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Contents

Executive Summary

Despite gains in knowledge about cholera and how to prevent and treat it, and despite the existence of a WHO prequalified oral cholera vaccine for years, cholera continues to be a major public health problem in developing countries. The lack of access to basic water and sanitation infrastructure remains a significant challenge, resulting in both cholera outbreaks and endemic disease. Its continual existence, as well as large, prolonged cholera epidemics in recent years has led to renewed interest within the international health community in addressing the disease. In particular there is increasing pressure to create an oral cholera vaccines (OCV) stockpile following the on-going epidemic in Haiti and earlier large-scale outbreaks

Against this background the WHO Initiative for Vaccine Research organized a meeting jointly with the WHO Global Task Force on Cholera Control to examine the feasibility of a global stockpile for OCVs. Having major stakeholders agree to the objectives and scope of an OCV stockpile is a critical first step towards its establishment. The objectives of this meeting were therefore to (1) Review and discuss potential objectives of an OCV reserve and stockpile and to explore questions related to the motivation for creating a stockpile; (2) Provide a landscape of the cholera vaccines currently available and those in the pipeline cholera vaccines; (3) Discuss key concepts and issues policymakers must address prior to actual development of an OCV reserve and stockpile.

Meeting participants stressed the importance of developing as soon as possible an action agenda that details steps needed to establish a vaccine stockpile and the role of various partners. Participants outlined two approaches: (1) For the control of endemic disease, countries need to plan for vaccine introduction through their national immunization programs. Some countries have yearly cholera outbreaks and would be ready to start vaccination (e.g., in major cities), if vaccine and funding were available; (2) For outbreak control, a small stockpile could be initiated in the near future, even before countries establish strong cholera surveillance capacities or national cholera control action plans. By creating this initial stockpile, experience can be gained and partnerships built, enabling it to improve and grow over time.

For the development of a cholera vaccine stockpile and for the overall control of cholera through immunization working groups made recommendations on: (1) intermediate (short-term) activities for cholera outbreak response; (2) longer-term activities for endemic and epidemic disease control; and (3)research activities to be conducted to determine optimal strategies for the use of OCVs to prevent and control outbreaks and measure their impact in these circumstances.

The group of experts expressed willingness to support the development of a detailed action plan related to OCV use for WHO to update the next WHA in 2012 on implementation of its 2011 resolution on cholera mechanism for prevention and control. This action plan will be based on the recommendations made during this meeting. Since many details will have to be worked out for the action plan, it was suggested to form four working groups to address the following issues: (1) criteria for determining when to vaccinate against cholera in outbreak situations and how best to target vaccination; (2) the optimal size of a long-term cholera vaccine stockpile, based on analyses of past outbreaks, the IVI's cholera vaccine investment case and other data; (3) mechanisms and procedures for a cholera vaccine stockpile, the make-up of the ICG, and other details for its operation; and (4) How to transition from the short term for cholera outbreak response activities to the long term activities for endemic and epidemic control in terms of future research needs and evidence required.

1. Introduction and background

1.1 Introductory remarks

(Pem Namgyal, WHO and Francisco Songane, Chair)

Despite gains in knowledge about cholera and how to prevent and treat it, and despite the existence of a WHO prequalified oral cholera vaccine for years, cholera continues to be a major public health problem in developing countries. The lack of access to basic water and sanitation infrastructure remains a significant challenge, resulting in both cholera outbreaks and endemic disease. Its continual existence, as well as large, prolonged cholera epidemics in recent years, such as in Haiti, has led to renewed interest within the international health community in addressing the disease. This interest has resulted in a resolution of the 64th World Health Assembly (WHA) in May 2011, calling for a renewed efforts for cholera control and prevention. In addition to standard recommendations for improving sanitation and safe water, the WHO recommends the use of oral cholera vaccine for those at risk. However recent experiences have demonstrated that oral cholera vaccine (OCV) has not been available in sufficient quantities when recent epidemics have struck, for example in Haiti. It would seem that the creation of a cholera vaccine stockpile would be one mechanism to insure that OCV is available for cholera outbreaks in humanitarian crises and emergencies.

1.2 Meeting introduction and objectives

(Raymond Hutubessy, WHO)

This meeting was organized jointly by the Global Task Force on Cholera Control and the Initiative for Vaccine Research (IVR), as part of a project funded by the Bill & Melinda Gates Foundation[1]. One of the objectives was to examine the feasibility of a global stockpile for OCVs. There is increasing pressure to create an OCV stockpile following the on-going epidemic in Haiti and earlier large-scale outbreaks. Due to the Haiti outbreak, significantly more cholera cases (nearly 325,000) were reported to WHO in 2010 than in any year in the past decade. In 2011 the WHO member states recognizing the reemergence of cholera as a significant public health problem issued a WHA resolution calling for an integrated, comprehensive strategy of cholera prevention and control, coordinated by WHO. This recommendation includes also 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" [1]. Existing barriers to the use of OCVs include:

[1] Grant ID 43387 entitled "Pre-emptive Use of Cholera Vaccine in Vulnerable Populations",

- The lack of good cholera surveillance in most endemic countries
- The stigma associated with the disease, making countries reluctant to report cases
- The lack of resources invested in cholera control, and
- Limitations with the currently available vaccines (e.g., moderate levels of protection, relatively high production costs and need for a buffer for some, the two-dose regimen of killed whole-cell based vaccines).

The establishment of an OCV stockpile (i.e. a supply of vaccines to respond to outbreaks and complex emergencies) and reserve (i.e. of a supply of OCVs for routine use to control endemic disease) should be considered as part of a cholera management strategy coordinated by WHO and based on lessons learned from existing vaccine stockpiles for polio, yellow fever and meningitis. There are at present a number of challenges and questions that need to be addressed before the precise design and scope of a stockpile can be recommended There is agreement that OCV should be used for vulnerable populations in endemic areas, and others at high risk of epidemics. During a recent WHO meeting consensus was reached to use OCVs reactively in large scale humanitarian crisis with the aim to diminish mortality in case humanitarian interventions can not be put in place. However, evidence of the vaccines effectiveness as a reactive strategy during outbreaks is lacking. Additionally, there are many administrative questions about how such a stockpile would be financed and administered. Having major stakeholders agree to the objectives and scope of an OCV stockpile is a critical first step towards its establishment.

