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International Efforts to Create and Distribute an Oral Cholera Vaccine

According to the April 2012 report by the World Health Organization (WHO), roughly 1.4-4.3 million cholera cases and 28000-142000 cholera-related deaths have been reported annually. The global impact of cholera, an infection of the small intestine, has led the WHO Departments of Pandemic and Endemic Diseases (PED) and Health Security and Environment (HSE) to collaborate on creating an oral cholera stockpile to regions in countries that are significantly affected by the outbreak. Haiti and Zimbabwe have had the two largest national cholera epidemics; these two countries have been the primary focus to control the disease as well as to create efficient methods that will improve the preparedness and response measures for any future outbreak. For the creation of the stockpile, WHO has prequalified two cholera vaccines, Dukoral® and Shanchol™, while a third vaccine, CVD 103-HgR, is currently undergoing additional research. In addition, guidelines have been written concerning the epidemiology of recent and past cholera outbreaks and concerning the optimal cholera vaccine stockpile.

Cholera, “bile” in Greek, has its origins dating back almost 200 years in 1817 with the first outbreak in Bengal and spreading to the east towards countries in Asia, such as China and Japan. Cholera is typically transmitted through contamination of food through feces of a contaminated person. This is usually the case in developing countries where the sewage systems and water treatment facilities lack modern technology. Symptoms of cholera include vomiting, diarrhea, and reduced turgor of the skin (decrease rate in elasticity of the skin), specifically around the hands. The frequent recurrence of diarrhea causes imbalances in electrolytes and, for

patients with severe cases, intravenous rehydration is required. With the lack of a developed immune system, children are more vulnerable to the disease and should be treated quickly. *Vibrio cholerae*, the bacteria associated with the disease, thrive in the mucus lining the small intestines. As shown in Figure 1, *V. Cholerae* are rod-like with flagella at one end.

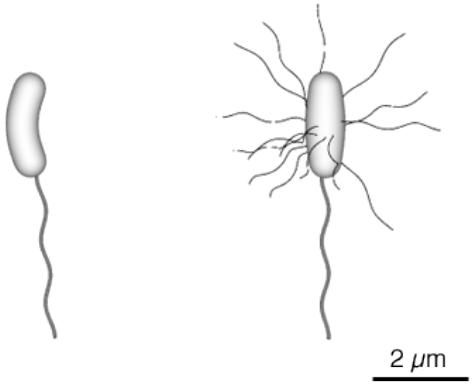

Figure 1: Diagram of Vibrio Cholerae[*]

Patients are tested for cholera either by swabbing the rectum or by analyzing a sample of the stool for presence of the bacteria. If a patient is tested positive, the treatment is any of the following, based on the severity of the infection:

- Oral rehydration therapy (ORT), a basic solution comprised of water, salt, and sugar, administered through the mouth.
- Replenishment of electrolytes, specifically raising in level of potassium ion that usually depletes from cholera.
- Antibiotics, such as doxycycline cotrimoxazole, erythromycin, tetracycline, chloramphenicol, and furazolidone.

[*] (1) in literature cited

As for prevention of a cholera outbreak, there are simple steps to improve hygiene and sanitation. Proper disposal techniques should be enforced when dealing with the contaminated clothing and excrement from infected patients. Hot water along with either chlorine or bleach provides an effective solution to disinfect any contaminated material. Boiling water before consumption is another technique to prevent the spreading of cholera. Bacteria, including *V. Cholerae*, cannot survive at high temperatures and therefore a simple technique is to improve hygiene and sanitation. Cloths filters, usually practiced in developing countries, have been proven effective in significantly reducing the bacteria present in groundwater. In addition to prevention, cholera vaccinations are widely available around the world and can be administered by doctors.

The only cholera vaccine that has been pre-qualified by WHO since 2001 is Dukoral®, licensed in 65 countries, contains three strains of *V. Cholerae* O1, the bacteria agent known to cause cholera. The recombinant B subunit of the cholera toxin is included to produce both anti-bacterial and anti-toxin antibodies. An oral dose of Dukoral® includes the buffer that, when mixed with water, prevents the cholera toxin from destruction by stomach acid. Children under 2 years cannot be administered the vaccine. Three doses are required for children between the ages of 2 and 5 along with a booster dose every 6 months. People over 6 years are given 2 doses within 1-6 weeks. Dukoral® has a shelf life of three years at 2-8°C and two weeks at room temperature (25°C).

Based on field studies, Dukoral® has proven to be 84-85% efficient. Statistics of the mass vaccination campaign in Zanzibar in 2008 indicate that there is no significant difference in birth outcomes between pregnant women exposed to the vaccine and those not vaccinated. Up to 2012, fifteen million doses of Dukoral® have been produced and distributed since 1991; however, each dose costs about $5.00.

Shanchol™ vaccine also contains three strains of *V. Cholera O1* and the serogroup O139, a bivalent vaccine.[*] WHO prequalified this vaccine in September 2011. Shanchol™ differs from Dukoral®; Shanchol™ does not require a buffer and is ready for use. Also, Shanchol™ is suitable for children ≥ 1 year and is proven to provide 67% percent protection for more than three years, based on a Phase-3 trial of the vaccine that was given to 67,000 people with ages ranging from 1 year and above. Shanchol™ has a shorter shelf life than Dukoral® with two years at 2-8 °C. However, current studies indicate that the vaccine's shelf life could be extended to three years. Shanchol™ is less expensive than Dukoral®; the current price is $l.85 per dose.

