Embracing Oral Cholera Vaccine — The Shifting Response to Cholera

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Cholera, a rapidly dehydrating diarrheal disease, is caused by ingestion of *Vibrio cholerae*, serogroup O1 or O139. The World Health Organization (WHO) estimates that 1.4 billion people were at risk for cholera in 2012.[1] More than 90% of reported cases occur in Africa, and most of the remainder occur in southern Asia. In 2010, only 10 months after it was hit by a major earthquake, Haiti experienced the most severe cholera epidemic of the past century, with 699,579 cases and 8539 related deaths reported as of February 11, 2014. This was the first time cholera had been documented in Haiti, despite the occurrence of devastating outbreaks in the Caribbean in the 19th century and in Latin America between 1991 and 2001 (see map).

Cholera is a disease of poverty, linked to poor sanitation and a lack of potable water. Establishment of an adequate sanitation and potable-water system is the most definitive way to prevent and limit its spread. However, the cost of instituting adequate sanitation systems, one of the United Nations Millennium Development Goals, is prohibitive for the countries that are affected by cholera: it would cost an estimated $2.2 billion, for example, to adequately improve access to water and sanitation in Haiti. Water, sanitation, and hygiene (WASH) practices are the cornerstones of cholera prevention and control. The promotion of WASH practices, the creation of rehydration centers, use of antibiotics, and training of health personnel during the first months of the Haitian epidemic led to a dramatic reduction in cholera-associated mortality, from 4% to 1.5%.[2] Yet a survey in the slums of Port-au-Prince showed that although people were aware of hand-washing methods, they did not have soap and water to implement them. What role should oral cholera vaccine (OCV) play, in combination with WASH practices, in epidemic conditions?

The three currently licensed OCVs are formulations of killed *V. cholerae* cells. Two of them, Dukoral and Shanchol, have been prequalified by the WHO for purchase by United Nations agencies. The third one, mORCVAX, is licensed and produced exclusively in Vietnam. For all three vaccines, there is evidence of safety and efficacy (66 to 85%) after two doses, with inferred herd protection and immunity lasting up to 5 years (in the case of Shanchol). Dukoral includes a cholera toxin B subunit requiring administration with a buffer, and it costs $3.64 to $6.00 per dose. Shanchol does not require a buffer and costs $1.85 per dose. Despite the evidence of safety and efficacy, international agencies cited several reasons for not including OCV in the prevention package during the 2010 Haitian epidemic.[2]

First, there was a limited number of OCV doses available worldwide. Second, Shanchol, the cheaper and easier-to-administer vaccine, could not be purchased by United Nations agencies until it received WHO approval in 2011. Third, there was concern that OCV implementation would compete with other WASH interventions in countries with fragile health systems.

After sustained lobbying by multiple institutions and organizations, a pilot intervention was initiated in Haiti using OCV with other WASH measures to control the outbreak ("reactive vaccination"). An urban project was con-

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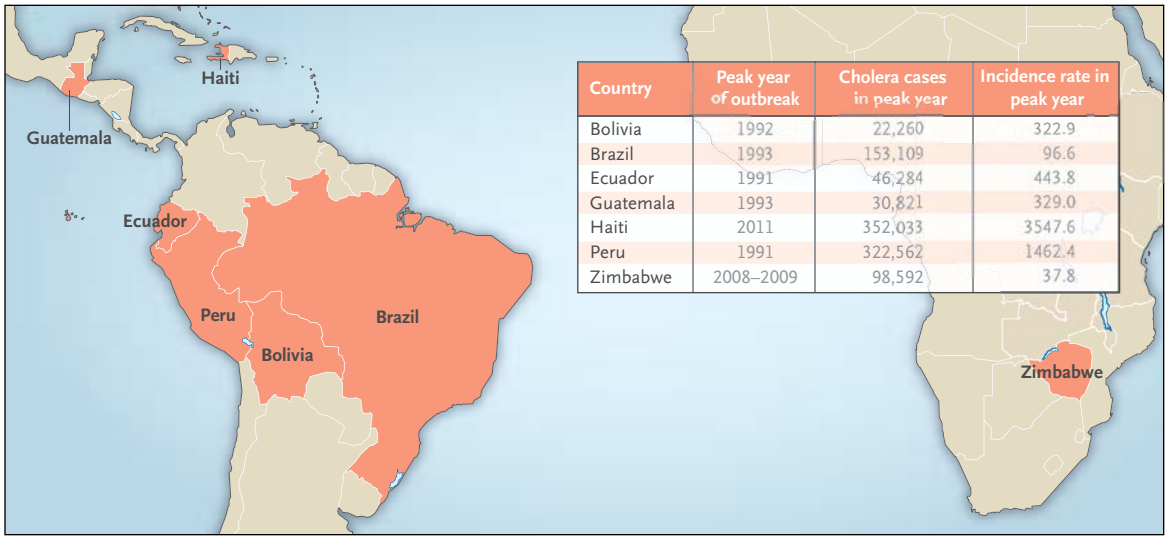