The objectives of this meeting were therefore to:

- Review and discuss potential objectives of an OCV reserve and stockpile and to explore questions related to the motivation for creating a stockpile;
- Provide a landscape of the cholera vaccines currently available and those in the pipeline cholera vaccines;
- Discuss key concepts and issues policymakers must address prior to actual development of an OCV reserve and stockpile.

1.3 Historic overview of WHO oral cholera vaccine policies

(Claire-Lise Chaignat, WHO)

A map of the world showing recent large-scale cholera outbreaks and hotspots highlights the unpredictable nature of cholera. Most recently, the epidemic in Haiti has caused more than 438,000 reported cases and more than 6,000 deaths (from October 2010 to August 2011), and an outbreak in Central Africa (i.e. Chad, Cameroon, Niger, Nigeria) in 2010 caused more than 62,000 reported cases. While most cases reported to WHO in the 1990s were in Latin America, following cholera re-introduction in Peru in 1991, the great majority of reported cases in the decade of 2000-2010 were in Africa. This changed in 2011, where less than 50% of reported cases were from Africa, due to the Haiti epidemic. However, it should be noted that "reported cases" likely represent a very small proportion of the true numbers of cases in the world, and that many endemic countries with large numbers of cases, including India, Bangladesh and Afghanistan, report few or no cases of cholera to WHO.

Once an outbreak has begun, a multi-sectoral, coordinated strategy is needed to limit its further spread and to reduce mortality, with the goal of achieving a case fatality rate of <1%. This approach includes the provision of clean water and adequate sanitation, food safety, community mobilization, case management, and potentially the use of OCVs.

Major milestones in WHO's development of policies regarding OCVs were reviewed. Three of the 10 requests made to the WHO Director-General in the 2011 WHA resolution concern vaccines: 1) to support further vaccine research and the building of vaccine production capacity in developing countries through technology transfer; 2) to develop practical policy guidelines on the appropriate and cost-effective use of OCVs, including how to target vaccination; and 3) to mobilize financial support from donor agencies for cholera vaccine introduction in low-income countries. The 2010 WHO Position Paper on cholera vaccines recommends immunization to control the disease in areas where it is endemic – in conjunction with other prevention and control strategies – and that it also is considered in areas at risk of outbreaks. Possible vaccination strategies recommended in the Position Paper for the control of endemic disease include targeting vaccination to high-risk areas and groups (e.g., children, pregnant women), periodic mass vaccination campaigns with an alternative strategy of incorporating the vaccine into the routine immunization schedule, and booster doses every two years. For outbreak control, the Position Paper recommends that pre-emptive vaccination be considered by local health authorities, and that reactive vaccination could also be considered, depending on the local infrastructure, an epidemiological investigation, and other criteria.

A WHO meeting in May 2011 on an "Integrated Response to Cholera Outbreaks in Large-Scale Humanitarian Crises" proposed reactive cholera vaccination to reduce mortality in hotspots during outbreaks. This recommendation was built on a history of experiences with OCV use with WHO participation – in refugee camps (in Uganda in 1997 and Darfur in 2004), in emergencies (in Aceh following the tsunami in 2005) and in Micronesia in 2000/01 during a cholera outbreak, and in endemic settings (Mozambique in 2003/04) and Zanzibar (2009). Each of these interventions was in response to WHO recommendations made during a series of meetings. A 1999 meeting on the potential use of OCVs in emergency situations recommended that OCVs be considered for pre-emptive use to prevent outbreaks among at-risk populations and that a two million dose vaccine stockpile be established. A meeting in 2002 called for the use of cholera vaccines in endemic and epidemic settings and the conduct of vaccine demonstration projects. A meeting held in Cairo in 2005 on OCV use in complex emergencies called for OCV use in emergency and endemic settings as part of a broader public health response, and the development and field testing of a decision-making tool to help countries determine when vaccination should and should not be used in emergencies[2].

There are several challenges to the use of OCVs, especially in emergency situations, and several lessons that have been learned. Access to the population following a natural disaster or during conflicts can be difficult due to destruction of existing infrastructure including roads and other transport networks e.g. due to the destruction of roads during the tsunami, vaccines had to be flown into the population in Aceh, significantly increasing vaccination costs (which were >$17 per person vaccinated compared to ≈$7.00/dose in Darfur including vaccine cost and cost of international consultants).

[2] The tool has been developed, but has yet to be field-tested.

Vaccinating reactively in time to halt an outbreak also presents a challenge, as it is critical to vaccinate early on in the epidemic (e.g., during the first 4-6 weeks) before it peaks, but it can take up to several weeks from the decision to vaccinate to actual vaccination. Further, a two dose vaccine presents major logistical and financial constraints to mount an effective vaccination campaign. Key lessons learned include the importance of good planning to ensure a successful vaccination campaign, the need for a strong commitment from political leaders for the vaccination; and the importance of well informing the population to attain its acceptance and high coverage.

1.4 Discussion

The need for cholera-endemic countries to have a long-term program to control the disease – as opposed to the short-term response of a vaccine reserve – was highlighted, since endemic cases make up most of the estimated incidence. The question was raised about the commitment of endemic countries to control the disease. It was noted that the Government of Bangladesh has shown a strong interest in recent years in controlling cholera, including through immunization. In addition to supporting the demonstration project involving cholera vaccination (using the killed whole-cell only Shanchol™ vaccine) and improved sanitation practices in an area of Dhaka, it was delegates from Bangladesh on the WHO Executive Board who submitted a request for the WHA to address the problem of cholera, leading to the 2011 resolution.

One key reason given for why cholera vaccines have not been used in Haiti since the outbreak began was the small supply of available vaccine (≈400,000 doses of Dukoral vaccines) and consequently, the difficulty in deciding who and where to target vaccination with this limited supply, since much of the country's population was considered at risk. Participants also stressed the need to vaccinate not only in the immediate area of an outbreak, but also in the larger at-risk population to prevent its spread. The question of what is an ideal range for the performance of cholera vaccines (e.g., for outbreak control) was also raised.

