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REVIEW

An overview of Vaxchora™, a live attenuated oral cholera vaccine

Tarun Saluja [a], Vijayalaxmi V. Mogasale [b], Jean-Louis Excler [a], Jerome H. Kim [a], and Vittal Mogasale [a]

[a]International Vaccine Institute, SNU Research Park, Seoul, Republic of Korea; [b]Department of Pediatrics, Yenepoya Medical College and Research Center, Yenepoya University, Mangalore, India

ABSTRACT

Cholera remains a public health threat among the least privileged populations and regions affected by conflicts and natural disasters. Together with Water, Sanitation and Hygiene practices, use of oral cholera vaccines (OCVs) is a key tool to prevent cholera. Bivalent whole-cell killed OCVs have been extensively used worldwide and found effective in protecting populations against cholera in endemic and outbreak settings. No cholera vaccine had been available for United States (US) travelers at risk for decades until 2016 when CVD 103-HgR (Vaxchora™), an oral live attenuated vaccine, was licensed by the US FDA. A single dose of Vaxchora™ protected US volunteers against experimental challenge 10 days and 3 months after vaccination. However, use of Vaxchora™ poses several challenges in resource poor settings as it requires reconstitution, is age-restricted to 18 to 64 years, has no data in populations endemic for cholera, and faces challenges related to cold chain and cost.

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Introduction

Cholera

Cholera is an intestinal infection caused by the bacterium *Vibrio cholerae (V. cholerae)*.[1] There are several serogroups of *V. cholerae*, but only two serogroups of *V. cholerae*, O1 and O139, are considered causative agents of endemic and epidemic cholera.[2] *V. cholerae* O1 has two biotypes, 'classical' and 'El Tor'. Each biotype has two serotypes: Ogawa, Inaba.[3] Few studies report a third serotype, *V. cholerae* O1 Hikojima, which rarely exists in nature due to its poor fitness.[4] However, the emergence of a more virulent O1 strain has raised concerns, suggesting that cholera outbreaks might be of greater severity and possibly higher case fatality rates.[3]

V. cholerae is spread mostly by water and food that have been contaminated with human feces containing the bacteria.[5] *Vibrio* species exist in aquatic habitats, and as a result are commonly found as contaminants in seafood; hence, undercooked seafood is a common source of *V. cholerae* infection.[6] Risk factors for the disease include poor sanitation, contaminated drinking water, and poverty.[7] Maintaining hygiene and sanitation are particularly challenging during humanitarian crises, and infrastructure damage following wars, conflicts and natural calamities, poses a significant risk of cholera outbreaks.

Although all age groups are susceptible to cholera infection, children appear to have greater susceptibility, with two to four year olds having the highest rates of infection.[8,9] Infection may be asymptomatic or result in mild to severe disease. Symptoms may start from a few hours to five days after exposure.[1] The cardinal symptom is profuse watery diarrhea that may last for a few days.[7] The diarrhea may lead to severe dehydration and electrolyte imbalance[8] within hours and may ultimately result in death in the absence of rehydration and treatment.[10]

Conventional culture methods for *V. cholerae* remain the gold standard for diagnosis, but this procedure is not very sensitive and requires skilled technicians and sophisticated laboratory infrastructure. In remote settings where cholera is endemic and modern laboratory facilities are often nonexistent, dark-field microscopy to detect cells showing characteristic darting motility is used to identify *V. cholerae* in stool specimens. Diagnostic tests such as cholera dipstick (DS) assays, which detect either cholera toxin[11] or lipopolysaccharide (LPS) antigens[12,13] have been introduced for rapid bedside detection of *V. cholerae* in stool. While the sensitivity of dipstick is over 95%, the specificity of the test has ranged from 65% to 85% in field settings.[14] The low specificity of DS tests may limit diagnostic utility in endemic areas, but a preponderance of positive tests in a small cohort of patients with diarrhea is useful to confirm a suspected outbreak in settings where cholera was not previously known to be endemic.[14]

Globally, cholera is estimated to cause 1.4–4.3 million cases a year with 30–140,000 deaths.[15] The major burden lies in resource-poor countries.[16] It is a challenge to understand the real number of cholera cases worldwide, as many go unreported due to concerns that an outbreak may have a negative impact on tourism and export industries.[17] In the past decade, large cholera outbreaks have been described in Africa, South Asia, and South-East Asia. In 2010, a recent outbreak of cholera in war-ravaged Yemen, which started in October 2016 recorded 275,987 suspected cases and 1,634 associated deaths as of July 2017.[18] In the Americas, Haiti – cholera free for 200 years – experienced a huge cholera outbreak which started

CONTACT Vittal Mogasale vmogasale@ivi.int International Vaccine Institute, SNU Research Park, 1 Gwanak-ro, Gwanak-gu, Seoul 08826, Republic of Korea

in 2010 with over 600,000 infected individuals and approximately 8,000 associated deaths.[19–21] In an era of globalization, travelers from high-income countries are at risk of *V. cholerae* infection when visiting such endemic areas.

