Oral Cholera Vaccine stockpile for cholera emergency response
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Background

Global burden of cholera

The real global burden of cholera is unknown. In cholera endemic countries, an estimated 1.4 billion people are at risk of cholera each year\(^1\) and 2.8 million cholera cases (uncertainty range: 1.4–4.3) and 91,000 cholera deaths (uncertainty range 28,000 to 142,000) occur every year. Another 87,000 cases and 2,500 deaths are expected in non-endemic countries annually.\(^1\)

Slow progress in providing access to safe water and sanitation to underserved populations, limitations of surveillance systems for early detection of cholera outbreaks, and lack of access to timely and appropriate healthcare have contributed to this burden of disease. Other factors contributing to make cholera a public health priority are the emergence in 1992 of new strains of *V. cholerae* more virulent and causing more severe clinical manifestations\(^2\), the increased antimicrobial resistance, climate change and rapid and unplanned urbanization.\(^3\)

Children under five bear the greatest burden of cholera and account for about half of the estimated cholera deaths.\(^4\)

Effective cholera prevention and treatment regimens are well established, yet cholera remains poorly controlled in both outbreak and endemic contexts.

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.

World Assembly resolution and WHO technical consultations

Recognizing the importance of cholera as a continuing public health problem, the World Health Assembly adopted Resolution 64.15 in May 2011.\(^5\) This resolution calls for implementation of an integrated and comprehensive approach to cholera control, which may include 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.”

In September 2011, the World Health Organization (WHO) Secretariat organized a technical consultation which recommended the creation of an OCV stockpile for outbreak control.\(^6\)

In April 2012, the WHO convened a Technical Working Group (WG) to address the creation of an oral cholera vaccine stockpile and to develop the implementation framework.
The WG agreed that the focus would be specifically to respond to outbreaks, as a means to complement but not replace existing guidance on other critical cholera outbreak prevention and control measures.\textsuperscript{7}

**Characteristics of currently prequalified OCV**

**General information**
For the creation of an immediate stockpile, two OCVs are currently prequalified by WHO: Dukoral\textsuperscript{®} and Shanchol\textsuperscript{™}. There is no known comparison of the two vaccines up to now. Their key attributes are briefly outlined below and summarized in table 1.

Overall, both WHO pre-qualified are oral killed whole-cell vaccines (WC) that provide sustained protection of >50\% for at least two years in endemic populations\textsuperscript{8-10} induce an immune response relatively quickly (7-10 days after the 2nd dose) and have a good safety profile.\textsuperscript{11} Shanchol\textsuperscript{™} has demonstrated longer term protection in children less than six years of age, as compared to Dukoral\textsuperscript{®} and therefore does not require booster dose after six months in this age group, as does Dukoral\textsuperscript{®}.\textsuperscript{12} On the other hand, Dukoral\textsuperscript{®} has been shown to provide better short-term protection against cholera, particularly among children 2-5 years old and also confers significant short-term protection against ETEC.