It was felt that the WHO 2010 Position Paper was not clear of what constitutes "appropriate use". An example from the Haiti epidemic of the difficulty in interpreting the 2010 WHO recommendations was whether use of OCV would have been "reactive" use of vaccine during the epidemic or whether there were areas in Haiti which were at high risk. Early in the epidemic, cholera was confined to a limited area, but within a few weeks, it spread to other areas in Haiti. These other areas could have been considered as areas of high risk and these areas would be recommended for vaccination (if the vaccine had been available) according to the 2010 recommendations. However, at the time, it was felt that any use of OCV in Haiti would be a "reactive use" so vaccine was not considered

Another example from Haiti was the assumption that vaccine would have to be used quickly if it was to be used at all. Since a sufficient supply was not available early on, no order was placed to provide vaccine for later use. The possibility that it would be needed as cholera became endemic – and therefore would be recommended according to the 2010 recommendations – was not considered. Thus, a year later, there is no more vaccine available than was available at the start of the epidemic.

There was discussion about the timing of the onset of protection from a two dose inactivated vaccine. What is know from clinical studies show that protection would only begin to be seen 2 weeks after the second dose, suggesting there would be no benefit from a vaccine program for at least 4 to 6 weeks after the first dose. Some participants however expected, based on serological testing, that there would be protection shortly after the first dose, but that the second dose was needed to prolong protection. Although a single dose trial may be undertaken, this will still not document the onset of the timing of protection since few cases will occur within a week of vaccination.

2. Experiences with existing vaccine stockpiles

2.1 Yellow fever and meningitis vaccine stockpiles

(Alejandro Costa, WHO)

Vaccine stockpiles are needed in the following circumstances:

- Demand for the vaccine is uncertain due to the epidemic nature of the disease;
- The vaccine is in short supply;
- To protect against bioterrorism (e.g., anthrax, smallpox);
- For re-emerging pathogens.

The meningitis vaccine stockpile was established in 1997 with an initial $1 million donation from WHO during large outbreaks in Nigeria, because of a shortage in vaccine supply. The yellow fever vaccine stockpile was created in 2001 in response to an outbreak in the Cote d'Ivoire, with an initial stock of two million doses. Both stockpiles use revolving stocks and are managed by an International Coordinating Group (ICG), made up of four partners (WHO, UNICEF, MSF and IFRC), with UNICEF handling vaccine procurement. Upon request from a country, the ICG makes a decision in 48 hours, with a maximum of seven days between the time the request is made and the vaccine arrives in the country. It was difficult to find funding in some years to keep both stockpiles functioning, affecting WHO's ability to respond to outbreaks (e.g., of yellow fever). This improved with recent GAVI financing for both stockpiles 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. Sixty-five million doses of meningitis vaccine have been used through the meningitis stockpile since 1997, as have 90 million doses of yellow fever vaccine since 2001.

Objectives for the current global vaccine stockpiles include ensuring rapid access to vaccines and injection supplies to countries experiencing epidemics, promoting the optimal use of these resources, promoting the use of vaccines of assured quality and safe injection practices, and coordinating an international response to epidemics. The basic principles for operating a vaccine stockpile were reviewed. An international partnership that functions through consensus is critical to its success; these stockpiles are not "owned" by WHO. The stockpile mechanism must also ensure the timely arrival of vaccine – so that it does not arrive too early before it has been determined that an outbreak is indeed taking place, nor too late after an outbreak is almost over. Clear criteria for use of the stockpile are also key to its success. These criteria include epidemiological evidence of an outbreak, including laboratory confirmation; availability of an action plan for mass vaccination; and adequate storage conditions and materials (e.g., auto-disabled syringes).

The design and characteristics of a vaccine stockpile differ for each disease and vaccine. It is easier to create a stockpile for a vaccine that can be used in preventive vaccination campaigns, such as yellow fever – which provides 10 years of protection, in order to use leftover stock (before it expires) in low-epidemic years. The yellow fever stockpile is now being used for preventive campaigns in 11 countries, as well as in response to outbreaks. In contrast, producers have had to throw out expiring meningitis polysaccharide (PS) vaccine when demand via the stockpile was low because there was no outbreak, since it is not generally used for preventive campaigns.

Issues to consider in establishing a cholera vaccine stockpile include the logistical challenges of a two-dose regimen (for killed whole-cell based vaccines) and whether a single dose of Shanchol™ provides protection[3]. Establishing a cholera vaccine stockpile will help create evidence of its impact in controlling cholera epidemics as well as additional evidence of the effectiveness of preventive vaccination to control endemic cholera.

2.2 Discussion

In regards to how the size of stockpiles are determined it was explained that the size of the yellow fever vaccine stockpile was fixed at six million doses per year (since 2007), while the size of the meningitis PS vaccine stockpile varies each year – between six and 12 million doses – based on forecasts of the ICG partners taking into account recent past outbreaks and immunization activities. This is done to minimize wastage since the vaccine is not used in preventive campaigns.

While it has been challenging to measure the impact of the two stockpiles on preventing or controlling outbreaks, one clear outcome has been the more certain demand and creation of markets for these vaccines, reducing the risks to manufacturers (of producing vaccines that won't be used and must be discarded). Through the stockpiles, trust has been built between the partners and producers, and while the vaccines in the stockpile are not pre-paid, the stockpile mechanism has created more confidence and certainty among producers that the vaccines will be used and paid for. As a direct result of the yellow fever stockpile, existing producers invested in increasing production capacity and new producers entered the market. In this regard, vaccine stockpiles are mainly a means of ensuring availability of a vaccine when needed, in the absence of a viable market, and can therefore be viewed as "pre-storage" of a vaccine. In some years, for instance, the only available meningitis vaccine has been the stockpile supply. If there is a sufficient global supply of a vaccine, such as in the case of measles vaccines, a stockpile should not be needed.

Several participants felt that a cholera vaccine stockpile by itself would only be a stop-gap measure until countries introduce the vaccine through their national immunization programs to control endemic disease, thereby creating a longer-term demand for the vaccine. However, others believed that a stockpile may be needed over the long-term to control unpredictable outbreaks, as part of a comprehensive approach towards cholera control. It was noted, for example, that Brazil's program to control yellow fever is multi-faceted, including vaccination through the routine immunization program, preventive campaigns, as well as a national stockpile to respond to outbreaks.

