1. Summary

- Oral Cholera Vaccines (OCVs) offer an effective, albeit short-term, intervention to control and prevent cholera outbreaks, complementing longer-term water, sanitation and health interventions.
- OCV demand is uncertain and contingent on vaccination campaigns, as part of emergency outbreak response, and driven by prevention activities in high-risk and endemic areas. Current demand through UNICEF is limited by supply availability, estimated to reach up to 19.3 million doses for the period 2015-2018, subject to an annual review based on programmatic considerations.
- At present, three OCVs are World Health Organization (WHO) prequalified, of which two are considered programmatically preferable, and are part of the International Coordinating Group’s (ICG) global OCV emergency stockpile, as well as the Global Task Force on Cholera Control’s (GTFCC) non-emergency reserve, hereafter collectively referred to as ‘the stockpile’.
- Gavi, the Vaccine Alliance (Gavi), currently provides financial support, committed for the period 2014-2018, to increase access to OCV through the stockpile.¹ Procurement responsibility for the stockpile is currently transitioning from WHO to UNICEF, anticipated to be finalised during 2016.
- UNICEF concluded its OCV tender during 2015, and awarded two manufacturers 19.3 million doses over 2016-2018 through long-term arrangements (LTA). The LTA awards will be subject to annual review based on programmatic considerations.

2. General Brief and Background

Cholera is an acute diarrhoeal disease caused by Vibrio cholerae bacteria. Cholera spreads through the ingestion of contaminated food and water and can quickly lead to severe dehydration from the rapid loss of fluid. It is a virulent infection associated with extreme poverty, closely linked to poor environmental health, water and sanitation. Whereas more than 200 V. cholerae strains exist, only two strains (O1 and O139) cause epidemics in humans. The recent emergence of a more virulent O1 strain has raised concerns, suggesting cholera with greater severity and possible higher case fatality rates.² Globally, cholera is estimated to cause 1.4 million to 4.3 million cases a year, and between 30 thousand to 140 thousand deaths.³ Cholera is easily treatable through the prompt administration of Oral Rehydration Solutions (ORS), intravenous fluids and antibiotics. Cholera is endemic in many countries, mostly in Africa and Asia (Figure 1). However, since 2010, the number and frequency of major cholera outbreaks has grown, and Africa and Latin America account for 94% of the total reported cases (Figure 2). Even though globally the general trend in cholera transmission is slightly increasing, the number of cases in Africa has decreased by 52% compared to 2005.⁴

Cholera prevention and treatment protocols are well established. WHO recommends a multidisciplinary approach to the prevention of cholera focusing on water, sanitation and environmental health.⁵ Immunization with current OCV’s can provide short-term effectiveness in immediate cholera outbreak response, control and prevention activities. Whereas cholera can affect all age groups, in resource-limited settings, WHO recommends prioritising children over one or two years of age for vaccination in accordance with product administrative recommendations, programmatic considerations, and in conjunction with other higher-priority interventions.⁶

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⁶ Ibid.
At present, WHO has prequalified three OCVs from three separate manufacturers, the most recent in December 2015. The vaccines now include a monovalent (O1) and two bivalent (O1 and O139) forms, all based on inactivated whole cell *V. cholerae*. All three vaccines provide short-term effectiveness and sustain efficacy over 50% over two years (Table 1).

Table 1 WHO Prequalified OCVs

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Type</th>
<th>WHO PQ</th>
<th>Presentation</th>
<th>Form.</th>
<th>Shelf Life</th>
<th>VVM</th>
<th>Cold C. Capacity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crucell (Sweden)</td>
<td>Monovalent</td>
<td>2001</td>
<td>1 dose vial + buffer</td>
<td>Liquid</td>
<td>36 months</td>
<td>n/a</td>
<td>44.0 cm³</td>
</tr>
<tr>
<td>Shantha Biotechnics (India)</td>
<td>Bivalent</td>
<td>2011</td>
<td>1 dose vial</td>
<td>Liquid</td>
<td>24 months</td>
<td>Type 14</td>
<td>16.8 cm³</td>
</tr>
<tr>
<td>EuBiologics (Rep. of Korea)</td>
<td>Bivalent</td>
<td>2015</td>
<td>1 dose vial</td>
<td>Liquid</td>
<td>24 months</td>
<td>Type 30</td>
<td>11.0 cm³</td>
</tr>
</tbody>
</table>

Source: WHO.