In terms of logistics and handling, both vaccines have a two-dose regimen between 1 and 6 weeks apart. (3 doses for Dukoral in children aged 2–5 years) and require a cold chain.
Table 1. Characteristics of WHO pre-qualified oral cholera vaccines.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Oral cholera vaccines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trade name</td>
<td>Dukoral®</td>
</tr>
<tr>
<td></td>
<td>Shanchol™</td>
</tr>
<tr>
<td>Type of vaccine</td>
<td>Killed whole cell vaccine <em>V. cholerae</em> O1 serogroup + recombinant B subunit of cholera toxin (WC/rBS)</td>
</tr>
<tr>
<td></td>
<td>Killed bivalent (O1 and O139 serogroups) whole-cell vaccine suspension. (BivWC)</td>
</tr>
<tr>
<td>Presentation (or packaging)</td>
<td>3 ml single dose vials and 5.6 g of effervescent granules of sodium bicarbonate buffer in a sachet</td>
</tr>
<tr>
<td></td>
<td>1.5 ml single dose vials (in 3 ml glass vial with aluminium cap)</td>
</tr>
<tr>
<td>Age</td>
<td>From 2 years of age</td>
</tr>
<tr>
<td></td>
<td>From 1 year of age</td>
</tr>
<tr>
<td>Administration course or (Dosing)</td>
<td>- Adults and children 6 years and older: 2 doses given orally 1-6 weeks apart. - Booster dose after 2 years.</td>
</tr>
<tr>
<td></td>
<td>- Children 2-5 years: 3 doses given orally 1-6 weeks apart. Booster dose after 6 months.</td>
</tr>
<tr>
<td></td>
<td>- Fasting required 1 hour before and after vaccination.</td>
</tr>
<tr>
<td></td>
<td>- 2 doses given orally 2 weeks apart.</td>
</tr>
<tr>
<td></td>
<td>- A period of +3 days is accepted for second dose.</td>
</tr>
<tr>
<td></td>
<td>- No official recommendation on booster yet.</td>
</tr>
</tbody>
</table>
| Buffer                        | Dilution in 150ml of water (75ml for children 2-5 years) mixed with buffer | - No buffer needed  
- Water may be offered following ingestion of the vaccine, but is not required. |
|------------------------------|--------------------------------------------------------------------------|--------------------------------------------------------------------|
| Protection/efficacy         | Earliest onset of protection 7 days after 2nd dose.                      | - Earliest onset of protection 7-10 days after 2nd dose.  
- 67% protection for at least 2 years in all ages |
| Adverse effects /contraindications | - No major adverse effects reported.  
- Currently not recommended for use in pregnancy (no specific studies performed)  
- Administration may be considered after benefit-risk evaluation.  
- Can be given to HIV-infected persons. | - No major adverse effects reported.  
- Currently not recommended in pregnancy (limited data)  
- Currently not recommended in HIV/AIDS or other immuno-compromised states (No clinical data)  
- Administration may be considered after benefit-risk evaluation. |
| Shelf life, storage and cold chain | - 3 year shelf life at 2-8°C.  
- Stable for 1 month at 37°C.  
- 2 weeks at < 27°C  
- **Do not freeze**  
- No VVM.  
- Packed volume per dose: 136cm³ (in 2-dose pack; also available in single and 20-dose pack) | - 30 months shelf life at 2-8°C  
- **Do not freeze**  
- VVM of type 14.  
- Stable for 14 days at 37°C  
- Packed volume per dose in 35-dose pack: 16.8cm³ (140 mm x105 mm x40 mm) |
<p>| Manufacturer                 | Crucell, (Sweden)                                                         | Shantha Biotechnics, (Hyderabad, India) Sanofi Company |</p>
<table>
<thead>
<tr>
<th>Current production capacity (2012)</th>
<th>2 million doses per year</th>
<th>2 million doses per year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Countries licensed (June 2013)</td>
<td>Licensed in 60 countries</td>
<td>India, Nepal, Malaysia, Philippines, Ivory Coast</td>
</tr>
<tr>
<td>Year first licensed</td>
<td>1991</td>
<td>2009</td>
</tr>
<tr>
<td>Date of WHO prequalification</td>
<td>25 Oct 2001</td>
<td>29 Sep 2011</td>
</tr>
<tr>
<td>Estimated prices per dose (2013)</td>
<td>~ $ 4.7-9.4 per dose</td>
<td>$1.85</td>
</tr>
</tbody>
</table>

**When to consider the use of OCV? WHO position paper**<sup>24</sup>

**Vaccination and cholera control**

Cholera control should be a priority in areas where the disease is endemic.

Given the availability of 2 oral cholera vaccines and data on their efficacy, field effectiveness, feasibility and acceptance in cholera-affected populations, immunization with these vaccines should be used in conjunction with other prevention and control strategies in areas where the disease is endemic and should be considered in areas at risk for outbreaks.