[3] A single-dose of Shanchol™ will be evaluated in a clinical trial in India.

3. Overview of existing cholera vaccines and ones in development

3.1 Shanchol™ vaccine
(Harish Iyer, Shantha Biotech)

Shanchol™ is a two-dose oral killed whole-cell vaccine containing three strains of *V. cholera* O1, as well as the serogroup, O139, making it a bivalent vaccine. The vaccine, produced by Shantha following technology transfer from the International Vaccine Institute (IVI), was licensed in India in 2009 and is pending pre-qualification by WHO[4]. In a Phase 3 trial among 67,000 persons aged one and above, the vaccine was found to confer 67% protection over two years in all ages combined. The third year of the trial shows that the same level of protection is sustained over three years (results still to be published in PLoS NTDs), indicating that it provides protection for at least three years. Efficacy data over five years will be available in 2012. The earliest onset of protection occurs 7-10 days after completion of the two doses, which are given two weeks apart. A study in Kolkata, India showed that 87% of children aged 1-17 and 65% of adults seroconverted after a single dose, and based on these results, a trial of a single dose of the vaccine is planned.

Shantha currently has a production capacity for the vaccine of two million doses per year, but plans to increase capacity to at least 10 million doses per year with the construction of additional production facilities. The company is also working to improve production yield. The vaccine s shelf life on its label is two years at 2-8ºC, but current studies indicate that the shelf life could be extended to three years. Stability tests also indicate that the vaccine can remain outside of the cold chain (to up to 37ºC) for 21 days, though this is not yet on label. The storage volume for 100,000 (single-dose) vials is ≈9 m^3 and the current public sector price is $1.85 per dose.

3.2 An investment case for oral cholera vaccines
(Brian Maskery, IVI)

A global investment case for oral cholera vaccines was prepared to provide evidence to donors, the international health community, vaccine producers, and others for investing in OCV production and use. The study identified 51 cholera-endemic countries in Africa and Asia – defined as having cholera reported through WHO, ProMed, GIDEON and other sources in three years out of a recent five-year period. It also identified 18 "non-endemic" countries that experience periodic outbreaks. The analysis estimated cholera incidence rates for each of the 51 endemic countries by applying incidence rates from various population-based cholera surveillance studies to countries

[4] Prequalification was granted by WHO after the meeting end of September 2011

in the same sub-region[5] where the studies took place. These rates were then applied in each country to the estimated population lacking access to adequate sanitation (as a proxy for the at-risk population). The study estimates an average annual global incidence of around three million cases seeking treatment and around 94,000 deaths (using CFRs for each sub-region raining from 1.0 – 3.8%). Most of the countries with the highest estimated incidence (>2/1,000 population) are in East, Central and Southern Africa, but also include Bangladesh.

A demand forecast identified 33 endemic countries (including two Indian states) that would introduce an OVC into its immunization program – if funding is available – between 2014 and 2020, based on a scoring system that includes cholera mortality rates, immunization program performance, vaccine introduction history and past experience with cholera surveillance or vaccine studies. The investment case estimates the demand, impact and cost-effectiveness of cholera vaccination for four targeting options (a Large Target strategy encompassing urban slums and rural populations without improved water supplies, a Small Target strategy consisting of 50% of these at-risk populations, and for each of these, an option for targeting children 1-14 years old only and another targeting all ages one and above. The analyses assume use of the two-dose oral killed whole-cell only vaccine (e.g., Shanchol™) and revaccination every three years, based on current data showing three years of protection with this vaccine.

By 2020, the projected demand for cholera vaccine introduced into national immunization programs ranges from ≈60 million to 280 million doses per year, depending on the targeting option. An analysis of the impact of vaccination was based on this estimated demand and on a dynamic transmission model constructed with data from Bangladesh and which takes estimated herd effects of the vaccine into account. From 2014 to 2030, cholera vaccination would prevent a total of 7-18 million cases and 280,000 – 600,000 deaths. Based on a vaccine price that starts at $1.85/dose and is reduced over time to $1.45, and delivery costs of $0.60/dose, cholera vaccination would cost between $120-$620 million/year by 2020, depending on the targeting option assumed. Vaccination would be "very cost-effective" (using the WHO definition of the cost/DALY ≤ the GNP/capita) for all children-only programs in all affected WHO regions (AFRO, EMRO, SEARO) – both with and without herd protection taken into account – and "very cost-effective" or "cost-effective" (cost/DALY ≤ 3 times the GNP/capita) for programs that include adults. Since incidence rates are much higher in children than adults, expanding vaccination from children to all ages would gain only around 15% in disease reduction, whereas expanding the vaccination of children to a larger geographical area (from the Small to the Large Target) would double the number of cases prevented.

The investment case also proposes the creation of a cholera vaccine stockpile to be used in response to outbreaks and emergency situations, with stocks remaining at the end of each year to be used for preventive campaigns. Based on an estimate of need from national reporting of cases and on experience with other global stockpiles, the analysis proposes starting with a two million dose stockpile (costing ≈$5.5 million per year assuming use of killed WC only vaccines such as Shanchol™), and having it grow to five million and eventually 10 million doses (costing ≈$23 million per year).

[5] These sub-regions or mortality strata are defined by WHO region and five levels of mortality (ranging from A – E) (e.g., AFRO-D, AFRO-E, SEARO-B).

A case-control study from Hanoi, Vietnam estimated that vaccinating reactively during an outbreak in 2008, using the locally-produced two-dose killed WC only vaccine was 75% effective in preventing the disease. According to a cost-effective analysis using a model based on the Haiti epidemic, reactive vaccination of high-risk areas and populations would be much more cost-effective ($210/DALY averted) than vaccinating the general population ($800/DALY averted).

In conclusion, the high estimated disease burden in South Asia and in many African countries, and the high cost-effectiveness of vaccination programs, especially those targeting children, support the introduction of oral cholera vaccines for the control of endemic disease. In addition, the establishment of a vaccine stockpile could act as a "gateway" to sustainable cholera vaccine introduction in endemic countries and to an adequate vaccine supply, by creating a demand to motivate producers to invest in increasing production capacity for the vaccine, by demonstrating the value of cholera vaccination to donors, and by mitigating outbreaks, if the vaccine is deployed rapidly and efficiently.