Several other OCV vaccines are currently under development. The International Vaccine Institute (IVI) has been instrumental in expanding OCV supply and quality by providing non-exclusive cholera inactivated whole cell technology transfer and technical assistance to manufacturers. A number of manufacturers have used IVI technology to develop OCVs, including Shantha (India), EuBiologics (Rep. of Korea), Vabiotech (Vietnam) and Incepta (Bangladesh).

Separately from IVI initiatives, another vaccine under development, derived from a live attenuated virus, could potentially provide longer-term protection with a single dose schedule.

In 1992, the World Health Assembly (WHA) launched the GTFCC. It coordinates the engagement by the United Nations (UN) aid agencies, non-governmental organizations (NGOs), government and scientific institutions to reduce cholera mortality and morbidity, as well as to address the social and economic consequences of cholera. In 2012, as part of its efforts to develop technical guidelines for an integrated and comprehensive approach to cholera control and prevention, WHO and partners recommended the establishment of a two million-dose stockpile for use in outbreak response (emergency stockpile), managed by the ICG, and two years later, for prevention campaigns (non-emergency reserve) in high-risk and endemic areas. The use of the non-emergency reserve was also expanded to include humanitarian emergencies.

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7 Ibid, p. 124.
The ICG is comprised of the International Federation of Red Cross and Red Crescent Societies (IFRC), Médecins Sans Frontières (MSF), UNICEF, and WHO, which also serves as the ICG Secretariat. The ICG coordinates the use of the emergency component of the stockpile in accordance with need prioritization and supply availability. The GTFCC OCV Working Group coordinates the use of the non-emergency reserve.

The Bill and Melinda Gates Foundation (BMGF), Cargill, the European Commission's Humanitarian aid and Civil Protection department (ECHO), ELMA Philanthropies Services, and the United States Agency for International Development (USAID) initially financially supported the stockpile. Since 2014, Gavi has financially supported the stockpile. As part of its 2013 Vaccine Investment Strategy review, Gavi noted the disease burden associated with cholera outbreaks and the current constraints in the OCV market. Accordingly, Gavi committed US$ 114.8 million over 2014-2018 to the global cholera stockpile for use in epidemic and endemic settings focusing on three key objectives: (i) to break the current cycle of low demand and low supply; (ii) to reduce disruptive epidemics; and (iii) to strengthen the evidence base for periodic, pre-emptive campaigns. At the same time, Gavi requested the responsibility for stockpile procurement transition from WHO to UNICEF.

Since its inception, the stockpile has never held the targeted two million doses on account of the small OCV manufacturing base, limited manufacturer production capacity, and the drawdown of doses in response to cholera outbreaks. UNICEF anticipates reaching the target of holding two million doses during 2016 and onwards.

3. **Current Market Situation**

3.1. **Demand and Forecast**

The lack of vaccine supply and subsequent lack of data supporting OCV effectiveness in non-emergency cholera control interventions hinders clear and precise OCV demand forecasting. Further, demand estimates based on disease incidence can underestimate the needs, as many cholera cases can go unreported. Demand is also contingent on chosen immunization programme strategies, including the target populations and campaign frequency.

As these immunization strategies are not defined, UNICEF demand forecasts mitigate demand uncertainty by securing maximum supply availability. UNICEF and partners anticipate a steady increase in demand for non-emergency response based on growing needs (Figure 2), and expected increases in supply/production capacity/availability (Table 2).