Vaccination should not disrupt the provision of other high-priority health interventions to control or prevent cholera outbreaks. Vaccines provide a short-term effect that can be implemented to bring about an immediate response while the longer term interventions of improving water and sanitation, which involve large investments, are put into place.

Although all age groups are vulnerable to cholera, where resources are limited immunization should be targeted at high-risk children aged ≥1 year (Shanchol™ or mORCVAX) or ≥2 years (Dukoral<sup>®</sup>). (For vaccine schedules and administration, see recommendations made by the manufacturers).

**Control of endemic cholera**

The following definition for endemic cholera has been suggested: “the occurrence of faecal culture-confirmed cholera diarrhoea in a population in at least 3 of the past 5 years”.<sup>25</sup> Even in endemic settings there may be surges in cholera incidence for which intensive public health interventions are required. While such surges might be termed endemic, in public health terms they are often treated as epidemic cholera.
In cholera-endemic countries, vaccinating the entire population is not warranted. Rather, vaccination should be targeted at high-risk areas and population groups.

The primary targets for cholera vaccination in many endemic areas are preschool-aged and school-aged children.

Other groups that are especially vulnerable to severe disease and for which the vaccines are not contraindicated may also be targeted, such as pregnant women and HIV-infected individuals. Countries should also consider vaccinating older age groups if funding is available.

Periodic mass vaccination campaigns are probably the most practical option for delivering cholera vaccines.

Schools, health-care facilities, religious institutions and other community settings may be appropriate venues for vaccination campaigns. Incorporating cholera vaccination into routine vaccination schedules may be an alternative or complementary strategy to mass vaccination campaigns, for example to reach young children between campaigns.

Since the documented duration of significant protection for the oral cholera vaccine is 2 years, it is recommended that initial vaccination with 2 doses be followed by a booster dose every second year. Once data on the longer-term efficacy of any oral cholera vaccine become available, the recommended interval between initial and booster vaccination may be extended.

**Control of cholera outbreaks**

The mainstays of control measures to be implemented during ongoing epidemics should remain (i) providing appropriate treatment to people with cholera, (ii) implementing interventions to improve water and sanitation and (iii) mobilizing communities.

Pre-emptive vaccination should be considered by local health authorities to help prevent potential outbreaks or the spread of current outbreaks to new areas. Finalizing of predictive risk-assessment tools to help countries determine when pre-emptive cholera vaccination might be used is needed urgently; these tools should be made available and field-tested as soon as possible.

Given the recent large and prolonged outbreaks of cholera (for example, in Angola and Zimbabwe), reactive vaccination could be considered by local health authorities as an additional control measure, depending on the local infrastructure and following a thorough investigation of the current and historical epidemiological situation, and clear identification of geographical areas to be targeted.

The 3-step decision-making tool developed for crisis situations should guide health authorities in their decisions on whether or not to use cholera vaccine during complex emergencies:
Considering the lack of experience with implementing reactive vaccination against cholera, the feasibility and impact of vaccination in halting ongoing outbreaks should be documented and widely disseminated.

Vaccination should cover as many people as possible who are eligible to receive the vaccine (for example, children aged ≥1 years or ≥2 years, depending on the vaccine), and should be conducted as quickly as possible.

**Surveillance**

It is strongly recommended that surveillance for microbiologically confirmed cases of cholera be instituted and integrated into already existing surveillance systems or networks to measure the burden of disease and monitor the seasonality and the impact of vaccination and other interventions in high-risk populations.
Previous experience of OCV use in mass vaccination campaigns

(Excluding randomized clinical trials)

Mass vaccination campaigns using oral cholera vaccines have been documented on 12 occasions over the last 15 years, either pre-emptively in endemic settings (n=3) or in post-crisis situations (n=4), or reactively as part of the response to a cholera outbreak (n=5). Vaccine effectiveness observed after vaccination campaigns was between 78% and 84% after the second dose at 5-6 months.