Improved water and sanitation facilities have contributed to a sharp decline in cholera in high-income countries. Improvement and implementation in water, sanitation, and hygiene practices (WASH) are critical for long-term cholera control.[22]

However, infrastructure improvements in resource-poor settings have been slow to materialize and are costly. Vaccination is therefore considered a short- to mid-term tool to control cholera along with early detection and improved case management.

The introduction of OCV and its use in mass vaccination campaigns have proved a game-changer in the fight against cholera. A two-dose OCV regimen has been shown to prevent cholera for three to five years by effectively bridging emergency response and longer-term cholera control with a WASH focus, demonstrating that cholera is not inevitable and that cholera control is not beyond reach.[23] In 2017 the WHO and UNICEF announced a plan to reduce cholera deaths 90% by 2030. This initiative emphasized a comprehensive approach to cholera prevention including WASH and vaccination.

Available drugs

Several antimicrobials can be used to treat cholera, including doxycycline, erythromycin, tetracycline, chloramphenicol, furazolidine and fluoroquinolones, such as ciprofloxacin.[24] However, resistance has been reported to many of the drugs including doxycycline, which is the drug of choice [5] There is no doubt that addressing a threat as significant and complex as antimicrobial resistance (AMR) requires a portfolio of solutions including new antimicrobials and better diagnostics. At the same time it requires measures that prevent infection and reduce the use of antimicrobials, including improved sanitation and the wider use of vaccines. Where AMR is common in *V. cholerae*, WASH and vaccines may be the best way to reduce morbidity and mortality.[24]

Available vaccines

Several safe and effective vaccines are available in the market to combat cholera.[25,26] WHO has prequalified four OCVs: Dukoral®, Shanchol™, and Euvichol® and Euvichol-Plus®. Dukoral® is a monovalent, killed whole-cell vaccine containing O1 serogroup and recombinant cholera toxin B subunit while Shanchol™ is a bivalent, killed whole-cell vaccine with O1 and O139 serogroups. Dukoral® has an overall efficacy of about 52% during the first year after vaccination and 62% in the second year, with minimal side effects.[27] In a Phase III cluster-randomized, double blind, placebo-controlled field trial in Kolkata, India, during two years of follow-up Shanchol™ conferred 67% protection against *V. cholerae* O1. During the 3- and 5-year follow-up, the vaccine conferred 66% and 65% cumulative protective efficacy against *V. cholerae* O1, respectively.[28–30] Euvichol® which is similar to Shanchol™ in terms of manufacturing process, quality, composition, and route of administration was licensed based on positive results from a non-inferiority immunogenicity study.[31–33]

Other locally licensed inactivated whole-cell vaccines mORC-Vax™ (similar to Shanchol™ and Euvichol®) and OraVacs® (similar to Dukoral®) are available in Vietnam and China, respectively.

Both Shanchol™ and Euvichol® contribute significantly to the WHO OCV stockpile. However, none of these WHO-prequalified vaccines is currently recommended by the Centers for Disease Control and Prevention (CDC) for people traveling from the United States (US) to endemic countries.[34] A single-dose, oral live attenuated vaccine, Vaxchora™, is approved by the FDA[35] (Table 1).

Table 1. Comparison between WHO-prequalified cholera vaccines and Vaxchora™.

