpile and disseminate epidemiological and operational criteria (October).

- Convene OCV stockpile working group to define a template for deployment evaluation (October).

- Liaise with SAGE Vaccination in Emergencies Working Group to ensure that the consensus of this meeting is compatible with the development of the SAGE Framework (June).

- Meet vaccine producers to discuss production capacity, vaccine presentation, storage capacity, etc (September).

WHO and UNICEF/SD will:

- Develop a strategy that includes milestones for different procurement processes (October).

- Convene a Procurement Reference Group to evaluate the bids. This will only be possible once finance is in place.

1. Introduction

A reduction in the contribution of cholera to the burden of disease in developing countries is a priority for the global health community. In endemic countries, an estimated 1.4 billion people are at risk and worldwide the reported number of cases and deaths has been increasing since 2000. It is widely acknowledged that under-reporting and weak surveillance mean that the true burden is unknown, however it is estimated that there are 1.4–4.3 million cholera cases and 28 000–142 000 cholera deaths annually. In recent years, two large national cholera epidemics in Zimbabwe and Haiti, which resulted in thousands of cases and deaths, focused the world's attention on the need not only to control endemic disease but also to put in place improved epidemic cholera preparedness and response measures.

Cholera prevention and treatment regimens that do not include vaccination are well established and mostly effective, yet cholera remains poorly controlled in both outbreak and endemic contexts. The emergence and prolonged occurrence of cholera reflects the weaknesses of water and sanitation programmes, the limitations of the surveillance systems for the early detection and monitoring of epidemics, and the lack of access to timely health care for patients.

In view of this situation, the 64th World Health Assembly in 2011 called for an integrated, comprehensive strategy of cholera prevention and control.[1] WHA resolution 64.15 included the consideration of the use of cholera vaccines "where appropriate, in conjunction with other recommended prevention and control methods and not as a substitute for such methods". This consideration was taken forward in September 2011 at a consultation convened by WHO and organized jointly by the Initiative for Vaccine Research (IVR) and the Global Task Force on Cholera Control, as part of a project funded by the Bill & Melinda Gates Foundation.

- Key point 1.1: **Vaccination has a role in prevention and control of cholera outbreaks together with timely treatment, access to potable water and adequate sanitation, and community involvement, all of which must be supported by effective epidemiological surveillance.**

2. Meeting background, objectives, and process

The September 2011 consultation emphasised the importance of developing an OCV action plan as soon as possible.[2] It outlined two approaches: (1) countries should consider vaccine

introduction through their national immunization programmes to control endemic disease; (2) for outbreak control, a stockpile could be initiated in the near future.

The current technical consultation concerned the second recommended approach, i.e. the creation of an OCV stockpile intended for use in epidemic control. The Working Group meeting's objectives were built on the following agreed premises:

- Key point 2.1: **The focus of this Working Group was to advise the creation of an OCV stockpile specifically to respond to outbreaks with the understanding that guidance on other cholera outbreak prevention and control measures already exists and the introduction of cholera vaccines in routine immunization programmes should be dealt with separately.**

- Key point 2.2: **Creation and use of the OCV stockpile should be guided by epidemiological, technical, and operational evidence, some of which remains incomplete and must be consolidated as experience is gained.**

Accordingly, the Working Group was invited to address the following questions:

- What criteria should be applied to the choice of cholera vaccine(s) to be stockpiled?
- What criteria should be set for determining when to vaccinate against cholera in outbreak situations and how can vaccination be best targeted?
- What should be the optimal size of a short-term cholera vaccine stockpile, based on current production capacity?
- What collaborative partnership and mechanism of oversight should be set in motion to ensure the appropriate use of the stockpile?
- What financing mechanism will guarantee the launch and sustainability of the stockpile?
- What monitoring and evaluation mechanisms should be applied to ascertain that experience is documented and knowledge gaps filled?

The Chair noted that not all the issues and questions above might be adequately debated and answered by the meeting and that it might be necessary to refer or defer some inquiries, provided that such additional investigation did not delay creation of the stockpile.

The Chair invited participants and observers to introduce themselves and declare any interest that may be perceived to be in conflict with the objectivity of their contribution. The Chair outlined the process by which the meeting would be conducted. During the majority of the meeting, which would be open to all members of the Working Group and observers, discussions on key issues would take the form of suggestions only. Presentations at the meeting (see Annex II) would stimulate discussion and debate. Development of consensus points would be informed by these discussions but would take place separately in closed sessions, from which participants with actual or perceived conflicts of interest would be excluded. The participants assented to this procedure and, to avoid any perception of potential conflict of interest, three invited participants agreed to absent themselves from sessions during which consensus decisions would be made, see Annex I for details.

It was agreed that comments made by participants would not be attributed. It was noted that one person would join a segment of the meeting by telephone.

3. Overarching principles

There were two recurring points of importance that the Working Group noted should be emphasised as overarching principles.