In cholera endemic settings, Vietnam has included an OCV component in its strategy to control cholera since 1998 and has by far the largest experience of using OCVs as a public health tool. Zanzibar took a similar decision in 2012 after piloting the project on a small scale. The other pre-emptive uses of OCVs that have been documented so far were essentially demonstration or pilot projects aimed at testing the feasibility of mass campaigns (Mozambique). When used in the context of complex emergencies, no cholera outbreak was reported following pre-emptive vaccination campaigns.

Reactive mass vaccination campaigns with OCVs in response to outbreaks have been organized up to 1 year after the report of the first cases of cholera. Although their impact remains difficult to evaluate for the time being, vaccine effectiveness was high when evaluated and cholera cases were absent or decreased in most vaccinated areas. Where reported, acceptance of OCVs by the communities targeted for vaccination was good, in both endemic and epidemic settings. The most commonly reported constraints are logistic and mention the important volume of the vaccines and the corresponding cold room storage capacities, and the handling of buffer / water during delivery. With 2 exceptions, reported from very specific contexts, the cost of delivery varies between $0.5 and $2.5 per fully immunized person.

Cost effectiveness studies were conducted in several endemic countries and concluded that cholera vaccination would be “cost effective” particularly when targeting children or when herd protection is taken into account.
Table 2: Historical summary of mass vaccination campaigns using oral cholera vaccines (excluding randomized clinical trials)

<table>
<thead>
<tr>
<th>Location/dates</th>
<th>Situation</th>
<th>Target population</th>
<th>Vaccine used</th>
<th>No. persons vaccinated</th>
<th>Vaccine coverage</th>
<th>Costs per fully immunized</th>
<th>Vaccine effectiveness (VE) and potential impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vietnam (1998 to present)(^{29,30})</td>
<td>Endemic area. Yearly campaigns used pre-emptively before the peak cholera season to control endemic cholera in high-risk areas and also used pre-emptively during floods</td>
<td>Children 1-15 years old, and residents of all ages during floods</td>
<td>ORC-Vax(^{30}) Vietnamese killed OCV</td>
<td>&gt;20 million doses delivered</td>
<td>From 75% to 95%, for 2 doses depending on years and place</td>
<td>Vaccine price/dose: $0.4</td>
<td>VE of 50% at 3 to 5 years</td>
</tr>
<tr>
<td>Location/dates</td>
<td>Situation</td>
<td>Target population</td>
<td>Vaccine used</td>
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</tr>
<tr>
<td>Beira, Mozambique (2003/04)(^{31,32})</td>
<td>Endemic area with frequent outbreaks Campaign before rainy season.</td>
<td>≥2 years old residents (n=19,550) Non-pregnant</td>
<td>Dukoral(^{10})</td>
<td>&gt; 98,000 doses delivered 53,700 received 1 dose; 44,000 received 2 doses (including many outside the targeted area)</td>
<td>54% fully immunized in targeted area</td>
<td>$2.1 per fully immunized (vaccine shipment and delivery). Vaccine donated</td>
<td>VE between 78% and 84% for two doses over a five-month period</td>
</tr>
<tr>
<td>Zanzibar (2009)(^{33,35})</td>
<td>Endemic area with frequent outbreaks</td>
<td>≥2 years old among 48,178 inhabitants Non-pregnant</td>
<td>Dukoral(^{10})</td>
<td>23,921 persons received 2 doses</td>
<td>50% fully immunized</td>
<td>$25.3 per fully immunized ($20.0 for the vaccines + $5.3 for delivery)</td>
<td>VE of 79% 15 months after the campaign for recipients of 2 doses Evidence of herd protection</td>
</tr>
</tbody>
</table>

