Oral Cholera Vaccines (OCV)
Cholera is an acute diarrhoeal disease, caused primarily by the O1 and O139 toxigenic serogroups of the *Vibrio cholerae* bacterium. The spread of cholera is exacerbated by poor sanitation and a lack of clean drinking water; the disease most seriously affects young children living in disease-endemic settings. WHO conservatively estimates there to be 2.8 million (uncertainty range: 1.2–4.3 million) cases of cholera globally per year resulting in 91,000 deaths (uncertainty range: 28,000–142,000). Morbidity and mortality estimates are probably under-reported because of a lack of consistent global surveillance.

Dukoral vaccine (Crucell) provides effective protection (100%) against cholera for children aged two to five years for up to six months after vaccination, but this efficacy drops to 47% at the end of two years. For children aged over five years, Dukoral has a protective efficacy at one and two years post-vaccination of 78% and 63%, respectively. After two doses, Shanchol vaccine (Shantha Biotechnics) offers a protective efficacy of 66% across all ages, and 50% overall, three to five years after vaccination.

WHO emphasises that cholera control should be a priority in disease-endemic regions and specific geographic areas susceptible to outbreaks. WHO recommends immunisation with existing vaccines, in conjunction with other preventive and control strategies, through periodic mass vaccination campaigns or the incorporation of cholera vaccination into routine immunisation efforts. High-risk populations, preschool and school-age children, HIV-infected individuals, pregnant mothers and the elderly are to be prioritised.

Pre-emptive or reactive vaccination, or both, can be considered depending on local infrastructure and an evaluation of the current and historical epidemiological situation for epidemic settings, but not to the exclusion of appropriate oral rehydration therapy and measures to improve water quality and sanitation.

There has been increasing evidence of the effectiveness of providing oral cholera vaccines in epidemic settings [see box, page 81], and the creation of a global oral cholera vaccine stockpile in 2012 [see box, page 81] will in the future allow for a robust and early response to potential epidemic outbreaks.
### Products & manufacturers

<table>
<thead>
<tr>
<th>Product</th>
<th>Manufacturer</th>
<th>WHO PQ date</th>
<th>Form and presentation</th>
<th>Lowest known price (UNICEF, US$)</th>
<th>Vaccine vial monitor (VVM) type and cold chain volume (per dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dukoral</strong></td>
<td>Crucell</td>
<td>Oct 2001</td>
<td>Liquid, 1-dose vial + buffer sachet</td>
<td>4.75&lt;sup&gt;278,8,292&lt;/sup&gt;</td>
<td>No VVM</td>
</tr>
<tr>
<td><strong>Shanchol</strong></td>
<td>Shantha Biotechnics</td>
<td>Sep 2011</td>
<td>Liquid, 1-dose vial</td>
<td>1.85&lt;sup&gt;281&lt;/sup&gt;</td>
<td>VVM 14</td>
</tr>
</tbody>
</table>

#### PIPELINE PRODUCTS
- Paxvax has a single-dose, oral, live, attenuated cholera vaccine (PVXV0200) in Phase III of clinical trials that is expected to be approved shortly by the US FDA. The vaccine is anticipated to be used in epidemic outbreak settings and for individuals travelling to cholera-endemic regions.<sup>284</sup>
- Vietnam-based VABIotech produces a reformulated, buffer-free, killed whole-cell cholera vaccine, designed to be administered in a two-dose regimen. This product has been redeveloped into a bivalent (O1/O139), whole-cell vaccine (mORCVAX) and has been licensed for use in Vietnam since 2009. WHO prequalification is expected to take place by 2015.<sup>285</sup>
- Korean manufacturer Eubiologics has an oral cholera vaccine undergoing licensing in Korea; the vaccine is expected to be WHO prequalified in 2015.<sup>286</sup>
- Cuba’s Finlay Instituto is developing a live and an inactivated oral cholera vaccine said to be in the “advanced stage” (probably Phase III) of clinical trials.<sup>287,288</sup>