Orochol®, produced by the Swiss Serum Institute/Berna Biotech, has been reintroduced since the early 2000's. This vaccine was licensed in six countries and used in Indonesia and Micronesia for field studies.

PaxVax of Menlo Park, California is attempting to recreate the oral CVD 103-HgR vaccine, a strain similar to Dukoral®. However, CVD 103-HgR does not contain the cholera toxin B subunit and requires a buffer. Orochol® is fast-acting and can provide protection within a week. In a retrospective case-control study in Micronesia, 79% of 15,000 people vaccinated during a cholera outbreak were protected. The shelf life of the vaccine is three years when frozen.

[*] Vaccine containing both strains of bacteria associated with cholera, V. cholerae O1 and V. cholerae O139.

PaxVax can manufacture the CVD 103-HgR rapidly; 200,000 doses can be produced in a matter of 2-3 weeks, a fast response to a cholera outbreak. Ages ≥ 2 years are able to take the vaccine, similar to Dukoral®. No price has been set on recreated Orochol® but PaxVax estimates near $1 per dose.

Epidemiological criteria provide a useful tool for determining when to proceed with a vaccine campaign in an area affected with a cholera outbreak. Transmission of cholera is not well understood; the ambiguity in the vibrio biology, the person-to-person and environmental transmission, and the particular spatial heterogeneity of cholera make it difficult to establish generalizations and universal characteristics of the deadly disease. Because the effects of cholera can be different from one location to another, WHO and the United Nations Children's Fund (UNICEF) have created a table of epidemiological and demographic considerations for OCV deployment. This table includes several criteria, indicators, and decision thresholds for whether the potential impact of a vaccination campaign should be high or low.

Criterion	Indicator	Decision Threshold	Potential Impact of vaccination campaign	
			High	Low
Susceptibility of the population	Number of cases reported in the affected area(s) during the past 2-3 years	No or few cases reported	X	
		High number of cases reported		X
Vulnerability of the population	Attack rate of previous outbreaks in the affected area(s)	High attack rate	X	
		Low attack rate		X
	Case-fatality rate (CFR) of previous outbreaks in the affected area(s)	High CFR	X	
		Low CFR		X
	Refugee camp, internally displaced people, or slums present in the affected area(s)	Yes	X	
		No		X
	Area(s) with important population movements (border, market hub, etc.)	Yes	X	
		No		X
	Population density in affected area(s)	High density	X	
		Low density		X
	Access to water, sanitation, hygiene, and health care?	Poor access	X	
		Good access		X
Risk of spatial extension	Time elapsed / maturity of the outbreak since first case reported	Few weeks	X	
		Few months		X
	Attack rate since the start of the current outbreak (i.e. cumulative cases)	Low attack rate	X	
		High attack rate		X
	Proportion of health units in the district reporting cases	Low Proportion	X	
		High Proportion		X
	Time at which first cases were notified during the epidemic season	First cases notified early in the season	X	
		First cases notified late in the season		X

Table 1: Epidemiological and demographic consideration for OCV stockpile deployment [*]

[*] (2) in literature cited.

Table 1 shows a thorough and concise evaluation of several cases where OCV deployment would be effective. High number of reported cases, a high case-fatality rate (CFR), and poor access to water and sanitation indicate a potential high impact of a vaccine campaign.

As yet, decisions have not been made considering which vaccines are to be included in a vaccine stockpile and when a stockpile should be distributed and used, perhaps for preventive use or in response to an outbreak. Design of an optimal cholera-vaccine stockpile, requires following factors: consideration of the

- Issues regarding supply-chain and production timing due to limited capacity and shelf life.
- Unpredictable demand of OCV in response to a cholera outbreak.
- Dynamic models that measure the impact of the vaccination via a stockpile. Modeling of cholera transmission is very complicated because it varies for different areas.
- Assessment of efficiently promoting public health and prevention.
- Costs concerning vaccine production, maintenance, and delivery.

Recent experience with cholera outbreaks in Haiti has demonstrated an insufficient supply of oral cholera vaccine. We need to create a cholera-vaccine stockpile that would insure availability in any unpredictable crisis and emergency. Of several types of oral cholera vaccines, only Dukoral® and Shanchol™ have been prequalified by WHO; however, no final conclusion has been set on which vaccines to include for the stockpile. Recent research on the CVD 103-HgR, the cheapest and most effective vaccine, has led WHO and UNICEF to delay until results are finalized. These organizations still need to seek financial support from foundations and to convene with vaccine producers to discuss vaccine production capacity and delivery before proceeding with establishing a cholera vaccine stockpile.

While science has created methods and drugs for treating or preventing cholera, such creation is not sufficient for helping victims (or potential victims) of this dreadful, often fatal disease. In addition to scientific creativity, we need efficient engineering for large-scale, low-cost production of pertinent drugs, and fund-raising and political action for effective distribution. For final results, science and engineering must interact with society.

Literature Cited

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2. "WHO Consultation on Oral Cholera Vaccine (OCV) Strategic Framework: Potential Objectives and Possible Policy Options." *World Health Organization*. N.p., n.d. Web. <http://whqlibdoc.who.int/hq/2012/WHO_IVB_12.05_eng.pdf>.

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