3.3 Update on Dukoral®

(Valérie Oriol Mathieu, Crucell)

Dukoral® is currently the only cholera vaccine that is pre-qualified by WHO (since 2001)[6]. It is licensed in 65 countries as a vaccine to prevent cholera, heat-labile (LT) ETEC and traveler's diarrhea. The vaccine is composed of three strains of *V. cholerae* O1 and the recombinant B subunit of the cholera toxin, thereby producing both anti-bacterial and anti-toxin antibodies. This oral vaccine, licensed for persons two years and older, includes a buffer (to neutralize stomach acid that would destroy the cholera toxin), which together with the vaccine is mixed with water. Its schedule is two doses given 1-6 weeks apart for persons six years and older (with a single booster dose after two years), and three doses for children 2-5 years old (with a booster dose every six months). The shelf life is three years (at 2-8ºC), but testing has shown that it can remain stable at up to 25ºC for two weeks. Stability testing up to 40ºC is currently underway. Two packaging options are available – a two-dose package that includes the buffer in sachets and requires ≈49 cm^3 per 10,000 doses, and a 170-dose package more suitable for mass vaccination campaigns, in which the buffer is packaged separately outside of the cold chain, thereby greatly reducing its cold storage requirements (to 0.25 m^3 for 10,000 doses).

Field studies on different continents have shown efficacy or effectiveness rates of 84-85% at five or six months of follow-up. Phase 3 trials in Bangladesh showed protection in persons six years and older of 64% at one year, dropping to 52% at two years and 19% at three years, while protection drops off more quickly in children under six (to 44% at one year and 33% at two years). Significant herd effects have also been demonstrated from the Bangladesh trial. Dukoral® has also been shown to provide short-term protection (e.g., three months or less) of 60-67% against LT ETEC. Use of the vaccine since 1991 has shown a strong safety profile, even in pregnant women and in areas with high rates of HIV. A recent study in Zanzibar, where mass vaccination preventive campaigns took place in 2008, found no statistically significant differences in birth outcomes (miscarriages, infant illnesses, deaths, etc.) between pregnant women exposed to the vaccine by accident and pregnant women not vaccinated.

[6] Prequalification was granted by WHO after the meeting end of September 2011

Dukoral® has been used in several instances in Africa and Asia both in endemic settings (e.g., Mozambique and Zanzibar) and to preempt outbreaks in emergency situations (e.g., in refugee camps), with a range of 50,000 – 137,000 doses provided in each instance.

Fifteen million doses of Dukoral® have been produced and distributed since 1991, when the vaccine was first licensed. Crucell has shown interest in increasing production capacity to contribute to the control of endemic and epidemic cholera. To respond to an outbreak, such as in Haiti, the company would have been able to produce and ship 3.2 million doses over a 13-15 month period, starting with 250,000 – 300,000 doses within one to three months. As a starting point, a stockpile of 2.4 million doses, consisting of both bulk and finished vaccine, could be established. Creating such a stockpile will require donor funding to produce, store, manage and replenish the stock, as well as a written agreement that includes a demand forecast, given the current low demand for the vaccine.

3.4 Re-introduction of an oral, single-dose, fast-acting cholera vaccine
(Andre Collioud, PaxVax)

PaxVax of Menlo Park, California is working towards re-introducing the live attenuated oral CVD 103-HgR vaccine, previously produced by Swiss Serum Institute/Berna Biotech and marketed as Orochol®. More than half a million people were given the vaccine in the 1990s and early 2000s in six countries where it was licensed and in field studies in Indonesia and Micronesia. The vaccine – a strain of classical Inaba attenuated by deletions of the A subunit of the cholera toxin, among other deletions – is given in a single dose with a buffer, and provides protection within a week. An application for licensure to the U.S. FDA was withdrawn and production was suspended in 2004, both for commercial reasons.

CVD 103-HgR was shown in a series of studies to be safe and immunogenic in all ages and in HIV positive individuals. A single dose was found in a series of challenge studies in the U.S. to confer protection against both classical and El Tor strains (49-100%). A retrospective case-control study conducted following mass vaccination of 15,000 persons during an outbreak in Micronesia estimated that the vaccine conferred 79% protection.

PaxVax plans to conduct clinical studies of the vaccine in 2012 and to apply for licensure with the FDA in 2013, with anticipated licensure by 2014. This first generation of the vaccine, which requires a cold chain and administration with a buffer, will be suitable for travelers as well as for a stockpile for use in controlling cholera outbreaks. It can be manufactured rapidly – in 2-3 weeks for 200,000 doses of the finished product, enabling fast re-stocking if needed for outbreak response. The company plans to store both bulk vaccine (which has a shelf life of three years when frozen) and the finished product (with a two-year shelf life). PaxVax also plans to develop a second generation product – if financing is available – that will be more suitable for use in endemic settings. The goal is to develop a higher-yield vaccine in powder form that does not require a buffer or cold chain.

3.5 Cholera vaccines in development

(Claire-Lise Chaignat, WHO)

WHO is aware of six other cholera vaccines in development. These include three single-dose live attenuated vaccines[7] (Peru-15 developed by VTI (China) and the IVI, VA 1.4 developed in India, and a vaccine developed in Cuba). The Cuban vaccine is ready to be tested in a Phase 3 trial once funding and a site are secured. The other three vaccines are early-stage candidates: a conjugate vaccine developed at Harvard University, a killed-whole cell vaccine under development at Johns Hopkins University, and a vaccine under development at the University of Goteborg. WHO is in the process of seeking information from the developers of these vaccines, including the status of clinical development; their characteristics, formulation and performance; storage requirements; and potential costs.

3.6 Discussion

Concerning the projected prices of cholera vaccines to the public sector, PaxVax estimates that the first generation of its live attenuated vaccine will be in the "low dollar" range per dose, while the goal of the second generation vaccine will be less than $1 per dose. The investment case uses the current public sector price for Shanchol™ of $1.85 per dose for the first several years, which is reduced to $1.45 per dose in later years, once the same vaccine is expected to be produced for export and pre-qualified in Vietnam and perhaps elsewhere. Crucell does not at present have an established public sector price for Dukoral®, but will negotiate price with prospective buyers.