**Pre-emptive use in post-crisis situations**

<table>
<thead>
<tr>
<th>Location</th>
<th>Setting</th>
<th>Population</th>
<th>Vaccine used</th>
<th>No. persons vaccinated</th>
<th>Vaccine coverage</th>
<th>Costs per fully immunized</th>
<th>Vaccine effectiveness (VE) and potential impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uganda (1997)(^{36,37})</td>
<td>Stable refugee setting</td>
<td>Around 44,000 refugees in 6</td>
<td>Dukoral(^{10})</td>
<td>&gt;35,000 for 1(^{st}) dose; 83% for 1(^{st}) dose; 76% for</td>
<td>83% for 1(^{st}) dose; 76% for</td>
<td>$0.53 per fully immunized for</td>
<td>No cases reported from the vaccinated settlements</td>
</tr>
<tr>
<td>Location/dates</td>
<td>Situation</td>
<td>Target population</td>
<td>Vaccine used</td>
<td>No. persons vaccinated</td>
<td>Vaccine coverage</td>
<td>Costs per fully immunized</td>
<td>Vaccine effectiveness (VE) and potential impact</td>
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<tr>
<td>Darfur, Sudan (2004)</td>
<td>Stable refugee setting</td>
<td>camps</td>
<td>Dukoral&lt;sup&gt;®&lt;/sup&gt;</td>
<td>47,302 IDPs received 2 doses</td>
<td>87% fully immunized</td>
<td>$7.1 per fully immunized, including $0.7 for delivery</td>
<td>N/A No outbreak reported</td>
</tr>
<tr>
<td></td>
<td>≥2 years old among &gt;53,000 IDPs in 2 camps</td>
<td></td>
<td></td>
<td>27,600 for 2&lt;sup&gt;nd&lt;/sup&gt; dose</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt; dose</td>
<td>delivery. Vaccine donated</td>
<td>during a cholera outbreak in the district one year after the campaign</td>
</tr>
<tr>
<td>Aceh, Indonesia (2005)</td>
<td>Complex emergency following tsunami</td>
<td>≈79,000 IDPs living in camps in 3 areas</td>
<td>Dukoral&lt;sup&gt;®&lt;/sup&gt;</td>
<td>54,627 received 2 doses</td>
<td>69% fully immunized</td>
<td>$17.6 per fully immunized, including $8.2 for delivery</td>
<td>N/A No outbreak reported</td>
</tr>
<tr>
<td></td>
<td>≈79,000 IDPs in 2 camps</td>
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<tr>
<td>Haiti (2012)&lt;sup&gt;40&lt;/sup&gt;</td>
<td>Post-earthquake and nationwide cholera outbreak</td>
<td>≈70,000 residents of 2 rural areas &gt; 1 year old.</td>
<td>Shanchol™</td>
<td>41,193 received 2 doses</td>
<td>76.7% and 62.4% fully immunized</td>
<td>$3.33 per dose administered including $2.13 for vaccine and $1.20 for delivery</td>
<td>N/A</td>
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</tbody>
</table>