Vaccine	Dukoral®	Shanchol™	Euvichol®	Vaxchora™
Manufacturer	Valneva, France	Shantha Biotechnics, (Hyderabad, India) Sanofi Company	Eubiologics, Seoul, Republic of Korea	PaxVax Inc., US
Developer	SBL Vaccin (Solna, Sweden)	IVI, Shantha	IVI, Eubiologics	PaxVax Inc. (US) Univ. of Maryland and Kentucky
Type	Monovalent, killed whole-cell vaccine O1 serogroup and recombinant cholera toxin B subunit	Bivalent, killed whole-cell (O1 and O139 serogroups)	Bivalent, killed whole-cell (O1 and O139 serogroups)	Monovalent, live, attenuated serogroup O1 classical Inaba strain 569B
Age range for vaccination	≥ 2 years	1 year and older	1 year and older	18–64 yrs
Regimen	2 doses given 7 to 14 days apart (3 doses for children 2 to 5 yrs old)	Two doses 14 days apart	Two doses 14 days apart	Single dose
Booster	Every 2 years for individual ≥6 yrs (every 6 mo for children 2 to 5 yrs)	No recommendation from manufacturer	No recommendation from manufacturer	No recommendation from manufacturer
Route	Oral	Oral	Oral	Oral
Buffer	Sodium bicarbonate buffer	No buffer required	No buffer required	Blend of sodium bicarbonate, sodium carbonate, ascorbic acid, and dried lactose
Duration of protection	2 years (6 months in children 2 to 5 yrs)	At least 3 years Up to 5 yrs	Not available	Not available
Storage	+2°C to +8°C	+2°C to +8°C	+2°C to +8°C	−25°C to −15°C
Shelf Life	36 months	24 months	24 months	24 months
Licensure	60 countries	28 countries	Zambia, Nepal and Pakistan	Approved US FDA, June 2016
WHO prequalification	25 Oct 2001	29 Sep 2011	23 Dec 2015	No

This paper provides an overview of the characteristics of the Vaxchora™, an oral cholera vaccine and discusses its relevance and limitations in cholera control.

Vaxchora™

Origin and design of the vaccine

CVD 103-HgR (Vaxchora™) is a live attenuated *V. cholerae* serogroup O1, serotype Inaba, classical biotype recombinant strain. It harbors a deletion of the A (ADP-ribosylating) subunit of classical cholera toxin (CT) but expresses the immunogenic B (binding) subunit, carries an Hg++ resistance marker gene inserted in inactivated Hemolysin A (hlyA) locus and expresses classical toxin co-regulated pili colonization factor.[36–38] A CVD 103-HgR formulation containing ~5 × 10^8 cfu (colony-forming unit) was originally licensed and commercialized as Orochol® and Mutacol® by the Swiss Serum and Vaccine Institute, Berne, Switzerland for protection of travelers from high-income countries (HICs),[39] while a ~ 5 × 10^9 cfu formulation (Orochol E®) was used in low- and middle-income countries.[40] The one-log higher dose level was needed to achieve adequate immunogenicity in individuals living in under-privileged conditions in developing countries.[41–44] In 2009, PaxVax, Inc. (in 2018 PaxVax was acquired by Emergent) acquired the licensure rights to CVD 103-HgR (earlier formulation) and commercialized it as Vaxchora™ (later formulation), as a cholera vaccine for US travelers.[38,45] A single dose of Vaxchora™ containing >2 × 10^8 cfu of CVD 103-HgR manufactured using PXVX0200 Master Cell Bank is highly immunogenic (> 90% seroconversion rate) and protected US volunteers against experimental challenge 10 days and 3 months after vaccination.[45] LPS-specific memory B-cell responses to CVD 103-HgR have been associated with protection against *V. cholerae* infection[46] and serum vibriocidal antibodies against vaccine strain are considered an immune correlate of protection[45,47–51]

Product characteristics

Vaxchora™ is supplied as a single-dose foil packet containing buffer (buffer component) and an accompanying single-dose foil packet of lyophilized CVD 103-HgR (active component). The other ingredients in the active component packet are sucrose, sodium chloride, ascorbic acid, dried lactose, and Hy-Case SF (hydrolyzed casein). The buffer component packet contains sodium bicarbonate, sodium carbonate, ascorbic acid and lactose. The composition of the Vaxchora™, final drug product and the functions of the ingredients are provided in Table 2.[52,53]

Storage

Vaxchora™ buffer component and active component packets should be stored frozen at −25°C to −15°C.[52]

Table 2. Composition of Vaxchora™ vaccine.