- Key point 3.1: **Establishment of an OCV stockpile should not detract attention from the key established responses to cholera outbreaks:**
  - **Detection, diagnosis, and treatment of cases with oral rehydration and antibiotic treatment;**
  - **Establishment of a safe water supply;**
  - **Implementation of adequate waste disposal and sanitation; and**
  - **Communication and social mobilization.**

- Key point 3.2: **Creation of an initial, necessarily small, OCV stockpile and its use will not in itself constitute sufficient preparedness for a large and/or sustained cholera epidemic.**

4. Criteria for the OCV to be stockpiled

The Working Group was asked to advise on the characteristics that would be essential for the vaccine selected to be held in the stockpile. Two OCVs are currently WHO-prequalified; both

are whole-cell, killed vaccines and are marketed under the names Dukoral® and Shanchol™; WHO is also aware of six cholera vaccines that are currently in development[2] that might be considered in the future for the stockpile.

For the creation of an immediate stockpile, both prequalified OCVs are under consideration. There is no known direct comparison of the two vaccines' efficacies published or in progress. Their key attributes are briefly outlined below.

Dukoral® (Crucell Ltd)

Each dose of Dukoral® consists of recombinant cholera toxin B subunit and inactivated whole cells of the classic and El Tor biotypes of *Vibrio cholerae* O1, serotypes Inaba and Ogawa. Dukoral® has been prequalified by WHO since 2001. The vaccine needs to be administered with buffer to neutralize stomach acid and protect the cholera toxin that requires 75–150 mL of clean water for preparation. Dukoral® is given in 2 doses 1–6 weeks apart in people aged ≥6 years, with a single booster dose after 2 years. Three doses are required for children aged 2–5 years, with a booster dose every 6 months. The vaccine is not licensed for use in children younger than 2 years.

This vaccine and its precursor, which contained chemically purified rather than recombinant cholera toxin B subunit, have been shown to be safe and protective. The earliest trial of Dukoral® precursor in Bangladesh compared whole-cell vaccine or precursor Dukoral® against placebo. At 6 months precursor Dukoral® exhibited 85% protective efficacy in all age groups against *V cholerae* O1; whole cell vaccine alone was 58% protective.[3] A subsequent analysis of the data from this study indicated that a herd immunity effect occurred in areas where vaccine coverage achieved levels of more than 50%.[4]

Use of Dukoral® in a non-endemic setting was assessed in a trial during an outbreak of cholera in Peruvian military personnel. Several weeks after vaccination, the protective efficacy against cholera in recipients of 2 doses of vaccine was 86%.[5]

Concerns that high rates of HIV infection might compromise the level of protection made possible by cholera vaccination were addressed by a case-control study during an outbreak of El Tor Ogawa cholera in urban Mozambique following a mass immunization campaign with Dukoral®. The HIV seroprevalence in the study population was 20–30%. 72% of the 19 550 target population received 1 dose of vaccine and 57% received both doses. Per-protocol

analysis indicated a protective efficacy of 84%. Intention-to-vaccinate analysis indicated a vaccine effectiveness of 78%.[6]

Shanchol™ (Shantha Biotechnics)

Each dose of Shanchol™ contains inactivated *V cholerae* O1 cells representing the El Tor and classical biotypes and the Inaba and Ogawa serotypes, as well as serogroup O139 cells. WHO prequalification of the vaccine was granted in September 2011.

Shanchol™ is ready for use and does not require buffer. The vaccine is given in 2 doses 2 weeks apart in people aged ≥1 year. The vaccine is not licensed for use in children aged <1 year.

The vaccine was assessed in a cluster-randomized, controlled field trial that enrolled more than 69 000 individuals aged 1 year and older living in urban slums of Kolkata, India. Shanchol™ provided 67% protection against clinically significant *V cholerae* O1 cholera for 2 years.[7] At further follow-up, the vaccinated population experienced 66% protection against all episodes of cholera during the 3 years after vaccination, and 65% protection against episodes occurring during the third year.[8] Follow-up of the study population will continue to 5 years.

Discussion and rationale for advice

As a template for their deliberations, this Working Group used the criteria for vaccines for use in cholera-affected countries set by the *ad hoc* Cholera Vaccine Working Group of the Strategic Advisory Group of Experts (SAGE) on Immunization in 2009.[9] The 2009 *ad hoc* group recommended that cholera vaccines must, at a minimum, protect against both Ogawa and Inaba serotypes of *V cholerae* O1 El Tor – and should provide at least 50% sustained protection for 2 years in cholera-affected countries. The vaccines should be safe and usable in people as young as 2 years old, as well as in pregnant women and HIV-infected and other immunocompromised individuals.

The Working Group decided that it would be useful to modify the matrix produced by the 2009 *ad hoc* group to create two sets of criteria. The first set concerns the essential characteristics of vaccine(s) that could be used immediately in a stockpile for emergency response. The second group outlines the desirable characteristics of cholera stockpile vaccine(s) of the future. With the first set, it was acknowledged that there was some difficulty

in developing *a priori* criteria, since two prequalified vaccines exist and their characteristics and relative strengths and weaknesses are well known in the cholera vaccine community. Nevertheless, participants followed the Chair's instruction that they should be guided not by what is known to be available but by what is assessed to be essential.

In addressing formulation of the advice, the Working Group reviewed evidence on and discussed the various issues including the following.