Table 2 UNICEF OCV Forecast Demand in Doses 2015-2018

<table>
<thead>
<tr>
<th>Use</th>
<th>2015</th>
<th>2016</th>
<th>2017</th>
<th>2018</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emergency Stockpile</td>
<td>-</td>
<td>2,000,000</td>
<td>2,000,000</td>
<td>2,000,000</td>
<td>6,000,000</td>
</tr>
<tr>
<td>Non-Emergency Reserve</td>
<td>1,300,000</td>
<td>3,000,000</td>
<td>4,000,000</td>
<td>5,000,000</td>
<td>13,300,000</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>1,300,000</td>
<td>5,000,000</td>
<td>6,000,000</td>
<td>7,000,000</td>
<td>19,300,000</td>
</tr>
</tbody>
</table>

Source: UNICEF Supply Division.

While the ICG currently recommends a stockpile for emergency outbreak response of two million doses, Gavi’s funding also includes support for a non-emergency reserve for non-emergency response. The non-emergency reserve, coordinated by the GTFCC OCV working group, started at 1.3 million doses in 2015. UNICEF expects the non-emergency reserve to be a key driver in increasing demand, subject to annual review, supply availability, country needs, and readiness, in consultation with Gavi and the GTFCC OCV working group.
3.2. Supply

UNICEF has traditionally only procured small quantities of OCV mainly in response to cholera outbreaks. Since 2012, UNICEF has procured 345,000 doses for four countries.

UNICEF recently concluded its 2015-2018 OCV tender and awarded two manufacturers three-year LTAs for 19.3 million OCV doses over 2016-2018 (Table 3). For emergency outbreak response, manufacturers must ensure that vaccines are ready for dispatch 96 hours (four days) after an order placement. UNICEF commits to deliver the vaccines in country within seven days of an ICG request.

Currently, programmatically preferable and WHO prequalified OCV supply availability is limited by manufacturers’ production capacity. UNICEF’s awarded manufacturers can currently each only allocate between three-four million doses per year through UNICEF.

Table 3 UNICEF OCV LTA Awards in Doses 2016-2018

<table>
<thead>
<tr>
<th>Year</th>
<th>Emergency Stockpile</th>
<th>Non-Emergency Reserve</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>2016</td>
<td>2,000,000</td>
<td>4,300,000</td>
<td>6,300,000</td>
</tr>
<tr>
<td>2017</td>
<td>2,000,000</td>
<td>4,000,000</td>
<td>6,000,000</td>
</tr>
<tr>
<td>2018</td>
<td>2,000,000</td>
<td>5,000,000</td>
<td>7,000,000</td>
</tr>
<tr>
<td>Total</td>
<td>6,000,000</td>
<td>13,300,000</td>
<td>19,300,000</td>
</tr>
</tbody>
</table>

Source: UNICEF Supply Division.

The LTAs will secure a stockpile for emergencies and non-emergency reserve through UNICEF as stockpile procurement responsibility transitions from WHO to UNICEF during 2016. UNICEF currently manages the non-emergency reserve and will assume full responsibility for stockpile procurement and management. The ICG will review the indicative quantities listed under the emergency stockpile on an annual basis to determine the actual quantities for procurement by UNICEF during 2017 and 2018, while the GTFCC OCV working group will review the non-emergency reserve.

4. Pricing

UNICEF’s OCV weighted average price (WAP) for existing awarded supply is US$ 1.77 per dose. A two-dose schedule, as per product administrative recommendations and programmatic considerations, would cost US$ 3.54 per course, excluding operational costs.

5. Issues and Challenges

- Current OCV demand is uncertain and dependent on the immunization strategy that is defined, setting size, age range and intervention frequency, which can vary total demand requirements widely.
- OCV current supply availability is limited to the production capacity of the WHO prequalified vaccines, which will be subject to annual review and supply availability.

6. Steps Forward

- UNICEF will work with the ICG, the GTFCC, and countries to identify the most cost-effective immunization strategies based on programme considerations, vaccine availability, and campaign activity.
- UNICEF will actively encourage potential new OCV market entrants to seek WHO prequalification to further diversify and increase supply availability.
- UNICEF will continue to support and encourage current manufacturers with awarded supply to plan and expand production capacity.
- UNICEF will continue to work with partners to ensure and conclude a smooth OCV stockpile procurement transition from WHO to UNICEF and preserve vaccine supply security.
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Other UNICEF information notes can be found at: http://www.unicef.org/supply/index_54214.html.