Country	Peak year of outbreak	Cholera cases in peak year	Incidence rate in peak year
Bolivia	1992	22,260	322.9
Brazil	1993	153,109	96.6
Ecuador	1991	46,284	443.8
Guatemala	1993	30,821	329.0
Haiti	2011	352,033	3547.6
Peru	1991	322,562	1462.4
Zimbabwe	2008–2009	98,592	37.8

Major Cholera Outbreaks since 1990.

Incidence rates are per 100,000 population during the year of the greatest mortality. Data are courtesy of Dr. Eric Mintz at the Centers for Disease Control and Prevention.

ducted by the Haitian Group for the Study of Kaposi's Sarcoma and Opportunistic Infections (GHESKIO), and a rural project was conducted by Partners in Health, both in collaboration with the Haitian Ministry of Health. The outcomes showed that OCV can be effectively employed as part of a comprehensive cholera-control program: 91% of 97,774 participants received two vaccine doses during a 90-day period.[3,4]

The WHO has since changed its policy and promotes OCV use in outbreaks worldwide.[5] During the past 3 years, more than 1.6 million doses of Shanchol have been administered in Asia, Africa, and the Caribbean. A remaining challenge to OCV implementation was the lack of field evidence for its effectiveness early in an epidemic. The matched case–control study in Guinea, reported on by Luquero et al. in this issue of the *Journal* (pages 2111–2120), clearly illustrates the role OCV can play in countering cholera epidemics, with greater than 86% protection after administration of two doses.

Although the global stockpile of Shanchol is growing — the WHO has 2 million doses, and the Global Alliance for Vaccines and Immunization (GAVI) has pledged support for 20 million doses over the next 5 years — the world will need millions more doses. Moreover, many questions remain. For instance, how should priorities be set for use of the stockpile when there are multiple simultaneous epidemics (requiring reactive vaccination), other high-risk situations (e.g., encampments of refugees who could benefit from preemptive vaccination), and regions where cholera is endemic and peaks in incidence are expected during the rainy season? Risk evaluation and cost-effectiveness will certainly be important considerations.

In addition, because of their study's small sample size, Luquero et al. could not test the efficacy of one versus two doses of OCV. A one-dose regimen would reduce the cost and logistic constraints for national scale-up programs. A collaborative double-blind, placebo-controlled study that the International Vaccine Institute and the International Center for Diarrheal Disease Research, Bangladesh, are conducting in Dhaka may provide this information.

Another question is whether OCV can be stored at room temperature so that the cold-chain requirement can be bypassed. In the study by Luquero et al., the vaccine was refrigerated during storage, but the cold chain was not maintained in the field. It will be important to determine how long the vaccine can retain its efficacy at room temperature.

Furthermore, can Shanchol be used in pregnancy and in children younger than 1 year of age? Although WHO recommendations suggest targeting pregnant women at high risk for cholera, the manufacturer has not approved use of the vaccine in pregnancy,

and there are no guidelines for children under 1 year old.

Since 2010, some major obstacles preventing the use of OCV have been overcome. Shanchol, the cheapest and easiest-to-administer vaccine, is being stockpiled. OCV has been used in 13 countries on three continents (Asia, Africa, and the North American Caribbean) and in three risk settings. The study by Luquero et al. provides further evidence in favor of using OCV in emerging outbreaks.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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1. Ali M, Lopez AL, You YA, et al. The global burden of cholera. Bull World Health Organ 2012;90:209A-218A.
2. Date AK, Vicari A, Hyde TB, et al. Considerations for oral cholera vaccine use during outbreak after earthquake in Haiti, 2010-2011. Emerg Infect Dis 2011;17:2105-12.
3. Ivers LC, Teng JE, Lascher J, et al. Use of oral cholera vaccine in Haiti: a rural demonstration project. Am J Trop Med Hyg 2013;89:617-24.
4. Rouzier V, Severe K, Juste MA, et al. Cholera vaccination in urban Haiti. Am J Trop Med Hyg 2013;89:671-81.
5. Cholera, 2011. Wkly Epidemiol Rec 2012;87:289-304.

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