

Vaxchora: The First FDA-Approved Cholera Vaccination in the United States

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ABSTRACT

Vaxchora is the first vaccine approved by the Food and Drug Administration for the prophylaxis of cholera infection. Cholera, a potentially life-threatening bacterial infection that occurs in the intestines and causes severe diarrhea and dehydration, has a low incidence in the U.S., but a high incidence in Africa, Southeast Asia, and other locations around the world. These areas draw travelers from the U.S., so cholera can present in patients who return from visits to these regions. Previous means of prophylaxis included the use of doxycycline for the prevention of traveler's diarrhea, but doxycycline is not specific for cholera. With the approval of Vaxchora, a live attenuated, single-dose, oral suspension vaccine, travelers can now visit these areas with less chance of contracting the bacterium *Vibrio cholerae*, which causes cholera infections.

Keywords: Vaxchora, vaccination, cholera, bacterial infections, international travel

INTRODUCTION

Worldwide transportation has revolutionized how individuals explore the globe. Every year, millions of Americans travel to foreign countries.¹ However, this exploration is not without risk. Those who travel to foreign lands can be exposed to unfamiliar infections or bacteria not typically seen in their homeland, such as *Vibrio cholerae*, which causes the cholera infection.

Cholera, an acute bacterial disease of the small intestine, causes severe vomiting, diarrhea, and dehydration that can become life threatening. It is estimated that three million to five million cases of cholera occur each year, causing nearly 100,000 fatalities worldwide. Most people infected with *V. cholerae* do not experience symptoms. However, the bacterium remains for up to 10 days in the feces, which is shed into the environment, potentially infecting other people. In people who do experience symptoms, the infection can lead to death within hours if not treated.²

Two serogroups of the bacterium *V. cholerae* cause outbreaks—O1 and O139. Serogroup O1 is responsible for the majority of outbreaks, whereas O139 is confined to Southeast Asia.³ *V. cholerae* serogroup O1 is usually found in areas with poor water sanitation and hygiene, and it is spread

through the ingestion of water contaminated with feces.² In the U.S., nearly all reported cases of cholera are acquired during international travel to areas with a high incidence of cholera infection, such as Africa, Southeast Asia, and Haiti.² Cholera infections in the U.S. can also stem from foodborne outbreaks, such as those caused by the consumption of contaminated imported seafood.² In 2013 and 2014, respectively, 14 cases and seven cases of *V. cholerae* serogroup O1 infection were reported in the U.S.; all were travel-related except for the case of a health care worker who helped treat a cholera patient. No cases of serogroup O139 infection were reported in either of these years.^{4,5}

Current standards of treatment for cholera include supportive care, such as intravenous fluids and oral rehydration through the use of rehydration salts, along with the use of antibiotic therapy for the treatment of the cholera infection if deemed clinically necessary. The antibiotics most commonly used to treat cholera are ciprofloxacin, doxycycline, and azithromycin.^{2,6}

To help protect travelers, the Food and Drug Administration (FDA) approved Vaxchora (PaxVax, Inc.), the first and only cholera vaccine available in the U.S., in June 2016.⁷ This article will focus on the target population, safety, and efficacy associated with the use of this live attenuated, single-dose, oral suspension vaccine.

INDICATIONS AND USAGE

Vaxchora is indicated for active immunization against cholera caused by the bacterium *V. cholerae* serogroup O1. It is approved for use in patients 18–64 years of age who are traveling to known cholera-infected areas. The vaccine has not been shown to offer protection against serogroup O139 or other non-O1 serogroups.^{8,9}

MECHANISM OF ACTION

Vaxchora contains a live attenuated cholera bacterium that replicates in the gastrointestinal tract of the recipient. The exact mechanism of immunity has not been established; however, it is hypothesized that exposure to *V. cholerae* causes an elevation in baseline vibriocidal antibody titers (antibodies against *V. cholerae*), which results in immunity.^{8,9}

PHARMACODYNAMICS

In a study of 53 healthy adult vaccine recipients, shedding of the vaccine, which refers to the expulsion and release of cholera following reproduction of the live attenuated vaccine in a host-cell infection, was evaluated for seven days after vaccination. Vaxchora was shed in the stool of approximately