Components	Properties	Dosage
Packet 1		
Viable CVD 103-HgR	Active ingredient	4 × 10^8 to 2 × 10^9 cfu
Sucrose	Cryoprotectant	≤165.37 mg
Sodium chloride	Stabilizer	≤17.11 mg
Hy-Case SF	Stabilizer (cryoprotectant)	≤17.11 mg
Ascorbic acid	Stabilizer (antioxidant)	≤8.55 mg
Dried lactose	Stabilizer (desiccant) and bulking agent	≤2.09 g
Packet 2		
Sodium bicarbonate	Buffer	2.16–2.41 g
Sodium carbonate	Buffer	0.24–0.49 g
Ascorbic acid	Buffer	1.50–1.80 g
Dried lactose	Flow ability	0.18–0.22 g

Packaging & dispensing

The vaccine is co-packaged in an individual, single-dose box containing a first packet (#1) with the lyophilized vaccine and a second packet (#2) with the buffer powder. Reconstitution is a multi-step process. Packets must be withdrawn from the freezer but do not require thawing prior to reconstitution. Reconstitution should be completed within 15 minutes of removing the two packets from the freezer. 100 mL of cold or room temperature (5–22°C) purified bottled water (not part of the box) is added to a clean, disposable cup. Tap water, non-purified bottled water, other beverages, or other liquids are not acceptable substitutes. The buffer powder from packet #2 is put into the disposable cup and effervescence ensues. Buffer and water are stirred until the contents are completely dissolved. Packet #1 of the lyophilized vaccine powder is then mixed with the buffer solution, stirred for at least 30 seconds until a slightly cloudy suspension is formed. The mixture must be administered within 15 minutes of reconstitution. The recipient must drink the full contents of the cup. If the order of reconstitution is violated the vaccine must be discarded. The vaccine recipient should not eat or drink for 60 minutes before and after ingesting the vaccine preparation.[52,53]

Pharmacodynamics

Vaxchora™ was evaluated for post-vaccination replication of the live attenuated vaccine in a host based on vaccine strain shedding. A study found 11% of 53 healthy adult vaccine recipients shed the Vaxchora™ strain for seven days after vaccination. The largest number of individuals shedding the vaccine strain was on Day 7 post vaccination. However, the duration and frequency of shedding beyond seven days is not known.[54]

Preclinical studies

As *V. cholerae* is a strictly human pathogen, there is no valid animal model available to assess non-clinical safety of this vaccine or predict the mucosal immune response in humans. Vaxchora™ has not been evaluated for the potential to cause carcinogenicity or genotoxicity, or to impair fertility.[55]

Mechanism of action

Cholera infection provides prolonged protective immunity against subsequent infection.[56–58] This immunity is mediated

by local mucosal secretory IgA (sIgA) antibodies produced in the small intestine and directed primarily against LPS and the cholera toxin B subunit (CTB). Immunological memory (antigen-specific B cells) is also induced.[59] The anti-LPS sIgA prevents the establishment of bacterial colonization; anti-CTB sIgA neutralizes cholera toxin and prevents its binding to the cells of the small intestine.[60] The presence of serum vibriocidal antibodies (SVA) in subjects previously exposed to cholera is associated with protection against subsequent infection.[61] The CVD 103-HgR vaccine strain was designed to induce immune responses similar to those against natural cholera infection but without causing cholera disease.

Vaxchora™ has been shown to induce SVA, serum anti-CTB antibodies, serum anti-LPS antibodies, and protects against cholera challenge in humans. Because it is an oral, live attenuated strain, it would also be expected to induce a local mucosal immune response in the small intestine in a similar way to wild type *V. cholerae* infection. The presence of anti-LPS sIgA antibodies in stool samples from vaccine recipients receiving the CVD 103-HgR strain had been demonstrated earlier and was therefore not studied in trials of Vaxchora™.[62]

Clinical trials with Vaxchora™

Several studies have evaluated the safety, immunogenicity and efficacy of the earlier formulation of CVD 103-HgR vaccine.[36,38,45,63,64] Four randomized, placebo-controlled, clinical trials were conducted prior to licensure to estimate the safety, immunogenicity and efficacy of Vaxchora™. These trials collectively enrolled 3,235 adults, 18–64 years of age (median 32.5 years), who received a single dose of CVD 103-HgR and 562 who received saline placebo (N = 551) or lactose (N = 11) (reviewed in[38]).

