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Editorial

The opportunities & challenges in delivering oral cholera vaccines

Globally, an estimated 1.3 billion people (14% of the world's population) are at risk for cholera[1]. Together with timely treatment, access to potable water, food hygiene, adequate sanitation and community engagement, the World Health Organization (WHO) recommends that oral cholera vaccination may be considered in areas where the disease is endemic (with seasonal peaks), as part of the response to outbreaks, or in a humanitarian crisis where there is a high risk of cholera[2].

There are three internationally-available and WHO-pre-qualified oral cholera vaccines (OCVs)[3]. The first is an inactivated vaccine containing killed whole cells of *Vibrio cholerae* O1 with recombinant B-subunit of cholera toxin marketed as Dukoral (Valneva, Sweden), which was pre-qualified in 2001[3]. Dukoral may be given to those aged two years and older and is taken with a bicarbonate buffer. The second, pre-qualified in 2011, is a bivalent inactivated vaccine containing killed whole cells of *V. cholerae* O1 and *V. cholerae* O139 and marketed as Shanchol (Shantha Biotechnics, Sanofi). Both Dukoral and Shanchol are given in two doses and confer direct and indirect (herd) immunity. Shanchol may be given to those aged one year and older, does not require a buffer, is therefore, less complicated to deliver and is less expensive than Dukoral[3]. The third is Euvichol (Eubiologics, South Korea), another bivalent inactivated OCV based on the same formulation as Shanchol. Following a study in Philippines[4], Euvichol has been recently licensed and WHO prequalified.

There is increasing experience with mass oral cholera vaccinations under diverse and difficult conditions. Mass oral cholera vaccinations of populations at risk can make an impact if OCV can be provided to the right populations at the right time[5], it is available in sufficient amounts and at reasonable cost, policy-makers learn how and when to use it and it is integrated with water, sanitation and hygiene interventions and case management.

In 2012, a global stockpile of two million doses of OCV was created by the WHO primarily for epidemic response (*http://www.who.int/cholera/vaccines/ocv_stockpile_2013/en/*). About four million doses of Shanchol have been deployed through the stockpile in mass vaccination campaigns in 11 countries[6]. The availability of a stockpile facilitates rapid deployment to control outbreaks. Data from the deployments confirm the effectiveness, safety and feasibility of mass oral cholera vaccination[7]. The OCV stockpile is managed as a rotating fund by the International Coordinating Group, which also manages similar stockpiles of meningococcal meningitis and Yellow Fever vaccines for outbreak response. For countries eligible to receive support from GAVI, the Global Alliance for Vaccine and Immunization, GAVI covers the purchase cost of the vaccine when there is an urgent need.

The Delivering Oral Vaccine Effectively (DOVE) project funded by the Bill and Melinda Gates Foundation and based at the Johns Hopkins Bloomberg School of Public Health was also created in 2012 (*http://www.stopcholera.org*). The goal of DOVE is to ensure that populations at risk will benefit from receiving OCV in an appropriate and effective manner. The DOVE project helps ministries and agencies decide when, where and how to use OCV as part of an integrated cholera control strategy. DOVE works with the WHO, UNICEF and other partners and is carrying out projects in Cameroon, India (Kolkata), Malawi, South Sudan, Uganda, Nepal and the Philippines. DOVE activities include helping to evaluate new and innovative strategies for vaccine campaigns, carrying out a safety study of OCV in pregnancy, assisting countries in applying for OCV

from the WHO stockpile and also in monitoring and evaluation, following OCV campaigns.

There are currently exciting opportunities for increased use of OCV to provide a major boost to cholera control measures. Several agencies now advocate OCV use, including the WHO, UNICEF and MSF (Doctors Without Borders). There is increasing demand from countries for OCV to control outbreaks. The vaccine can be a key component in an integrated strategy for cholera control, including integration into national cholera control plans. However, several challenges in delivering OCV remain. First, the supply of OCV is not sufficient to meet epidemic and endemic needs worldwide. Currently, nearly all available Shanchol doses are in the stockpile and reserved for use in outbreaks or complex emergencies. With the availability of Euvichol, OCV distribution will likely increase[6]. Second, packaging could be improved. Shanchol is currently supplied in single-dose vials with a rubber top sealed with an aluminium strip. Easier to administer vials, for example, like the plastic dropper containers used for oral polio vaccine, would facilitate distribution during mass oral cholera campaigns. Third, validation of thermostability so that OCV can be used entirely outside the cold chain would facilitate increased use of OCV where it is needed. Ideally, all future vaccine formulations should be kept at reasonable price.

In summary, there is increasing use and demand for OCV. The availability of an OCV stockpile facilitates its rapid deployment during outbreaks and humanitarian crises. Several agencies now advocate OCV use. Insufficient OCV supply is a major challenge that is being addressed by the recent availability of a third WHO-prequalified vaccine.

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