- Is the vaccine safe and effective in pregnant women?
- Does the vaccine protect against both Inaba and Ogawa serotypes?
- Does the vaccine need to be given with a buffer?
- Can the vaccine be administered without water or liquid other than the formulated vaccine?
- Does the vaccine require a cold chain in the field?
- Can a single dose confer protection?
- How soon after immunization is protection evident?
- What is the shelf-life of the vaccine?
- What is the vaccine's final shipping package weight and volume?
- Could health workers who administer oral polio vaccine also give the OCV?
- How is the vaccine packaged and presented, e.g. in single or multiple doses?

The Working Group concurred on the points summarized in Table 1. These criteria for vaccine(s) for use in an immediate stockpile mainly mirror those provided by the 2009 *ad hoc* group; differences are listed in the footnotes. The criteria for a stockpile vaccine for the medium term reflect key areas for future OCV research and development that would simplify and facilitate administration in the field.

- Key point 4.1: **The Working Group agreed on a matrix of criteria to guide the choice of vaccine(s) to be stockpiled. OCV characteristics that should guide the development of new vaccine were also outlined.**

Table 1: Criteria for candidate stockpile oral cholera vaccines

	Candidate oral cholera vaccine requirements	
	For immediate stockpile[a]	**For medium-term stockpile**
Confers protection against	O1 El Tor (Inaba and Ogawa)	O1 El Tor (Inaba and Ogawa)
Number of doses required for protection	2 doses	1 dose
Indication ages	≥2 years	All age groups
Safety/tolerability profile	Only mild, short-term side-effects acceptable	Only mild, short-term side-effects acceptable
Immunocompromised status (including HIV infection) contraindicated?	No known risk of whole-cell killed vaccines in pregnant women and immunocompromised individuals[b]	Safe and immunogenic for administration
Time of onset of protection after full vaccination	2–4 weeks	< 2 weeks
Efficacy 6 months[c] after vaccination	≥50%	≥50%
Minimum duration of sustained protection	1 year	1 year

[a] Criteria are the same as those listed for cholera vaccines proposed by the *ad hoc* Cholera Vaccine Working Group of the Strategic Advisory group of Experts (SAGE) on Immunization, unless listed in these footnotes.
[b] See Cholera Vaccines: WHO position paper. *Weekly Epidemiological Record*. 2010;85:117–128.
[c] *ad hoc* Cholera Vaccine Working Group noted: 2 years.

	Candidate oral cholera vaccine requirements	
	For immediate stockpile[a]	**For medium-term stockpile**
Ability to confer herd protection?	Desirable but not necessary	Desirable but not necessary
Formulation	Single formulation for all ages, including very young children	Single formulation for all ages, including very young children
Buffer acceptable?	Yes	Yes
Can be administered with local water (with or without chlorination)?	Yes	Yes
Presentation and packaging	Multi-vial packaging of single-dose vials[d]	Multi-vial packaging of single-dose vials or multi-dose vials
Cold chain requirements	2–8°C	Heat stable
Minimum shelf life	2 years	≥3 years
Country registration	Preferable but not necessary (authorization to use still needed)	Preferable but not necessary (authorization to use still needed)
WHO prequalification	Necessary[e]	Necessary

[d] *ad hoc* Cholera Vaccine Working Group noted: Multi-dose or single-dose packaging.
[e] *ad hoc* Cholera Vaccine Working Group noted: Not if a specific country wants to use and is willing to pay for the vaccine (prequalification required for donor funding and UN procurement).

5. Epidemiological criteria for OCV stockpile use

In some cholera-endemic countries, targeted cholera vaccination is being considered as an addition to the classical prevention and control measures of surveillance, case management, and improving water, sanitation, and hygiene. The Working Group acknowledged that as such activities progress, more evidence to help inform the use of vaccination as a complementary cholera epidemic prevention and control measure will accrue.

The Working Group reviewed the complexity in forecasting the severity of cholera epidemics and the likely impacts of interventions. Cholera presents particular challenges to quantitative modelling, which include lack of understanding of the vibrio biology, the respective roles of person-to-person and environmental transmission, and the particular spatial heterogeneity of cholera that makes it difficult to generalize insights from one location to another.

While acknowledging the difficulty in predicting cholera epidemics and forecasting the likely impact of vaccination, the Working Group agreed that, pending more detailed empirical data, the following points might be considered when assessing the projected severity of a newly detected cholera outbreak.

- Severity is, in this context, defined by the anticipated morbidity, mortality and the likelihood of spread of cholera from an affected area to a non-affected area.
- The impact of vaccination would depend on:
    - Susceptibility of the population, i.e. the level of herd immunity that may have been conferred by earlier exposure to cholera (i.e. from previous outbreaks or from endemic situations) or by vaccination in a particular population.
    - Vulnerability of the population, i.e. behavioural, social, and environmental factors likely to impact on the risk of acquiring infection and engaging in risk minimization (e.g. mobility; health-seeking behaviours and access to health care; hygienic practices; and access to safer food, water, and sanitation).
    - Risk of spatial extension, i.e. the projected likelihood of geographic spread when susceptibility and vulnerability are taken into account.
- A cholera outbreak is defined at the level of a district, a town, a neighbourhood, or a refugee or transient community settlement. Nationwide outbreaks consist of the succession and addition of several epidemic waves evolving over time and place.
- Any given area, e.g. district, town, neighbourhood, or refugee/internally displaced persons site, is considered endemic for cholera if cases or deaths have been reported

and laboratory confirmed during 3 of the previous 5 years. Otherwise, it is considered non endemic.