Concerning the investment case, it was pointed out that, due to the great discrepancy between the projected demand for vaccine for endemic disease control – up to 100s of millions of doses per year, and the projected production capacity – only in the tens of millions of doses at most, expanding the vaccine supply will be a critical issue. It was suggested that, since the disease burden analysis in the investment case uses facility-based mortality rates and does not include cases that result in death before reaching the hospital, the study may have under-estimated the death toll from the disease. The study based its analyses on estimates of the number of cases seeking treatment on either an inpatient or outpatient basis. Given the wide spectrum of the disease and the high costs involved, a further suggestion was made to instead estimate the incidence of the most severe cases (cholera gravis) and to focus the analyses of the need for and impact of vaccination on these most severe cases.

[7] In addition to the CVD 103-HgR in development for re-introduction, as described above.

4. Potential objectives, scope and framework of an OCV reserve and stockpile

4.1 Rationale, scope, potential strategies and issues to consider for an OCV reserve and stockpile

(K. Thompson and R. Tebbens, Kid Risk, Inc.)

While only around 50 countries report cholera cases to WHO in any given year, over the first decade of the 2000s around 115 countries have reported the disease. Including imported cases, cholera affects all regions of the world and is therefore a global problem. The epidemic in Haiti highlights the seriousness of cholera and the need for an international vaccine stockpile to guarantee vaccine supplies and their rapid deployment. An analysis of the Haiti outbreak by Chao et.al. [2] suggested that it would have been effective to vaccinate preemptively in high-risk areas before cases appear. This would have required both the availability of a stockpile and knowledge of the key risk factors for transmission for this particular outbreak.

There are a number of reasons for the limited use of OCVs to date. These include:

- The "acceptance" of the status quo in many places. This is due to under-reporting of the disease (as a result of the stigma associated with countries reporting cholera and poor surveillance), the existence of preventive measures (e.g., water and sanitation improvements) and treatment, the fact that cholera mainly impacts marginalized populations, and the fact that the disease has been eliminated in developed countries.
- Limited data on the impact of OCVs in controlling disease outbreaks and endemic disease.

Consequently, there is no market at present for OCVs for the control of endemic disease, which limits the opportunity to establish a stockpile with a rotating stock (to minimize expiry of vaccines). The prevention and control of cholera, as called for in the 2011 WHA resolution, will require stakeholders – international agencies including WHO, national policymakers, donors, producers, NGOs – to create solutions for the long-term and to develop global markets for cholera vaccines, which will involve risk management and the creation of incentives for producers.

Kid Risk, Inc. was commissioned by WHO to develop a draft framework including a mathematical model for an OCV reserve and emergency stockpile. The framework proposes that WHO facilitate the development of a supply of OCVs for routine use to control endemic disease (e.g. a reserve) and to respond to outbreaks and complex emergencies (e.g., using an emergency stockpile). The impact of vaccination in both types of circumstances would be evaluated to increase the evidence base, with WHO playing a catalysing role. WHO would also develop guidelines for the use of

OCVs both for endemic disease and outbreak control, based on these experiences. WHO could request countries to develop national cholera management plans, to include cholera surveillance and potentially vaccination for endemic disease control and/or for outbreak response. These plans could be an important step in creating a more predictable demand for the vaccine that could lead manufacturers to invest in OCV production or expansion. Donor funding will be needed to support the evaluation of not just OCVs, but overall cholera control programs.

Key decisions to be made in designing a stockpile include:

- Which vaccines to include in the stockpile (Dukoral®, Shanchol™, the re-introduced CVD 103-HgR currently in development, or a combination of vaccines);
- Whether the stockpile should be used for routine (preventive) use, pre-emptive campaigns, reactively in response to outbreaks, or for all three purposes;

The optimal size of the stockpile.

- Issues to consider in designing an optimal cholera vaccine stockpile include:
- Supply chain issues and timing, including production constraints due to limited capacity (at least initially), and the need to plan for a limited shelf life. Having a regular stock or reserve will facilitate the maintenance of an emergency stockpile to enable stock rotation;
- The demand for OCVs, which can be predictable for routine vaccination in endemic areas, but unpredictable when used in response to cholera outbreaks;
- Measuring the impact of vaccination via a stockpile. This will require dynamic modeling and in the case of reactive vaccination, consideration of the time of onset of immunity. Modeling of cholera transmission is complicated by the variability in disease transmission patterns in different locations, and the limited evidence of herd protection, among other factors;
- The public health benefits of prevention, including a reduction in treatment costs and in the negative macro-economic effects of cholera outbreaks (e.g., on tourism and food exports);
- Financial costs, including the costs of vaccine production, maintenance of a large stock, and vaccine delivery/administration.

4.2 Discussion

It was questioned whether there is a need for additional data, especially for vaccination to control endemic disease, as there have been a number of studies evaluating the feasibility and effectiveness of OCVs[8]. In addition to gathering more evidence, it is important to conduct advocacy, as learned from the experience with Hib vaccine introduction. Countries were slow to adopt the vaccine despite GAVI support, until there was a major advocacy effort made through the Hib Initiative. The need to deconstruct the barriers to OCV use in Haiti was also suggested.

[8] Including in Mozambique, Vietnam, Zanzibar, Kolkata, India, and currently in Dhaka and Orissa State, India).

Since countries may not respond to requests for comprehensive actions plans for cholera control, and may need assistance in their preparation, several experts felt that it would be preferable to create a vaccine stock and have countries apply for its use before the country (or all countries) develops these plans, in order to avoid long delays in vaccine use. The extent to which countries must significantly improve cholera surveillance before developing national action plans (e.g., to determine where to target vaccination) was also discussed. According to several participants, policymakers and researchers in many endemic countries know where the cholera hotspots are – places where outbreaks can be highly predictable – and should be encouraged to draw cholera maps of their countries, using available data that may or may not be in the public sector. It was pointed out, however, that surveillance will be critical not only to determine where to target vaccination, but also to decide which age groups to target, when best to vaccinate, as well as to measure impact. Without being able to demonstrate a reduction in disease – as has been the case for some countries that introduced Hib vaccine without baseline disease burden data – it may be difficult to sustain political support for cholera vaccination.