Safety

The most comprehensive dataset documenting the clinical acceptability of Vaxchora™ comes from a multicenter, double-blind, randomized (8:1), placebo-controlled lot-to-lot (3 lots) consistency trial conducted among adults 18–45 years of age in the United States of America (USA) and Australia (NCT02094586). The safety analysis included 2789 CVD 103-HgR recipients and 350 placebo recipients. Adverse reactions were recorded daily for 7 days following vaccination by 2734 of the 2789 vaccinees (98.0%) and by 343 of 350 placebo recipients (98.0%).[38] In the first study, the overall rate of diarrhea among vaccinees was significantly higher (3.9%) than among placebo recipients (1.2%); 61.5% of the diarrheal complaints in vaccinees were mild. Fever was recorded in <1% of vaccines.[65] Three other studies provided similar evidence of the vaccine clinical safety in adults aged 18–45 years[45,66] and 45–64 years[38] In a pooled analysis of serious adverse events (SAE) in the four clinical trials, 20 of 3235 Vaxchora™ recipients (0.6%) and 3 of 562 placebo recipients (0.5%) reported an SAE up to 6 months of vaccination. None of these SAEs were vaccine-related (reviewed in[38]).

Immunogenicity

A single oral dose of >2x10^8 cfu CVD 103-HgR elicits ~90% seroconversion assessed by serum vibriocidal antibody.[45,67,68] With regard to immunogenicity assessed by SVA, responses to Vaxchora™ in a lot-to-lot (3 lots) consistency trial (NCT01895855) the O1 Inaba vibriocidal antibody seroconversion rates were 93.5% [95% CI, 92.5–94.4%] in vaccine recipients and 4.2% [95% CI, 2.3–6.9%] in placebo recipients at 10 days post vaccination.[65] A randomized, double blind, placebo-controlled reactogenicity and immunogenicity study (NCT02100631) was conducted on 398 adults (46–64 years, mean age 53.8; 45.7% males) with no prior history of cholera infection or travel to a cholera-endemic area in the previous 5 years. Seroconversion rate of O1 Inaba vibriocidal antibody at Day 10 post-vaccination was 93.5% [95% CI, 92.5–94.4%] in vaccine recipients and 4.2% [95% CI, 2.3–6.9%] in placebo recipients.[65] The age range study in adults (18–45 and 46–64 years) showed that while reactogenicity event rates were comparable between the two age groups, there was a continuous decline in SVA but not in memory B-cell responses in the older age group.[69]

Efficacy in human challenge study

A randomized, placebo-controlled human challenge study (NCT01895855) to assess vaccine efficacy enrolled 197 healthy adult volunteers, 18–45 years of age in three US sites. Subjects were randomly allocated to receive a single dose of CVD 103-HgR (N = 95) or saline placebo (N = 102). Because blood group O individuals are at higher risk for severe cholera (cholera gravis),[70–72] the study population enrolled more blood group O volunteers to assess vaccine efficacy in these high-risk hosts.

Challenge with virulent *V. cholerae* O1 at 10 days post vaccination (approximately 10^5 cfu of wild-type *V. cholerae* O1 El Tor Inaba strain N16961) elicited moderate to severe cholera diarrhea in 59.1% of the placebo recipients, significantly higher than the rate among vaccine recipients (5.7%) (efficacy 90.3%). Three months after vaccination the rate of moderate to severe diarrhea among vaccinees after *V. cholerae* challenge was 12.1% (efficacy 79.5%).[45] The efficacy against moderate to severe cholera among the high-risk blood group O volunteers at 10 days and 3 months were 84.8% (95% CI, 50.4%–100%) and 78.4% (95% CI, 44.2%–100%), respectively.[45]

There was a strong correlation between SVA seroconversion and protection against moderate to severe cholera. Only 3.2% of the vaccinees who manifested ≥4-fold titer had moderate to severe cholera, while moderate to severe diarrhea occurred in 75% of those who failed to seroconvert. The two vaccinees who developed moderate to severe cholera despite seroconversion exhibited only modest SVA titers (80 and 160) post vaccination. Indeed, no vaccinee who seroconverted and achieved a day 10 titer ≥320 experienced moderate to severe cholera.[45]

Co-administration

Three randomized controlled trials and one observational cohort study reported co- administration of an earlier formulation of CVD 103-HgR with Live Oral Ty21a Typhoid vaccine and measured anti-Salmonella serotype Typhi LPS antibodies among vaccine recipients of both vaccines.[73–77] Anti-Typhi LPS serum antibodies were detected in 62–83% of participants (470 adults) after primary immunization. One study examined the immunogenicity of yellow fever (YF) 17D vaccine in combination with an older formulation of CVD 103-HgR or CVD 103-HgR and YF; all 58 individuals who received both

