

Technical Note

The Use of Oral Cholera Vaccines for International Workers and Travelers to and from Cholera-Affected Countries

November 2016

Background

Three Oral Cholera Vaccines (OCVs) are currently pre-qualified by WHO: Dukoral® – a vaccine used mainly by travelers that includes killed whole cells and a component of the cholera toxin – and Shanchol™ and Euvichol®, which contain only killed whole cells. All three vaccines have a two-dose regimen with an interval between doses of two weeks or more (three doses for Dukoral® in children aged 2–5 years). All also have a good safety profile. Shanchol™ and Euvichol® have the same formulation and comparable safety and immunogenicity profiles and are reformulated versions of Dukoral®.^{1,2} Unlike Dukoral®, Shanchol™ and Euvichol® do not require a buffer to administer. Shanchol™ has demonstrated longer term protection – a rather stable 65 – 67% from Year 2 to Year 5,^{3,4,5} as compared to Dukoral®.⁶ Concerning short-term protection – of most relevance to travelers – Dukoral® has been shown to provide 79-86% for three to six months in a series of studies,^{4,7,8,9} while the single published study of the short-term effectiveness of Shanchol™ found a similar rate (87%) over six months.¹⁰ Dukoral® has been shown to also confer significant short-term protection against enterotoxigenic *E. coli* (ETEC).¹¹

Purpose of the Technical Note

Concern has been raised in the past several years about the risk of international workers and other travelers getting cholera while in an endemic country or a country affected by an outbreak. At the same time, international workers and travelers from a cholera-affected country can – if infected – potentially be the source of spreading the infection when travelling to another country.

The purpose of this technical note is to provide recommendations concerning:

- a) Whether international workers and other travelers should get vaccinated against cholera before traveling to a cholera-endemic country or one at risk of outbreaks in order to protect themselves from the disease and prevent possible transmission back to their home countries; and
- b) Whether vaccinating international workers or travelers from cholera-affected countries can help prevent transmission of the disease to the host country.

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For the purpose of this note, “international workers” can include UN or other international peacekeepers, international agency personnel, and other aid or relief workers working outside of their country.

The risk of international workers and travelers getting cholera in an endemic or epidemic area

Only three studies have examined the risk of international workers of getting cholera, with widely varying results. One study in Peru during the early 1990s found an annual incidence rate among U.S. Embassy staff of 5.3 cases/1,000 people or 44 cases per 100,000 months of stay,¹² while a recent study of health care workers from Latin America assisting with the outbreak in Haiti found a very low risk of their getting cholera (0.23%).¹³ Cholera outbreaks among international workers, while rarely reported, can take place, as occurred among French health volunteers and military police in Haiti, who combined had an attack rate of 24%.¹⁴

Concerning other travelers, such as tourists, business travelers, migrants visiting home countries, the only data available on cholera incidence come from national disease reporting systems in developed countries. These report very few cases of cholera among travelers – e.g., an average of 3-8 cases per year reported to the U.S. CDC^{11,15} and an average of 0.2 – 0.3 per 100,000 trips or travelers from industrialized countries, but many times higher for those traveling to high-risk countries such as India and Pakistan (2-3/100,000 to 3.7/100,000).¹⁶ However, these reports are based on passive surveillance, cases diagnosed and treated in the country where cholera was acquired are usually not included, and laboratory testing is often not requested nor adequate – all factors likely resulting in under-reporting of the disease. A more active surveillance system employed in Japan found rates as high as 13/100,000 trips.¹⁷ Thus, while the true risk of cholera among travelers to endemic countries is unknown, there is evidence of a higher risk in certain highly-endemic areas (e.g., South Asia) and among certain types of travelers, especially immigrants visiting relatives or friends in their home countries, who in one study accounted for 73% of cases acquired among U.S. travelers to Hispaniola.¹⁸

The likelihood of international workers or travelers from cholera-affected countries who are not currently ill transmitting the disease to another country

People from a country with cholera could get on a plane and could theoretically transmit the disease to another country, even if they do not have diarrhea symptoms. Studies show low overall rates of asymptomatic infections in communities or neighborhoods where cholera cases are occurring ($\leq 2\%$), but rates of 6-35% among household members of confirmed cholera patients.^{19,20,21,22,23,24,25} Most people with asymptomatic infections stop shedding vibrios within one or two days, but 17-24% shed for four or more days, while convalescent cases can be infected for weeks or even months. According to data from the Philippines, asymptomatic carriers have concentrations of 10^2 – 10^5 vibrios per gram of stool

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(compared to $10^6 - 10^9$ for most symptomatic cases).²⁴ Whether concentrations of 10^5 or less is sufficient to transmit the disease is unknown, though there is qualitative evidence from Asia of asymptomatic infections causing disease in others.^{26,27}

Overall, there is a risk that international workers and other asymptomatic travelers from cholera-affected countries can transmit the infection to another country. The impact of such an inadvertent introduction into another country depends on that country's water and sanitation system. For example, an introduction of *V. cholerae* into the USA or Western Europe is unlikely to result in any new cases of cholera but an introduction into a poor country can result in further transmission of the disease and outbreaks of cholera in areas where access to safe water and sanitation is compromised.

The risk of international workers and travelers bringing the disease back home to their country and causing its spread

Most data on the transmission of cholera from travelers or overseas workers back to their home countries come from studies of short-term travelers from industrialized countries. There is no evidence that cholera has been transmitted to others (i.e., secondary infections) by a traveler from an industrialized country returning home.^{28,29,30} The risk of outbreaks from infected persons travelling home to countries with poor water and sanitary conditions is theoretically possible but has never been documented.

Evidence of the ability of OCVs to eliminate asymptomatic or convalescent infections or reduce the ability of carriers to transmit the disease

There is limited evidence from two field studies that killed oral cholera vaccines provide modest (42-46%) protection against asymptomatic cholera infections,^{5,31} and stronger evidence from challenge studies that these vaccines reduce the amount of vibrios excreted, but do not eliminate the infection altogether.³² Thus, because OCV reduces the risk of disease and reduces the concentration of vibrio, the vaccine would reduce the risk of international transmission, but would not likely eliminate this risk.

Recommendations

a) Controlling the risk to international workers and travelers to cholera-affected countries of acquiring cholera

It is recommended that international workers and travelers to cholera-affected countries adhere to precautions concerning hygienic practices to reduce their risk of getting cholera. These include:

- Drinking only safe water and avoiding tap water and ice cubes. If the access to safe water is not possible, water purification tablets, chloramine, portable filters or boiling can be used to make the water safe for drinking. If the water is turbid/dirty, it should be filtered first;

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- Washing hands frequently with soap and water or with alcohol hand rub lotions, especially before preparing food and before eating, and after going to the toilet or touching surfaces or items likely to be dirty;
- Eating only safe food by cooking food thoroughly and consuming it while hot, covering the food, separating raw and cooked food, storing food at safe temperatures, using water and raw ingredients that are safe.

In addition, in accordance with the WHO recommendations in the 2012 *International Travel and Health*,³³ OCV should be considered for travelers at high risk (emergency / relief workers); that is workers who are likely to be directly exposed to cholera patients or to contaminated food or water, particularly those staying in areas with poor access to health care facilities. Concerning other (long- or short-term) travelers to cholera-affected countries, vaccination is generally not recommended.

b) Controlling the risk of international workers and travelers from cholera-affected countries of spreading cholera to another country

There is insufficient data on the potential effectiveness of vaccination in eliminating vibrio carriage. Given the lack of data, studies are needed to determine the benefits of vaccinating international workers to reduce risk of international transmission.

While OCV may benefit travelers, the GTFCC does not recommend any requirement that a traveler receives vaccine as a condition to travel from an area with cholera or to an area without cholera.

¹ Desai SN, Pezzoli L, Martin S, Costa A, Rodriguez C, Legros D, et al. A second affordable oral cholera vaccine: implications for the global vaccine stockpile. *Lancet Global Health*. 2016 Apr;4(4):e223-4..

² Baik YO, Choi SK, Olveda RM, Espos RA, Ligsay AD, Montellano MB, et al. A randomized, non-inferiority trial comparing two bivalent killed, whole cell, oral cholera vaccines (Euvichol vs Shanchol) in the Philippines. *Vaccine*. 2015 Nov 17;33(46):6360-5.

³ Sur D, Lopez AL, Kanungo S, Paisley A, Manna B, Ali M, et al. Efficacy and safety of a modified killed whole-cell oral cholera vaccine in India: an interim analysis of a cluster-randomised, double-blind, placebo-controlled trial. *Lancet* 2009/Nov 14; 374(9702):1694-1702.

⁴ Sur D, Kanungo S, Sah B, Manna B, Ali M, Paisley AM et al. Efficacy of a low-cost, inactivated whole-cell oral cholera vaccine: results from 3 years of follow-up of a randomized, controlled trial. *PLoS Neglected Tropical Diseases* 2011/Oct; 5(10):e1289.

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⁶ Clemens JD, Sack DA, Harris JR, van Loon F, Chakraborty J, Ahmed F et al. Field trial of oral cholera vaccines in Bangladesh: results from three-year follow-up. *Lancet* 1990/Feb 3; 335:270-3.

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