Ethical considerations were raised in the situation of limited vaccine supply on how to prioritize target groups. It would be difficult to argue that since there are not enough vaccines for everybody that nobody should have access at all. Policy makers should rather aim to establish positive criteria for identifying groups that should have priority access to OCVs. The criteria could be based on complex epidemiological and technical evidence but non-discrimination criteria such as on gender, race and ethnicity should be avoided. The WHO Ethics and Health unit has produced several WHO guidance documents on distributive justice and fair access to health services for example in the field of HIV/AIDS and pandemic influenza.

It is also critical that vaccine introduction be integrated into an overall cholera control strategy and that national plans do not end up focusing solely on vaccination. The use of ORS, for example, must be a critical component of any cholera control plan.

A strategy to consider, proposed by several participants, is to make OCVs widely available at affordable prices in the private sector in order to generate demand and to avoid the need for governments to deal with the stigma of admitting that there is cholera in their country. Such as approach – which may not require donor funding – has been successful in

Bangladesh in the distribution and use of zinc and in the treatment of tuberculosis and malaria. Since they are administered orally, cholera vaccines could be provided by private pharmacies. Arguments against this approach include the fact that private sector distribution often misses the people most in need, it could lead to fraud, and it would complicate surveillance and reporting of adverse events.

Many of the participants felt the analysis presented by Kidrisk was overly complex and did not take into account much of the evidence about cholera control and the efficacy of OCV. These participants felt that there was need to proceed quickly with establishment of the stockpile and to begin to gain experience with OCV in endemic and epidemic situations as quickly as possible rather than continuing to develop models of vaccine effectiveness in various situations.

5. Options and recommendations for the design of a cholera vaccine stockpile and accompanying research in the broader context of cholera control through immunization

5.1 Introduction

Meeting participants stressed the importance of developing as soon as possible an action agenda that details steps needed to establish a vaccine stockpile and the role of various partners. Participants outlined two approaches:

1) For the control of endemic disease, countries need to plan for vaccine introduction through their national immunization programs. Some countries have yearly cholera outbreaks and would be ready to start vaccination (e.g., in major cities), if vaccine and funding were available;

2) For outbreak control, a small stockpile could be initiated in the near future, even before countries establish strong cholera surveillance capacities or national cholera control action plans. By creating this initial stockpile, experience can be gained and partnerships built, enabling it to improve and grow over time.

It will also be important to reach on consensus on the definition of terms such as "endemic" cholera, "pre-emptive" vs. "reactive" vaccination, vaccine "reserve", and "stockpile". Although precise definitions may be desirable, development of consensus definitions should not inhibit the creation of the stockpile nor the use of OCV. As an interim, the definition of endemic cholera presented in the 2010 WHO recommendations can serve as a useful working definition.

Working groups made the following recommendations for the development of a cholera vaccine stockpile and for the overall control of cholera through immunization:

5.2 Immediate (short-term) activities for cholera outbreak response

- A short-term emergency supply of at least two million doses should be established in the next 12 months, leading up to the creation of a longer-term stockpile. The emergency supply should prioritize the use in pre-emptive and reactive vaccination in emergencies, such as during floods, in refugee/displaced persons settings in cholera-endemic areas, and once an outbreak begins;
- A starter fund is needed to establish the emergency supply and a detailed investment case should be prepared for the vaccine stockpile to secure donor funding;
- Many of the mechanisms and procedures used for the yellow fever and meningitis vaccine stockpiles could be used for a cholera vaccine stockpile, including the establishment of an ICG and existing country request forms (adapted for cholera);

- The stockpile should be kept at the manufacturer(s)' facilities, as is the case with the yellow fever and meningitis vaccine stockpiles. If the stockpile is not utilized in the priority settings, options to send it to an endemic area should be evaluated as is the case with yellow fever.
- Advocacy is needed to encourage countries with endemic or epidemic cholera when and how to use OCV to control cholera

5.3 Longer-term activities for endemic and epidemic disease control

To address the mismatch between vaccine supply and potential demand, this working group recommended:

1) Development of a stockpile like yellow fever, in which vaccine would be used both for emergencies (e.g., ≈20%) and for preventive campaigns (≈80%);
2) A coordinated set of activities to be conducted to ensure demand for routine cholera vaccination in endemic countries and thus a vaccine supply, to include:
   - advocacy for use of OCVs in endemic countries
   - the development of national action plans for cholera control
   - upgrading of cholera surveillance to demonstrate the need to control the disease, to better direct OCV use and to measure impact of OCVs; and
   - development of funding strategies, including consideration by GAVI.

5.4 Research activities

- A series of studies should be conducted to determine optimal strategies for the use of OCVs to prevent or control outbreaks and to measure their impact in these circumstances, including:
  - A study to determine how best to target vaccination for outbreak response when vaccine supply is limited (e.g., whether to start in affected area, or in neighboring areas to prevent its spread?; whether to focus on urban areas or hard-to-reach rural areas with higher mortality risk due to poor access to health care?); Given that a SAGE working group is working on recommendations for the use of vaccines in humanitarian emergencies there is an urgent need to link the proposed activities into the ongoing discussion for that that working group.
  - An analysis of previous outbreaks to determine the optimal timing of OCV use;
  - A study of the feasibility and impact of different vaccine delivery strategies (such as vaccination incorporated into other campaigns (e.g., measles vaccination, child health weeks.
- Conduct a study of the efficacy of a single dose of killed WC vaccines (e.g., Shanchol™) and the time to onset of protection after one dose of this vaccine;
- Complete testing of heat stability of cholera vaccines to determine how long they can be kept outside of the cold chain (e.g., for emergency response in difficult field conditions);

- Study the lessons learned about policymaking regarding cholera vaccine use, including for what circumstances a vaccine is requested, when vaccine is used and not used, and factors involved in order to determine the information and conditions needed for decision-making about cholera vaccine use;
- Develop and evaluate an advocacy toolkit to assist decision-making on use of cholera vaccines.
- Development of additional vaccines or vaccine formulations as well as increasing manufacturing capacity to fill the required needs for OCV.
- Interchangeability of the existing cholera vaccines

5.5 Recommended next steps

The group of experts expressed willingness to support the development of a detailed action plan related to OCV use for WHO to update the next WHA in 2012 on implementation of its 2011 resolution on cholera mechanism for prevention and control. This action plan will be based on the recommendations made during this meeting. Since many details will have to be worked out for the action plan, it was suggested to form four working groups to address key issues concerning the design of and required steps for creation of a cholera vaccine stockpile.