- Stockpile vaccine will be deployed only *after* the reporting of a culture-confirmed cholera outbreak (with consideration for the number of specimens collected, type of strain, and laboratory capacity) in any given area, if the impact of the vaccination campaign is estimated to be potentially high.
- Stockpile vaccine will *not* be deployed if an OCV campaign has been conducted in the previous 2 years in the same area (with consideration for the quality of the campaign, the vaccine coverage, and any population movements).

Once an outbreak of cholera has been **laboratory confirmed** in a given area, a number of indicators may be considered to estimate the potential impact of the vaccination campaign, based on the susceptibility of the population, the overall vulnerability of the population exposed, and the risk of spatial extension as defined above (Table 2). Since an OCV strategy is likely to cover a broader geographical area than the district, town, or neighbourhood originally affected, the indicators should be applied not only to the affected community but also to surrounding areas where the outbreak could potentially spread. Ethical issues involved in the fair distribution of vaccines should be considered in parallel with epidemiological criteria.

- Key point 5.1: **The Working Group agreed a set of epidemiological criteria that should inform a decision to release stockpile vaccine in response to an outbreak.**

Table 2: Epidemiological and demographic considerations for OCV stockpile deployment

Criterion	Indicator	Decision threshold	Potential impact of vaccination campaign	
			High	Low
Susceptibility of the population	Number of cases reported in the affected area(s) during the past 2–3 years	No or few cases reported	X	
		High number of cases reported		X
	Attack rate of previous outbreaks in the affected area(s)[a]	High attack rate	X	
		Low attack rate		X
Vulnerability of the population	Case-fatality rate (CFR) of previous outbreaks in the affected area(s)[b]	High CFR	X	
		Low CFR		X
	Refugee camp, internally displaced people, or slums present in the affected area(s)	Yes	X	
		No		X
	Area(s) with important population movements (border, market hub, etc)	Yes	X	
		No		X
	Population density in affected area(s)	High density	X	
		Low density		X
	Access to water, sanitation, hygiene, and health care?	Poor access	X	
		Good access		X

Risk of spatial extension	Time elapsed / maturity of the outbreak since first case reported[c]	Few weeks	X	
		Few months		X
	Attack rate since the start of the current outbreak (i.e. cumulative cases)[a]	Low attack rate	X	
		High attack rate		X
	Proportion of health units in the district reporting cases[d]	Low proportion	X	
		High proportion		X
	Time at which first cases were notified during the epidemic season[e]	First cases notified early in the season	X	
		First cases notified late in the season		X

[a] The calculation of attack rates will rely on the availability of population figures. In some instances, cholera attack rates are overestimated because all cases of acute watery diarrhoea are included in the numerator. In general, the quality of the data should be checked when using this indicator. According to Médecins Sans Frontières (MSF) guidelines,[10] the maximum expected attack rate (i.e. the "worst case scenario") would be 5% of the entire population in refugee settings and urban slums, and 2% in rural areas. These figures might however be exceeded in completely naive population as occurred in 2010 in Haiti.

[b] The CFR is likely to be underestimated if all cases of acute watery diarrhoea (and not only cases of cholera) are included in the denominator. Only deaths occurring in health-care facilities are usually reported. In general, the quality of the data should be checked when applying this indicator. According to WHO, CFR should remain below 1% with proper treatment.[11]

[c] The duration of cholera outbreaks within a given area present a high degree of variability. Examples include Mozambique: range 1–25 weeks, mean 7.2 weeks;[12] and Uganda: range 4–27 weeks.[13]

[d] The localisation of the health units is used as a proxy indicator for the localisation of the cases to estimate the current extension of the outbreak, since the exact addresses of cases would most likely be unavailable at national level. Countries applying for stockpile vaccines should actively seek reliable information about cases of acute watery diarrhoea from all health units in the affected district(s).

[e] In some areas, cholera outbreaks occur on a regular basis, every year or so, usually during the rainy season.

The Working Group emphasized that the indicators presented in Table 2 should be used only as advice to inform decision-making and should be considered together with a thorough awareness of the operational capacity of the country to complete a mass vaccination campaign. None should be considered sufficient to make a final decision. Deployment of vaccines from the OCV stockpile should follow analysis of not only the indicators presented in the table but also assessment of programmatic factors such as the local capacity to organize a campaign and the prevailing security conditions.

The WHO Strategic Advisory Group of Experts on Immunization (SAGE) has created a Working Group to develop a framework for public health decision-making for vaccination in humanitarian emergencies.[14] The SAGE Working Group is developing a similar matrix of issues to consider when assessing the need for an emergency vaccine response, which includes implementation capacities, local context factors, and ethical aspects. This matrix was used by the Working Group to frame their discussions. Participants noted the alliance between their work and that of the SAGE Working Group and recognized the merits of sustained, close collaboration in the future.