#### CHALLENGES
- Manufacturing capacity is limited, but manufacturers have announced that they could scale up production if there is a committed demand. Shanchol’s manufacturer, for example, has indicated the immediate availability of up to 600,000 doses and the capacity to scale up production to two to four million doses in 2013 and to ten to twenty million doses in 2014 if merited by the demand,<sup>289</sup> but managing irregular demand is thought to pose a challenge.<sup>290</sup>
- Questions remain regarding prioritisation and usage of the cholera vaccine stockpile when faced with multiple simultaneous epidemics or emergency situations combined with seasonal peaks in incidence in endemic countries.<sup>290,291</sup>
- There are as yet no guidelines for the use of cholera vaccine among children aged under one year.<sup>291</sup>
- Shanchol is stable for at least 5 days at up to 40°C, according to research by both Sanofi Pasteur<sup>292</sup> (Shantha Biotechnic’s parent company) and independent scientists.<sup>293</sup> Relabelling Shancol for use under controlled temperature chain (CTC) settings has progressed with Indian drug regulatory authorities and could be a precursor for future WHO prequalification for use in CTC.
THE GROWING EVIDENCE THAT ORAL CHOLERA VACCINE SHOULD BE USED TO CONTROL CHOLERA OUTBREAKS

In Haiti, after the onset of the cholera epidemic in October 2010, a decision was made not to use oral cholera vaccine (OCV), in part because not enough doses of the vaccine were available. In early 2011, it was decided to consider cholera vaccination if sufficient volumes could be made. At the same time, both manufacturers announced that they could scale up production capacity, provided that firm orders and commitments were made. In 2012, the PAHO Technical Advisory Group recommended introduction of OCV in Haiti’s routine immunisation schedule while conducting Supplemental Immunisation Activities (SIA) in camps and rural areas. In 2012, Partners in Health sponsored one pilot project and provided 45,000 doses of OCV in the Artibonite region of the country and reached very high coverage, showing that the vaccine could be used in the midst of an epidemic.

In 2012, the Ministry of Health in Guinea and MSF organised Guinea’s first mass vaccination campaign, with two doses of OCV (Shanchol) as an additional tool to control the epidemic in the country. Researchers found that the two doses of OCV provided 86% protective effectiveness against cholera.

A study of the outbreak response campaign shows that cholera immunisation was well accepted and reached high coverage, validating the benefits of cholera immunisation as “an additional tool in the outbreak response strategies.”

THE ORAL CHOLERA VACCINE STOCKPILE

The use of oral cholera vaccine (OCV) in low-income countries was first mentioned in a World Health Assembly resolution in 2011. Following several rounds of technical consultations, a global OCV stockpile was created in 2013, with the aim that it would serve as an additional tool to control cholera epidemics and outbreaks, especially in low-income countries. The stockpile is managed by the International Coordinating Group (ICG), composed of four decision-making partners (IFRC, MSF, UNICEF and WHO), and has received financial commitments from the Bill & Melinda Gates Foundation, the European Union and other donors. The OCV stockpile was planned to initially comprise two million doses per year, stored and maintained by participating manufacturers. Between July 2013 and June 2014, the stockpile made its first two million doses available.

In November 2013, the Gavi Board decided to support the stockpile by gradually increasing its capacity to 20 million doses per year for the period 2014–2018, for use in epidemic and endemic settings. The total contribution from Gavi is estimated at US$115 million over the five-year period. The stockpile was used for the first time in February 2014 in South Sudan, where MSF and MedAir delivered 132,925 doses of the vaccine for use in internally displaced populations.
Several cost-effectiveness studies have been conducted on the use of OCV in endemic situations and in refugee settings, but there is a lack of information relative to the synergistic impact of immunisation when coupled with traditional cholera interventions (e.g. sanitation and education). The most recent cost-effectiveness study showed that immunisation was cost effective at US$1 per dose of the vaccine (with an additional cost of delivering the vaccine of US$0.50 in low-income countries and US$1 in middle-income countries), under specific conditions and taking into account the benefits of vaccination herd immunity. This study shows that cost effectiveness is reachable, but with a low-priced vaccine.

Dukoral was the only WHO prequalified OCV available prior to 2011 and it was quite expensive not only because of the manufacturer’s monopoly, but also because of low and unpredictable demand. A background paper prepared by UNICEF for the 2009 WHO SAGE showed that the cost of immunisation mainly comprised the high cost of the vaccine. For instance, in a refugee setting in Sudan in 2004 the cost of protection against cholera was US$7.10 per fully immunised person, 90% of which was the vaccine price (US$6.40 for two doses).

The momentum for increased use of OCV has followed the entrance in 2011 of a new product – Shanchol by Shanta Biotech – offered at a much lower price than the pre-existing Dukoral vaccine. Shanchol costs about US$1.85 per dose, which is about one-third the price per dose of Dukoral (US$4.75). If demand for Shanchol increases, the price could potentially decrease further.

As shown in the table on page 80, Shanchol’s form and presentation offer operational and programmatic advantages compared to Dukoral; in particular, it does not need to be reconstituted with a glass of water and presents a lower cold chain volume.