The four working groups will address the following issues:

1) Criteria for determining when to vaccinate against cholera in outbreak situations and how best to target vaccination;
2) The optimal size of a long-term cholera vaccine stockpile, based on analyses of past outbreaks, the IVI's cholera vaccine investment case and other data;
3) Mechanisms and procedures for a cholera vaccine stockpile, the make-up of the ICG, and other details for its operation;
4) How to transition from the short term for cholera outbreak response activities to the long term activities for endemic and epidemic control in terms of future research needs and evidence required.
5) It was also clearly suggested to start in the meantime with the short terms activities for cholera outbreak response.

References

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2) Cholera vaccines: WHO position paper. Wkly Epidemiol Rec 2010, 85:117-128.

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Annex 1:
Meeting agenda

Final Agenda

Objectives:	• To review and discuss potential objectives of an OCV reserve and stockpile and to explore questions related to the motivation to creating a OCV stockpile • To provide a landscape of the currently available and pipeline cholera vaccines • To discuss the key concepts and issues policy makers must address prior to actual development of an OCV reserve and stockpile	
Expected outcomes	• A framework of different options for an OCV reserve and stockpile for both endemic and epidemic use.	
Chair: F. Songane *Co-Chair: Z. Hallaj* *Rapporteur: D. DeRoeck*		
Tuesday, 6 September 2011		
08:30 – 09:00	Registration	
09:00 – 09:15	Welcome and introduction	P. Namgyal
Session 1: Introduction and background information		
09.15 – 09.30	Meeting introduction and objectives	R. Hutubessy
09.30 – 10.30	Historical evolution of WHO policies (15' presentation) **Discussion**	C-L. Chaignat
10.30 – 11.00	*Coffee break*	
Session 2: Experiences from existing vaccine stockpiles		
11.00 – 12.30	ICG mechanism for Yellow Fever and Meningitis vaccines (20' presentation) **Discussion**	A. Costa
12.30 – 13.30	*Lunch break*	

Session 3: Overview of existing cholera vaccines and ones in development		
13.30 – 14.00	ShanChol - IVI investment case (15' presentation)	B. Maskery/J. Smit
14.00 – 14.30	Crucell (15' presentation)	O. Mathieu
14.30 – 15.00	PaxVax (15' presentation)	A. Collioud/ M. Gurwit
15:00 – 15.30	**Discussion on vaccines in development** Introduction (10')	C-L. Chaignat
15.30 – 16.00	*Coffee break*	
Session 4: Potential objectives, scope and framework of an OCV reserve and stockpile		
16.00 – 16.45	Rationale, scope and potential strategies (25') **Discussion**	K. Thompson
16.45 – 17.30	Components of the framework (25') **Discussion**	R. Tebbens
17:30	Adjourn	
17:30	*WHO Reception Main Cafeteria*	
Wednesday, 7 September 2011		
Session 5: Components and management of an OCV reserve and stockpile		
08:30 – 10:00	Summary of first day (10') **Discussion on Strategic Concepts**	Chair/Co-chair All
09:00 – 09:15	Welcome and introduction	P. Namgyal
10.00 – 10.30	Introduction of Working Groups (Salle D)	Chair/Co-chair
10.30 – 11.00	*Coffee break*	
Session 6: Working Groups		
11.00 – 13.00	Working Groups Group 1: Salle D Group 2: Salle X7 Group 3: Salle C202	All
13:00 – 14:00	*Lunch break*	
Session 6 *(continued)*: Feedback Working Groups		
14.00 – 15.30	Feedback from working groups in plenary sessions and discussions (Salle D)	WG Rapporteurs All
15.30 – 16.00	*Coffee break*	
Session 7: Closing session		
16.00 – 17.00	Wrap up and closure	Chair/Co-chair
17.00	Adjourn	

Annex 2:
List of participants

List of participants

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The World Health Organization has provided technical support to its Member States in the field of vaccine-preventable diseases since 1975. The office carrying out this function at WHO headquarters is the Department of Immunization,Vaccines and Biologicals (IVB).

IVB's mission is the achievement of a world in which all people at risk are protected against vaccine-preventable diseases. The Department covers a range of activities including research and development, standard-setting, vaccine regulation and quality, vaccine supply and immunization financing, and immunization system strengthening.

These activities are carried out by three technical units: the Initiative for Vaccine Research; the Quality, Safety and Standards team; and the Expanded Programme on Immunization.

The Initiative for Vaccine Research guides, facilitates and provides a vision for worldwide vaccine and immunization technology research and development efforts. It focuses on current and emerging diseases of global public health importance, including pandemic influenza. Its main activities cover: i) research and development of key candidate vaccines; ii) implementation research to promote evidence-based decision-making on the early introduction of new vaccines; and iii) promotion of the development, evaluation and future availability of HIV, tuberculosis and malaria vaccines.

The Quality, Safety and Standards team focuses on supporting the use of vaccines, other biological products and immunization-related equipment that meet current international norms and standards of quality and safety. Activities cover: i) setting norms and standards and establishing reference preparation materials; ii) ensuring the use of quality vaccines and immunization equipment through prequalification activities and strengthening national regulatory authorities; and iii) monitoring, assessing and responding to immunization safety issues of global concern.

The Expanded Programme on Immunization focuses on maximizing access to high quality immunization services, accelerating disease control and linking to other health interventions that can be delivered during immunization contacts. Activities cover: i) immunization systems strengthening, including expansion of immunization services beyond the infant age group; ii) accelerated control of measles and maternal and neonatal tetanus; iii) introduction of new and underutilized vaccines; iv) vaccine supply and immunization financing; and v) disease surveillance and immunization coverage monitoring for tracking global progress.

The Director's Office directs the work of these units through oversight of immunization programme policy, planning, coordination and management. It also mobilizes resources and carries out communication, advocacy and media-related work.

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