The Working Group noted that the primary purpose of the stockpile is for outbreak response. However, there may be instances when OCV supply (from the market or other sources) for vaccination in humanitarian emergency settings is not readily available. The Working Group agreed that, in such situations, OCV could be considered for release from the stockpile to enable prompt and timely action, and should then be replenished as soon as possible using emergency response funds.

- Key point 5.2: **The Working Group agreed that requests for use of OCV from the stockpile in humanitarian emergencies could be considered if vaccine supply from standard sources is not readily available. Emergency response funds should be used to replenish the vaccine used from the stockpile.**

6. Global governance of the OCV stockpile

Participants discussed the background to the creation of the two existing stockpiles for meningococcal and yellow fever vaccines, and whether they would serve as a viable model for the OCV stockpile. In 1996, Africa experienced the largest recorded outbreak of epidemic meningitis in history, with more than 200 000 cases and 20 000 deaths. The emergency response fully exhausted international vaccine reserves. In 1997, an International

Coordinating Group (ICG) to oversee a vaccine stockpile was created with an initial US$1 million donation from WHO. The aim was "to assure a well-coordinated and equitable distribution of meningococcal vaccines and related material during meningitis epidemics". The yellow fever vaccine stockpile was created in 2001 in response to an outbreak in Côte d'Ivoire, with an initial stock of 2 million doses.

The ICG decision-making body is composed of representatives from Médecins sans Frontières (MSF), the International Federation of the Red Cross and Red Crescent Societies (IFRC), UNICEF, and WHO. Additional expertise and technical advice might be sought on a case-by-case base from a range of partners including the Agence de Médecine Preventive in Paris, Epicentre in Paris, and WHO Collaborating Centres. Vaccine manufacturers, vaccine equipment providers, and financial donor institutions are also engaged in ICG operations. A meeting with participation of key stakeholders is organized annually.

The overarching goal of the ICG is to ensure timely and targeted deployment such that vaccine can be used as an effective outbreak response where it is most needed. The ICG manages the global stock and liaison with manufacturers ensures that emergency supplies are available at the global level. The ICG decision-making body uses, and promotes the need for, epidemiological and operational criteria for vaccine release. Standard operating procedures are followed, which are transparent and allow lessons to be learned and activities to be improved.

Since the inception of the ICG, much progress has been made on refining the procurement and deployment of vaccines for meningitis and yellow fever. Work has been done at the country level to improve the quality of requests to the ICG, guidelines and forms have been revised and improved, and direct support has been given to countries, including evaluations of epidemic detection and response. The ICG mechanism has also contributed to improvements in surveillance and laboratory confirmation as countries must demonstrate an ongoing epidemic in order to access the ICG stockpile.

On average, 10–35 vaccine requests are received and assessed within a 3-month meningitis epidemic season. The day-to-day running and executive coordination is done by the ICG decision-making group, which makes a decision on each request within 48 hours. Vaccine is delivered to the requesting country within seven days of a positive response. More than 50 million doses of meningococcal vaccines have been deployed via the stockpile since 1997, all for outbreak response. Ninety million doses of yellow fever vaccines have been released for both outbreak and preventive use since 2001.

Initial funding shortfalls limited the ICG's ability to respond to outbreaks but GAVI financing for both stockpiles is now secured until 2013. A revolving fund mechanism was established in 2010 for both stockpiles – in which donors or countries will reimburse the fund for vaccines used – in order to sustain the stockpiles once GAVI funding ends. Since this mechanism was put in place, US$ 4 million has been reimbursed, with 94% fund recovery in 2011.

The Working Group members agreed that there was a clear rationale for employing a similar structure for oversight the OCV stockpile. Representatives of the four members of the ICG decision-making group indicated their organizations' readiness, in principle, to extend their mandate to the governance of the OCV stockpile.

The Working Group agreed that this decision-making group would be charged with developing its own terms of reference. Participants underscored the need to be aware of the sensitivity about cholera reporting and for discretion regarding stockpile request procedures, such as to encourage countries to meet their reporting requirements under the International Health Regulations (2005).[15]

The Working Group acknowledged that other international bodies might wish to join the OCV ICG decision-making group. Participants therefore agreed that any members beyond MSF, IFRC, UNICEF, and WHO must fulfil the criteria below. Applications should be made via the ICG Secretariat at WHO and applicants must:

- Be an international agency or organization.
- Have no conflict of interest, i.e. must not be involved in cholera vaccine manufacture, perform consultancies for and/or receive funding from such manufacturers, be involved in research for development of cholera vaccines, or expect profits of any kind from membership.
- Demonstrate involvement in cholera prevention and control interventions.
- Be committed to be available for emergency consultation at any time, at least through electronic means.
- Undertake to act with discretion with respect to data received for decision-making purposes, given the sensitivities of cholera data to national interests.

The Working Group agreed that the decision-making body should be supported by a wider, consultative, assembly of partners allied with cholera prevention and control. A key objective of this ICG partnership should be to stimulate coordination of international efforts in

preparing for and responding to epidemics, especially through enhanced synergy between the use of OCV and other cholera control measures. The Working Group emphasized that such collaboration and synchronization is essential, since there are many different organizations and projects within the global cholera-response community, thus a risk of duplication of efforts exists.

In addition, the partnership should contribute to rapid access to vaccines by countries experiencing cholera epidemics and promote optimal use of cholera vaccines during epidemics, especially when stocks are limited.