YF 17D and CVD 103-HgR developed anti-YF antibodies.[78] One study evaluated an earlier formulation of CVD 103-HgR in combination with different vaccines and medications including Ty21a, YF 17D, oral polio vaccine, mefloquine, chloroquine, and proguanil.[78] Significantly lower rates of vibriocidal seroconversion were noted when CVD 103-HgR was co-administered with chloroquine (67%) vs. alone (91%), $P < .001$. No decrease in immunogenicity was noted for CVD 103-HgR when co-administered with mefloquine, proguanil, YF 17D, or oral polio vaccine.[76]

Post-marketing data

CVD 103-HgR was previously marketed as Orochol® or Mutachol® in several countries before manufacture ceased for business reasons. Of more than 500,000 Orochol® doses sold, the following adverse events after vaccination were spontaneously reported: hospitalization with fever, gastroenteritis, vomiting, and hemorrhagic cerebrospinal fluid in a 11 month old infant (one report); Guillain-Barré syndrome in a single person who received CVD 103-HgR, yellow fever vaccine, Ty21a vaccine, and diphtheria and polio vaccines (one report); angioedema (one report); and loss of hair (one report).[73,79,80] Of more than 250,000 Orochol® E (a higher dose formulation) doses sold, no self-reported adverse reactions were reported.[73] Post marketing data for the current formulation (Vaxchora™) are not available.

Issues & challenges

Limitations and gaps with Vaxchora™ include lack of effectiveness data in cholera endemic areas and among populations with pre-existing immunity due to previous exposure to *V. cholerae* or receipt of a cholera vaccine. Vaxchora™ has not been shown to protect against cholera disease caused by *V. cholerae* serogroup O139 or other non-O1 serogroups. Also, there are no data on effectiveness in infants (<1 year of age) and children of (1–17 years) either in non-endemic settings or in endemic settings. The safety and effectiveness of Vaxchora™ has also not been established in immune-compromised individuals. The Vaxchora™ strain may be shed in the stool of vaccine recipients for at least 7 days so there is a potential for transmission of the vaccine strain to non-vaccinated close contacts (e.g. household contacts).[53,54]

As a live attenuated vaccine, concomitant administration of Vaxchora™ with systemic antibiotics is not recommended since these compounds may be active against the vaccine strain. Hence it is not recommended to administer Vaxchora™ to patients who have received oral or parenteral antibiotics within 14 days prior to vaccination.[53] This may also limit the utility of Vaxchora™ in outbreaks where the use of antibiotics may be an important part of the outbreak response.

The current Vaxchora™ formulation must be kept frozen (−25°C to −15°C), which significantly increases cold chain stringency and logistics of vaccination. The CVD 103-HgR formulation containing $\geq 2 \times 10^9$ cfu is not stable outside of cold chain at tropical temperatures for an extended period and requires clean drinking water to administer the vaccine, which is also not practical during large scale delivery scenarios in resource-poor settings or humanitarian crises where logistics and simplicity of mass administration are a premium.[78]