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11% of vaccine recipients on any of those seven post-vaccination days, with the largest number of individuals shedding the vaccination on day 7. However, the duration of shedding of the vaccine is unknown.⁹

CLINICAL TRIALS

The efficacy and adverse effects of Vaxchora were evaluated primarily based on the results of four clinical, randomized, multicenter, placebo-controlled studies. Efficacy was assessed by administering a single dose of Vaxchora to 95 participants 18 to 45 years of age and administering placebo to 102 participants, followed by a *V. cholerae* O1 challenge at 10 days and 90 days post-vaccination. Vaxchora was shown to be 90.3% effective against *V. cholerae* O1 10 days after vaccination and 79.5% effective 90 days after vaccination. Seroconversion rates correlated with protection, showing rates of 94% and 88% 10 days and 90 days post-vaccination, respectively. Of the recipients challenged, 91% seroconverted prior to challenge, and 9% developed moderate to severe cholera following challenge, while 2% of placebo recipients seroconverted prior to challenge and 59% developed moderate to severe cholera following challenge. Seroconversion was defined as a fourfold or greater rise in serum vibriocidal antibody from baseline to 10 days post-vaccination.^{9,10}

To assess the adverse effects of Vaxchora, a total of 3,235 adults 18 to 64 years of age (mean, 32.5 years) received one dose of Vaxchora, while 562 adults received placebo. Table 1 reports additional study demographics. Participants were monitored for seven days after administration for adverse events. They were reassessed for serious adverse events at 10 days, 90 days, and six months post-vaccination. Participants were specifically monitored for tiredness, headache, abdominal pain, nausea/vomiting, lack of appetite, and diarrhea. Rates of solicited adverse reactions during the seven days post-vaccination are given in Table 2.⁹

The primary outcomes of the trials were whether a single dose of Vaxchora provided significant protection against a challenge with virulent *V. cholerae* O1 at 10 days and 90 days after vaccination. The secondary outcome measures were disease severity and the tolerability of the vaccine. Disease severity pertained to the total weight of diarrheal stools, incidence of diarrhea of any severity, incidence of fever, and incidence of fecal shedding of wild-type *V. cholerae*. Tolerability of the vaccine included the incidence and severity of signs and symptoms of reactogenicity, such as diarrhea or fever, and the incidence and severity of unsolicited adverse events.⁸

ADVERSE EFFECTS

Overall, the vaccine was well tolerated in clinical trials, and no significant adverse effects were reported throughout the course of the studies. The frequency of diarrhea was 1.1% within seven days of the vaccination, and there were no significant differences compared with placebo. Among the adverse events were reports of headache, abdominal pain, nausea, vomiting, and fever.⁹⁻¹¹

FOOD AND DRUG INTERACTIONS

Individuals receiving the vaccine should avoid eating and drinking for one hour before and after Vaxchora administration.⁹

Table 1 Gender and Ethnicity of Vaxchora Study Participants⁹

Gender	
Male	46.2%
Female	53.8%
Ethnicity	
Caucasian	67.1%
African-American	27.3%
Hispanic/Latino	9.3%
Asian	1.8%
Other	1.3%
American Indian/Alaskan Native	0.6%
Native Hawaiian/Pacific Islander	0.3%

Table 2 Solicited Adverse Reactions in Participants During Seven Days Post-Vaccination⁹

Adverse Reaction	Vaxchora, % (n = 2,789)*	Placebo, % (n = 350)*
Tiredness	31.3	27.4
Headache	28.9	23.6
Abdominal pain	18.7	16.9
Nausea/vomiting	18.3	15.2
Lack of appetite	16.5	16.6
Diarrhea	3.9	1.2
Fever	0.6	1.2

* Number of participants 18 to 64 years of age who completed a memory aid

Do not administer Vaxchora to patients who have received antibiotic treatment within 14 days prior to vaccination. Systemic antibiotics may be active against the vaccine strain and may prevent a protective immune response.⁹