Reactive campaigns during cholera outbreaks

<table>
<thead>
<tr>
<th>Location</th>
<th>Situation</th>
<th>Target population</th>
<th>Vaccine used</th>
<th>No. persons vaccinated</th>
<th>Vaccine coverage</th>
<th>Costs per fully immunized</th>
<th>Vaccine effectiveness (VE) and potential impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Micronesia</td>
<td>Ongoing</td>
<td>&gt; 2 years old</td>
<td>Orochol®</td>
<td>N/A</td>
<td>47% of target</td>
<td>$1.23 per</td>
<td>VE of 79%</td>
</tr>
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<tr>
<td>Location/dates</td>
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<td>Vaccine used</td>
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</tr>
<tr>
<td>(2000)(^{41})</td>
<td>outbreak on the island since 5 months</td>
<td>among 34,486 residents non-pregnant</td>
<td>single-dose live-attenuated CVD 103-HgR vaccine (not marketed anymore)</td>
<td>population</td>
<td>person vaccinated for delivery</td>
<td>Decrease of cholera attack rate Not spread to surrounding islands</td>
<td></td>
</tr>
<tr>
<td>Mayotte (2000)(^{42-44})</td>
<td>Ongoing outbreak in the archipelago since 1 year Sporadic cases on the island since 9 months</td>
<td>≥2 years old among 175,000 residents and illegal migrants</td>
<td>Dukoral(^{10})</td>
<td>93,000 persons vaccinated</td>
<td>64%</td>
<td>26.9€ per person vaccinated (all included), i.e. about $24.5 in 2000</td>
<td>Only sporadic cases reported after the campaign</td>
</tr>
<tr>
<td>Marshall islands (2000)(^{45})</td>
<td>Ongoing outbreak on the island since &lt; 1 month</td>
<td>Vulnerable groups among 9345 inhabitants</td>
<td>Orochol(^{11})</td>
<td>N/A</td>
<td>32% total population</td>
<td>N/A</td>
<td>Outbreak ended during the month following the campaign and did not spread to surrounding islands</td>
</tr>
<tr>
<td>Location/dates</td>
<td>Situation</td>
<td>Target population</td>
<td>Vaccine used</td>
<td>No. persons vaccinated</td>
<td>Vaccine coverage</td>
<td>Costs per fully immunized</td>
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</tr>
<tr>
<td>Hanoi, Vietnam (2008)&lt;sup&gt;46&lt;/sup&gt;</td>
<td>Ongoing outbreak in an urban setting since 3 months</td>
<td>462,570 residents of 2 hard hit districts age &gt;=10 years, non-pregnant</td>
<td>ORC-Vax&lt;sup&gt;30&lt;/sup&gt; Vietnamese killed OCV</td>
<td>N/A</td>
<td>80% for at least one dose</td>
<td>N/A</td>
<td>VE of 76% for at least one dose 3 to 4 months after the campaign. New wave of the outbreak reported 3 months after the campaign</td>
</tr>
<tr>
<td>Guinea Conakry (2012) &lt;sup&gt;47&lt;/sup&gt;</td>
<td>Ongoing outbreak in a rural setting since 3 months</td>
<td>&gt;1 year old among ≈200,000 residents of 2 rural districts. Non-pregnant</td>
<td>Shanchol® Controlled Temperature Chain (CTC) strategy was used on the day of vaccination.</td>
<td>172,544 for 1st dose, 143,706 for 2nd dose</td>
<td>76% fully immunized, &gt;90% with at least one dose</td>
<td>$7.4 per fully immunized ($4.9 for the vaccines + $2.5 for airfreight and delivery Cost per dose of vaccine delivered $2.89 inclusing £1.85 for the vaccine and $1 for direct costs</td>
<td>VE of 84% for 2 doses 6 months after vaccination (Data analysis ongoing Luquero F) Cases remained low in vaccinated districts during rainy season compared to other parts of Guinea</td>
</tr>
</tbody>
</table>
**Stockpile mechanism overview**

The OCV stockpile has been created on the principle that vaccines have a role in the prevention and control of cholera outbreaks when used in conjunction with accessible healthcare and improvements in water and sanitation. It has also been established with the understanding that the stockpile will have a limited number of doses relative to the need for vaccine and that the use of OCV through the stockpile will not significantly alter global cholera disease trends. However, evidence generated through stockpile OCV use may help indicate the vaccine’s potential to control outbreaks and to impact disease trends when used on a larger scale.

Given the limited global supply of licensed, WHO-prequalified cholera vaccines, a global stockpile is likely to improve the timely access of OCV for countries that may benefit from its use. Moreover, increased OCV use may lead to a larger global vaccine supply through more consistent and predictable demand for vaccine.

**Objectives of OCV stockpile**

The use of the vaccine in emergency response situations is expected to help reduce cholera morbidity and mortality in epidemic situations and alleviate the disease burden on at-risk populations.

While vaccines provide a short-term effect as an immediate intervention to a potential cholera outbreak, expanding access to improved drinking-water sources and sanitation constitutes a longer-term solution for most waterborne diseases, including cholera.