Market value

The annual market value for OCV used outside the OCV stockpile in 2017 was estimated at $65 million driven mostly by private market sales by travel clinics in HICs and projected to be $207 million by 2025.[81] The current market share of Vaxchora™ is not known. Overall production/production plans for Vaxchora, since the takeover of Paxvax by Emergent are unknown and subsequent lack of data supporting vaccine effectiveness in non-emergency cholera control interventions hinders precise Vaxchora™ demand forecasting. Public market pricing of OCVs are typically much lower than private market pricing[82] and currently ranges from $1.20 to $1.85 depending upon the product, country or price negotiation. The OCV weighted average price is $1.77 per dose.[83,84] Compared to that, the average market price of Vaxchora™ in US is estimated to be $270 per dose.[85] Furthermore, demand estimates of OCVs based on disease incidence may underestimate the need, as many cholera cases go unreported. Demand is also contingent on chosen immunization program strategies, including target populations and campaign frequency. As these immunization strategies are not defined, United Nations International Children's Emergency Fund (UNICEF) demand forecasts mitigate demand uncertainty by securing maximum supply availability. UNICEF and partners anticipate a steady increase in demand for non-emergency response based on growing needs and expected increases in supply, production capacity, and availability. Since the establishment of OCV stockpile in 2013, about 36 million doses of OCV were used in 22 Low and Middle Income Countries (LMICs) through more than 100 campaigns.[86] During the first 11 months of 2018, around 17.5 million doses of OCVs were shipped from the stockpile to LMICs. The current demand through UNICEF is limited by supply availability, estimated to reach up to 19.3 million doses for the period 2015–2018, subject to an annual review based on programmatic considerations. UNICEF concluded its OCV tender during 2015, and awarded two manufacturers 19.3 million doses over 2016–2018 through long-term arrangements (LTA). The LTA awards will be subject to annual review based on programmatic considerations.[83] Keeping in mind recent humanitarian crises, reports of various cholera outbreaks, and availability of cholera vaccine from additional manufacturers, vaccine demand is expected to increase significantly over the next years.[87] OCV demand for travelers to cholera-endemic regions and use or plan for use among military and peacekeeping forces is not known. However, the market value of Vaxchora™ is unlikely to be affected by global OCV demand because the vaccine is not WHO-prequalified, hence it is not included in Gavi, the Vaccine Alliance, or UNICEF financing and procurement schemes. Use will be driven by high-income country traveler vaccine needs. Should Vaxchora™ reach WHO prequalification, its cost-effectiveness compared to the current killed whole-cell vaccines ($1.20–1.88 per dose) would need to be further considered.

Public health perspective

The Global Task Force on Cholera Control (GTFCC) has estimated cholera to be endemic in 47 countries primarily in Africa and Asia, where ingestion of contaminated water or food plays a major role in transmission.[87] Annually, millions

of people around the world are impacted. However, cholera remains under detected and underreported in LMICs countries as well as in high-income countries. A recent report from the CDC suggests that the true number of cholera cases in the US is at least 30 times higher than that observed by national surveillance systems.[88] Although the avoidance of contaminated water and food is a good strategy for cholera prevention, studies have shown that 98% of travelers do not comply with these precautions when travelling,[89] making the vaccine a useful intervention for travelers. Developing countries and humanitarian crises present a more complex situation, where epidemics occur over a pattern of endemic disease exacerbated acutely by wars or natural disasters. Events like the one that occurred in Haiti, where further degradation of safe water and sanitation occurred after Hurricane Matthew on October 4, 2016[90] triggered serious cholera outbreaks requiring a public health response. Similarly, an ongoing cholera outbreak affecting hundreds of thousands of people in war-torn Yemen[18] has highlighted the need for better coordination of cholera control efforts. There is growing consensus that multi-sectoral coordinated cholera interventions inclusive of OCVs and WASH is necessary. The 2017 announcement of "Ending Cholera – a Global Roadmap to 2030" by the GTFCC partners including both WASH and OCV advocates represents an unprecedented engagement in the fight against cholera, with a target to reduce deaths from cholera by 90% by 2030.[85] Vaxchora™, a non WHO prequalified vaccine with high price, is at this point, unfortunately, relevant only for US travelers.

Summary

The oral live attenuated vaccine Vaxchora™ licensed in USA can play role in the prevention of cholera among US travelers to cholera-affected countries. However, it would need to surmount a number of technical issues in order for its use to be extended in campaign or outbreak settings worldwide. Notably, stringent cold chain requirements, complexity of administration, age indication restrictions, lack of data regarding its utility in cholera endemic populations and high cost currently limit its general use in cholera-affected LMICs.

Abbreviations

AMR	antimicrobial resistance
CDC	Centers for Disease Control and Prevention
CTB	cholera toxin B subunit
cfu	colony-forming unit
DS	dipstick
GTFCC	Global Task Force on Cholera Control
LPS	lipopolysaccharide
LMIC	Low and Middle Income Countries
LTA	long-term arrangements
OCV	Oral cholera vaccine
UNICEF	United Nations International Children's Emergency Fund
USA	United States of America
US	United States
WASH	water, sanitation, and hygiene
WHO	World Health Organization.

Disclosure of potential conflict of interest

There is no conflict of interest declared

ORCID

Tarun Saluja http://orcid.org/0000-0001-9771-7021
Vijayalaxmi V. Mogasale http://orcid.org/0000-0002-9564-8760
Jean-Louis Excler http://orcid.org/0000-0002-6462-5101
Jerome H. Kim http://orcid.org/0000-0003-0461-6438
Vittal Mogasale http://orcid.org/0000-0003-0596-8072

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