Do not administer Vaxchora within 10 days of antimalarial prophylaxis. Chloroquine may diminish the immune response of Vaxchora, as previously shown in products similar to Vaxchora.⁹

Administration with concomitant immunosuppressive therapy, such as corticosteroids, irradiation, antimetabolites, alkylating agents, and cytotoxic drugs, may alter the immune response of Vaxchora. The vaccine has not been evaluated in immunocompromised patients, such as those with human immunodeficiency virus/acquired immunodeficiency syndrome or those being treated with chemotherapy.⁹

CONTRAINDICATIONS

Vaxchora should not be used in patients who have had a previous allergic response to any cholera vaccination or who are allergic to any ingredient in Vaxchora.⁹

WARNINGS AND PRECAUTIONS

Vaxchora may be shed in the stool of immunized individuals for at least seven days. In light of this shedding, there is a potential to transmit the vaccine strain to unvaccinated

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individuals who may come in close contact. Caution should be used when considering whether to administer Vaxchora to immunocompromised individuals.⁹

DOSAGE AND ADMINISTRATION

Vaxchora is approved for oral administration only. A single dose must be administered a minimum of 10 days before potential exposure to cholera or travel to cholera-endemic areas. Vaxchora is supplied as a packet of active component and a packet of a buffer component. The buffer component is added to 100 mL of cold water, followed by the active component. Vaxchora should be taken within 15 minutes of reconstitution. Recipients should avoid eating and drinking within one hour before and after oral administration. Both the active component and the buffer component should be stored frozen (between -25°C and -15°C) and do not require thawing prior to reconstitution. Studies have shown that Vaxchora is highly effective against *V. cholerae* for up to 90 days after vaccination.⁹ No studies have been completed to show efficacy of any intervals after the 90-day period.

COST

The average wholesale price for a single dose of Vaxchora is \$270.¹² Various discount cards are available to assist with the cost if needed.

DISCUSSION

Researchers have estimated that approximately 21,000 to 143,000 people die each year globally due to cholera infections; this wide range in the estimate of fatalities is due to the majority of infections and deaths going unreported.¹³ Cholera infection has a short incubation period (two hours to five days), which triggers the rapid outbreak response.³ The shedding of the bacterium back into the environment creates the potential to infect other people, including travelers. Once a person exhibits the signs and symptoms of a severe infection, there is little time to act. If not treated promptly, the persistent, watery diarrhea and severe dehydration can be fatal. The cost of treating an infection can be high.¹⁴

Although cholera is rare in the United States thanks to modern water and sewage treatment systems, it can occur in individuals who travel to other countries. Among those U.S. citizens who become infected, 80% of the cases are travel related.³ Countries with high *V. cholerae* incidence often have inadequate water supplies and poor environmental management.

Vaxchora provides protection against *V. cholerae* serogroup O1, but does not provide protection against serotype O139, the prominent strain in Southeast Asia.^{3,8} Travelers to this region may still receive Vaxchora, but they should take into account the probable lack of protection against serotype O139 and should exercise caution.

Vaxchora is the first vaccine indicated for cholera prevention to become available in the U.S.⁷ Previously, the only form of prophylaxis was antibiotic therapy indicated for traveler's diarrhea. Having a disease-specific vaccine for travelers at potential risk is highly beneficial. The well-being of the patient and potential transmission to others should be considered when choosing to take prophylactic measures against cholera. With the availability of Vaxchora, patients are now able to minimize

potential treatment-associated costs and reduce the chance of acquiring this potentially life-threatening infection.

CONCLUSION

In the U.S., cholera is a rare but dangerous disease. While cholera is not endemic in the U.S., many travelers are at risk for this life-threatening infection, creating the potential for an outbreak. Recent studies have provided evidence that Vaxchora is safe and effective in the prevention of cholera caused by the bacterium *V. cholerae* serotype O1. Its one-time, single-dose administration makes it convenient for busy travelers. With the FDA's approval of Vaxchora, individuals who visit countries with a high incidence of cholera can now reduce their risk of infection while traveling.

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