The use of OCV from the stockpile should not detract attention from the key established responses to cholera outbreaks, which are: detection, diagnosis, and treatment of cases with oral rehydration and antibiotic treatment; establishment of a safe water supply; and implementation of adequate waste disposal and sanitation.

The main objective of the OCV stockpile is to ensure the timely and targeted deployment of OCV such that vaccine can be used as an effective outbreak response where it is most needed.
Use of the stockpile

The main use of this stockpile will be for outbreak response, either in the form of reactive campaigns in areas experiencing an active outbreak or pre-emptive vaccination campaigns among populations at elevated risk for cholera due to outbreaks in adjacent areas or at heightened vulnerability due to humanitarian crisis.

Reactive vaccination occurs after the start of an outbreak and aims to limit the extent of the outbreak in communities at imminent risk (i.e., neighbouring communities - across borders, or linked by river systems or water and sanitation systems), provided the local infrastructure allows it, and an in-depth analysis of past cholera data and identification of a defined target area have been performed.48,49

“An outbreak of cholera at the national level commonly consists of a succession of several outbreaks as it spreads through the country or across borders. Vaccinating communities in areas at imminent risk during such a succession would have greater impact than in areas where the transmission has already been active for several weeks or months. Many of the individuals in a community where there is active transmission may have already been infected with cholera even if they are asymptomatic. In fact, an estimated 80 per cent of infected individuals will be asymptomatic but still shed the bacteria. This reactive strategy is particularly important in areas where response mechanisms cannot deliver typical cholera control measures”49

Pre-emptive vaccination of populations takes place before likely upsurges in cholera transmission or outbreaks. It may be considered, based on risk assessment and epidemiological data, to limit the spread of outbreaks to new areas at risk.

Ideally pre-emptive and reactive vaccination, during an outbreak response, should cover as many people as possible who are eligible, and should occur as quickly as possible.

Management and governance of the OCV stockpile for emergency response

The International Coordinating Group (ICG) comprising Médecins Sans Frontières (MSF), the International Federation of Red Cross and Red Crescent Societies (IFRC), the United Nations Children’s Fund (UNICEF), and WHO will be the decision-making body for deployment of OCV through the stockpile. This group also coordinates vaccine release from the international Yellow Fever and Meningococcal vaccine stockpiles.
Additional expertise and technical advice might be sought on a case-by-case base from a range of partners. A meeting with participation of key stakeholders is organized annually.

The ICG manages the global stock, liaison with manufacturers and 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. The ICG mechanism has also contributed to reinforce surveillance and laboratory confirmation since countries must demonstrate an ongoing epidemic to access the ICG stockpile.

The OCV stockpile initially comprises two million doses of vaccine per year for an initial period of 2-3 years (2013 – 2015). Start-up funding for the stockpile will be provided by donors. A revolving fund will be established as with other ICG stockpiles, to assure longer-term financial stability. Collected funds will support the procurement of vaccine, country preparedness and planned operational costs for the use of the OCV stockpile vaccination campaign and evaluation of the stockpile mechanism initial period of 3 years.

After an intermediate evaluation, an extension could be made up to 5 years with additional investments and/or with funds generated through the revolving fund mechanism.

**Application procedure to OCV in IGC stockpile**

Vaccine requests may be made by any national or international organization, and the ICG will provide a decision of approval or denial of vaccine release within 48 hours of request receipt, depending on whether additional information is required. Vaccine and supplies then will be deployed if approved (Fig 2).

The minimum situational requirements for a request to be considered are:

- **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. Diagnosis of cholera is confirmed by isolating V. cholerae O1 or O139 from faeces through laboratory testing. To ensure the quality of samples, Cary Blair transport medium should be used for transport and storage of rectal swabs.

-
- An OCV campaign has NOT 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).
Decision criteria for the release of OCV

- Once an outbreak of cholera has been laboratory confirmed in a given area, a number of indicators may be considered to estimate the projected severity of the cholera outbreak and the potential impact of the vaccination campaign.