- Key point 6.1: **The International Coordinating Group (ICG) decision-making body comprising MSF, IFRC, UNICEF, and WHO that oversees the meningococcal and yellow fever vaccine stockpiles should extend its mandate to include OCV. This body is charged with developing its own terms of reference and will require funding to cover the added operational costs. Criteria for any additional members were defined. The OCV ICG should be nested within a wider group of organizations (e.g. technical, commercial, civil society, funding) that can inform the partnership on their specific areas of expertise.**

Given the work done by the existing ICG in recent years to refine the mechanism for application and decision-making, the Working Group agreed that the OCV ICG should mirror this procedure. Thus, a request for stockpile vaccine deployment may be submitted by any national or international organization, such as a Ministry of Health or nongovernmental organization. A decision must be made on any such request within 48 hours (2 working days). Decisions should be made by use of pre-established epidemiological criteria. Each of the four organizations in the decision-making group has one vote. Decisions should be reached by consensus, usually by e-mail. If there is disagreement, a teleconference should be convened immediately so that consensus might be reached. If disagreement persists, the decision should be made by majority. The decision types available should be: (1) approval; (2) partial approval (e.g. where less vaccine than requested is approved); (3) more information needed; or (4) rejection.

- Key point 6.2: **The Working Group agreed that submission of a vaccine request may be made by any national or international organization. On receipt of such a request, the ICG should make a decision within 48 hours.**

- Key point 6.3: **The OCV stockpile vaccine should be targeted at epidemics in those countries where cholera is going to cause a significant burden. Participants agreed that the OCV stockpile vaccine should be targeted at epidemics in low-income countries.**

7. Working mechanism of the OCV stockpile

The Working Group referred to various aspects of the mechanism of the ICG for the meningitis and yellow fever stockpiles, stock management, storage, applications procurement, shipping, and financing. Members felt that the most pragmatic approach was to examine the current ICG's working mechanism and replicate this process for the OCV stockpile, with modifications relevant to a cholera outbreak response where appropriate.

Decisions on the size of the stockpile were informed by realistic forecasts of what might be achievable in the short term with either or both of the candidate prequalified vaccines. An initial stockpile of two million doses per year was advised by the Working Group. This size might, and indeed should, change as the stockpile and vaccine development and production capacities evolve and financing grows.

- Key point 7.1: **The Working Group agreed that the OCV stockpile should initially comprise two million doses per year.**

Participants agreed that a 5-year projected stockpile timeframe would be sufficient in the first instance, with a mid-term evaluation. Stock management should mirror experience with the meningococcal and yellow fever vaccine stockpiles, whereby stocks are held by the manufacturers. This arrangement facilitates rapid delivery via established air connections, optimizes the vaccine shelf-life, and simplifies the overall management of the stockpile logistics.

The Working Group agreed that, as with the existing stockpiles, country receipt of OCV should be within 7 days of approval of a request. Whether this target should apply to all the vaccine required (i.e. 2 doses for each individual targeted) or to only the first dose of a regimen, the Working Group noted that this goal would depend on the vaccine/manufacturer selected, as well as such variables as geographical remoteness of the target population and need to be flexible and opportunistic with availability of flights, likelihood of the acceptance of vaccines by the target communities, capacity of the national cold-chain, and other logistic factors.

A key concern was how to ensure that deployed OCV will be used appropriately, given that anticipated stock will be low and demand high. While the Working Group agreed that no binding advice could or should be made at this stage, it emphasized that monitoring and evaluating the efficiency and effectiveness of the stockpile should inform development of such procedures as the scheme is rolled-out.

With regard to financing, the Working Group agreed that the most prudent option would be to seek initial donor funding to finance the first 2–3 years of the stockpile. Such funding would be used to finance procurement of two million OCV doses per year and operating costs to strengthen surveillance and preparedness to mount epidemic vaccination campaigns at the country level. As with the existing meningococcal and yellow fever vaccine stockpiles, a revolving fund mechanism should be established such that financial stability is maintained once initial donor funding has expired.

- Key point 7.2: **The Working Group agreed the storage of stockpile vaccine should be the responsibility of the manufacturer. The stockpile should be maintained on a rotating stock basis.**

- Key point 7.3: **Initial donor contributions should be sought to fund vaccine procurement, country preparedness, and planned operational costs for the first 2-3 years based on the extensive experience of the ICG. A revolving fund should be established to assure longer-term financial stability.**

8. Procurement of OCV for a stockpile

UNICEF Supply Division (UNICEF/SD) acts as the procurement agency for the existing ICG for meningococcal and yellow fever vaccines. The Working Group agreed that, although other procurement organizations exist, it would be prudent for UNICEF/SD to act in this capacity for the OCV stockpile. UNICEF/SD's procurement strategies are focused on achieving vaccine security – the sustained, uninterrupted supply of affordable, quality vaccines – while acknowledging the different forces in individual markets. UNICEF abides by seven procurement principles, which were invoked following the supply crisis in the traditional vaccine markets:

- There should be procurement from multiple suppliers for each vaccine presentation.
- Procurement should be from manufacturers in both developing and industrialized countries.

- The price paid should be affordable to governments and donors and should reasonably cover manufacturers' minimum requirements.
- UNICEF should provide manufacturers with accurate and long-term forecasts; manufacturers should provide UNICEF with accurate and long-term production plans.
- Since UNICEF is a public buyer, provision of grants is not the most effective method of increasing capacity.
- Manufacturers should have the option of quoting tiered pricing.
- A healthy vaccine industry is vital to ensuring uninterrupted and sustainable supply.

The Working Group agreed that UNICEF/SD should establish a Procurement Reference Group to advise on technical issues regarding OCV and stockpile specifications and to evaluate tender applications. The membership, terms of reference, and decision-making process for this group should be defined jointly by UNICEF and WHO.

Participants agreed that the initial tender issued by UNICEF/SD should be for the establishment of a 3-year supply of vaccine. Should that arrangement not be possible within the OCV market, the initial supply could be set at 1 year, with an option of extension to 3 years. The Working Group agreed that a tender for a 5-year supply agreement would not be advisable.

Members of the Working Group agreed that a reserved rather than pre-paid stockpile would be preferable. A reserved stockpile would have the advantages that there would be no risk of unused purchased vaccine and availability of supply would be assured. As with the meningococcal and yellow fever vaccine stockpiles, once the ICG has approved the release of vaccine, UNICEF/SD would issue a procurement order to instruct the manufacturer(s) to ship the vaccine to the country where the outbreak is located. Payment of the vaccine is made 30 days after the issuance of the procurement order.

- Key point 8.1: **The Working Group agreed that a Procurement Reference Group should be established by UNICEF/SD to advise on technical issues regarding vaccine and stockpile specifications. A reserved rather than prepaid stockpile is preferred.**

9. Evaluation and external review of OCV stockpile

The Working Group agreed that clear mechanisms should be put in place for 1) evaluation of outbreak response and 2) monitoring and evaluation of the functioning of the ICG. As a first principle, the OCV ICG should mirror the oversight of the meningococcal and yellow fever stockpiles, with annual meetings of all the extended ICG partners. In addition, the group underscored that a rigorous system of short- and longer-term monitoring and evaluation should be embedded within the OCV stockpile mechanism. The Working Group noted that successful assessment of a stockpile vaccination campaign would require reinforcement of surveillance systems in most locations where an epidemic is likely to arise.

Participants agreed that WHO should establish a stockpile evaluation group to define and implement the detailed monitoring required. As experience and data accrue, the results of this evaluation should enable continuous improvement in the structure and functioning of the stockpile. The evaluation group should report to all relevant stakeholders, including stockpile decision-makers, past and potential requesting countries or organizations, donors, and technical partners. While the evaluation group will define the data to be collected and assessed, the Working Group suggested the following baseline activities, evaluations, and indicators.

- The timeliness and transparency of the ICG decision-making body's approval process should be monitored.
- Where approval is granted, wholly or partially, the timeliness of deployment should be evaluated.
- Evaluation of an OCV stockpile deployment should be done by the collection and assessment of data that include:

    - Number of cases of cholera (clinical and laboratory confirmed) in the vaccinated area
    - Population acceptability of the vaccination campaign
    - Vaccine coverage per round and per age group
    - Drop-out rate between the first and second round (and third, if applicable) and off-target vaccinated populations
    - Vaccine effectiveness in population receiving 1 dose and in those receiving 2 doses (and 3 doses, if applicable); such studies will take some time to complete
    - Overall duration and cost of campaign: actual versus projected
    - Material resources required

- Human resources required, including training and supervision
- Logistics and infrastructure issues: transport, impact of the OCV campaign on Expanded Programme of Immunization and cold-chain infrastructure
- Vaccine wastage

- Where the vaccine request is refused, the impact of this decision should be evaluated. Suggested indicators to monitor include the duration of the outbreak and weekly number of cases, plus the availability, functioning, and impact of treatment and non-vaccine prevention measures within the outbreak area as well as ability of the local authority to procure vaccine from alternative sources.
- In the longer term, an evaluation of the worldwide effect of the existence of the OCV stockpile will be required. Assessments should be made of the efficiency and impact of the stockpile and its effects on total OCV demand and use, manufacturing capacity, and global cholera trends.
- More detailed analysis of the utility of the stockpile should be done in selected areas to assess: vaccine effectiveness; local disease trends; impact on water, sanitation, and hygiene activities; cost-effectiveness; and acceptability.

➢ Key point 9.1: **The Working Group agreed that a rigorous system of short- and longer-term monitoring and evaluation should be embedded within the OCV stockpile mechanism. WHO should establish a stockpile evaluation group to define and implement the detailed monitoring required. As experience and data accrue, the results of this evaluation should enable continuous improvement in the structure and functioning of the stockpile.**

10. Next steps and timeline

The Working Group agreed next steps and a timeline for action during 2012. These are summarized below. WHO will:

- Recruit ICG focal points for cholera stockpile from partner institutions and agree terms of reference agreed (July).
- Advocate for and seek financial support and prepare and submit proposals to: the European Union, the Bill & Melinda Gates Foundation, GAVI, the United Kingdom

Department for International Development, and the United States Agency for International Development (ongoing).

- Inform WHO Headquarters, Regional Offices, Member States, and partners about the planned availability of OCV stockpile and disseminate of epidemiological and operational criteria (October).
- Convene OCV stockpile working group to define a template for deployment evaluation (October).
- Liaise with SAGE Vaccination in Emergencies Working Group to ensure that the consensus of this meeting is compatible with the development of the SAGE Framework (June).
- Meet vaccine producers to discuss production capacity, vaccine presentation, storage capacity, etc (September).

WHO and UNICEF/SD will:

- Develop a procurement strategy that includes milestones for different tender processes (October).
- Convene a Procurement Reference Group to evaluate the bids. This will only be possible once finance is in place.

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12. Annex I: List of participants

Technical Working Group: Oral Cholera Vaccine Stockpile

26–27 April 2012

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Dr William Perea	HSE/PED/CED

The following participants, for reasons of interest in the subject matter of the meeting, agreed to absent themselves from the sessions at which the meeting recommendations were developed. Their participation was thus strictly limited to the sessions dealing with the general exchange of information and views.

Dr J. Clemens: The research unit at the International Vaccine Institute, Seoul, Korea (of which Dr Clemens was Director from 1999 to 2010) developed to licensure the oral cholera vaccine Shanchol™. As part of this development, his unit received a significant in-kind donation of vaccine for the conduct of vaccine trials.

Dr M. M. Levine: Dr Levine has provided advice to and received reimbursement of travel expenses from companies with an interest in oral cholera vaccine. In addition, Dr Levine is co-inventor of an oral cholera vaccine candidate which is being developed in collaboration with a vaccine manufacturer.

Dr Tom Wierzba: Dr Wierzba is a member of the Executive Leadership Team of the International Vaccine Institute, Seoul, Korea which has been closely involved with the development of an oral cholera vaccine.

13. Annex II: Meeting agenda

Chair: Professor Daniel Tarantola

Day One: Thursday, 26 April 2012

Objectives

1. Reach consensus on criteria for inclusion of cholera vaccines in stockpile
2. Reach consensus on epidemiological criteria, indicators for predictability of o/b severity:
3. Agree on principles of stockpile intervention evaluation

TIME	DURATION (minutes)	SESSION TITLE	FACILITATOR
8:30 - 8:45	15	Participant registration	
8:45 - 9:00	15	Introduction, opening remarks Overview of scope of meeting, expected results	Keiji Fukuda Daniel Tarantola
9:00 - 9:20	20	Overview WHO prequalified cholera vaccines	Mike Levine
9:20 – 9:30	10	Overview of OCV criteria for stockpile inclusion	Dominique Legros
9:30 - 10:00	30	Discussion : vaccine criteria for inclusion in stockpile	
10:00 - 10:15	15	Summary: suggestions stockpile vaccine criteria	
10:15 – 10:30	***15***	***COFFEE BREAK***	
10:30 – 10:50	20	Epidemiological criteria for use of OCV stockpile	R. Freeman-Grais
10:50 – 11:10	20	Cholera modelling: Challenges of quantitative analysis and prediction of the impact of interventions	Yonatan Grad
11:10 – 11:30	20	Epidemiological definitions, suggested criteria	Dominique Legros
11:30 – 12:30	80	Discussion	
12:30 – 13:30	***60***	***LUNCH***	
13:30 – 15:15	120	Continued discussion epidemiological criteria	
15:15 – 15:30	15	Summary: suggested epidemiological criteria	
15:30 – 15:45	***15***	***COFFEE BREAK***	
15:45 – 16:30	45	Evaluation/external review of OCV stockpile in epidemic response and validation of criteria	Catherine Yen
16:30 – 18:00	90	Closed session: Recommendations on vaccine, epidemiological criteria + evaluation	

Day Two: Friday, 27 April 2012

Objectives:

1. Agree on stockpile mechanisms (partnerships, decision making, financial, size, storage, rotation, shipment and procurement)
2. Agree on next steps for implementation

TIME	DURATION (minutes)	SESSION TITLE	FACILITATOR
8:45 – 9:00	15	Debrief of Day 1, overview of Day 2	Daniel Tarantola
9:00 – 9:30	30	Partnership. Review mechanisms for Meningitis, Yellow Fever, ICG Decision making process Financing mechanisms. GAVI + other donors. Revolving fund. Donation versus reimbursement	Alejandro Costa Katya Fernandez
9:30 – 10:30	30	Vaccine procurement, tendering process, timelines, prepaid versus reserved stock. OCV stockpile: Size, timeframe, storage, stock rotation, shipment time, logistics	Ana Balmes Ian Lewis
10:30 – 10:45	***15***	***COFFEE BREAK***	
10:45 – 11:15	30	Stockpile Discussion: suggested partnership	
11:15 – 11:45	30	Stockpile discussion: suggested decision making process and mechanisms for deployment	
11:45 – 12:15	30	Stockpile discussion: suggested financial mechanisms	
12:15 – 13:00	***45***	***LUNCH***	
13:00 – 13:30	30	Stockpile discussion: suggested procurement mechanisms	
13:30 – 15:30	120	Closed session: recommendations and next steps	
15:30		***TEA + MEETING CLOSES***	