  - **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: (table 3)
    - **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; 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.

  - The list of indicators presented in Table 3 will be used to inform decision-making but none should be considered sufficient to make a final decision.
  - Deployment of vaccines from the OCV stockpile will also take into consideration **programmatic** factors such as the local capacity to organize a campaign and the prevailing security conditions.

### Table 3: Epidemiological and demographic considerations for OCV stockpile deployment

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Indicator</th>
<th>Decision threshold</th>
<th>Potential impact of vaccination campaign</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Susceptibility of the population</strong></td>
<td>Number of cases reported in the affected area(s) during the past 2–3 years</td>
<td>No or few cases reported</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High number of cases reported</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Attack rate of previous outbreaks in the affected area(s)(^1)</td>
<td>High attack rate</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Low attack rate</td>
<td>X</td>
</tr>
<tr>
<td><strong>Vulnerability of the population</strong></td>
<td>Case-fatality rate (CFR) of previous outbreaks in the affected area(s)(^2)</td>
<td>High CFR</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Low CFR</td>
<td>X</td>
</tr>
</tbody>
</table>

\(^1\) 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, 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.

\(^2\) 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.
<table>
<thead>
<tr>
<th>Risk of spatial extension</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Refugee camp, internally displaced people, or slums present in the affected area(s)</strong></td>
<td>Yes</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>X</td>
</tr>
<tr>
<td><strong>Area(s) with important population movements (border, market hub, etc.)</strong></td>
<td>Yes</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>X</td>
</tr>
<tr>
<td><strong>Population density in the affected area(s)</strong></td>
<td>High density</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Low density</td>
<td>X</td>
</tr>
<tr>
<td><strong>Access to water, sanitation, and hygiene</strong></td>
<td>Poor access</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Good access</td>
<td>X</td>
</tr>
<tr>
<td><strong>Time elapsed / maturity of the outbreak since first case reported</strong>&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Few weeks</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>Few months</td>
<td>X</td>
</tr>
<tr>
<td><strong>Attack rate since the start of the current outbreak (i.e. cumulative cases)</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Low attack rate</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>High attack rate</td>
<td>X</td>
</tr>
<tr>
<td><strong>Proportion of health units in the district reporting cases</strong>&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Low proportion</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>High proportion</td>
<td>X</td>
</tr>
<tr>
<td><strong>Time at which first cases were notified during the epidemic season</strong>&lt;sup&gt;5&lt;/sup&gt;</td>
<td>First cases notified early in the season</td>
<td>X</td>
</tr>
<tr>
<td></td>
<td>First cases notified late in the season</td>
<td>X</td>
</tr>
</tbody>
</table>

<sup>3</sup> 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<sup>5</sup>

<sup>4</sup> 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).

<sup>5</sup> In some areas, cholera outbreaks occur on a regular basis, every year or so, usually during the rainy season.
Monitoring and evaluation of the OCV stockpile

While there is evidence that the use of OCV in pre-emptive and preventive campaigns will have a positive impact on reducing mortality and morbidity, there is currently insufficient evidence to determine the role of the vaccine in outbreak response.

Given the limited global supply of OCV compared with the potential need, it will be crucial to document the impact of the stockpile on cholera prevention and control plans and on disease burden, both locally and globally.

Documenting both the decision and outcomes of use or non-use of OCV will also be vital to developing evidence-based guidance and strengthening recommendations for future OCV use.

To address this need a rigorous system for monitoring and evaluating should be embedded within the OCV stockpile mechanism.53

Findings will be reported to all relevant stakeholders, including stockpile decision-makers, past and potential requesting countries or organizations, donors, and technical partners.

As one of the objectives of the 3 years period stockpile is to gather the evidence of the impact of vaccination on cholera epidemics, countries requesting access to OCV-ICG stockpile will be requested to implement and/or provide the necessary data for M&E purpose. Specific M&E protocols will be available for their implementation.
References:


