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REVIEW

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Oral cholera vaccines and their impact on the global burden of disease

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ABSTRACT

With one-third of nations at risk of cholera, we can expect to experience massive, rapidly disseminated, and prolonged cholera outbreaks such as those recently experienced in Yemen and Haiti. The prevention of cholera outbreaks like these includes the provision of potable water, sanitation, and hygiene (WASH). This approach has been known for generations. However, it will be many years before universal global access to WASH is achieved. While working toward universal WASH, study data has shown that licensed and WHO prequalified cholera vaccines are important tools for cholera prevention. Oral inactivated whole-cell vaccines such as Shanchol and Euvichol-plus provide well-documented direct benefits to vaccine recipients and to the unimmunized through herd protection. Manufacturers have now increased the cholera vaccine supply, and since 2013 vaccine doses have been available for emergency and endemic control through a global stockpile. Advances in packaging and vaccine temperature control, reduced vaccine costs, the inclusion of pregnant women in vaccine campaigns, and a targeted approach to high incidence endemic areas are further increasing the usefulness of these vaccines for reducing the global cholera burden.

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Background

For 160 years, we have known that cholera transmission is preventable through access to clean water, sanitation, and improved personal hygiene. Unfortunately, we have not achieved universal global access to clean water and sanitation and cholera remains a serious global threat. Between 2008 and 2012, investigators estimated 2.9 million cholera cases and 95,000 deaths annually in 69 endemic countries.[1] At risk of cholera, are 1.3 billion people living in endemic countries, primarily in sub-Saharan Africa and South Asia. Cholera is a health risk in one-third of nations.

While these estimates describe the cholera global burden, they do not capture the massive, rapidly disseminated, and prolonged outbreaks that often strike troubled nations. The cholera epidemic in Yemen, a war-torn nation, is one of the largest and most intense outbreaks in recent memory. From April 2017 through February 2018, there were more than 1 million cases and 2,258 deaths throughout the country.[2,3] Cholera also struck Haiti with similar ferocity. Starting in October 2010, likely ignited by a strain brought to Haiti from South Asia, the Haitian outbreak includes 818,000 episodes and is approaching 10,000 deaths.[4,5] Before 2010, Haiti had been cholera-free for nearly a century.

V. cholerae and cholera

Cholera is caused by a comma-shaped, gram-negative bacterium, *V. cholerae*. There are more than 200 serogroups, but only serogroups O1 and O139 cause epidemic disease. O139 emerged in 1992 is now rarely isolated.[6] The O1 group is further divided into classical and El Tor biotypes each of which produces a cholera enterotoxin. Each biotype has two distinct serotypes, Inaba and Ogawa, based on the structure of the lipopolysaccharide membrane. A third serotype, Hikojima, is rarely isolated.[7]

To cause disease, *V. cholerae* colonizes the proximal small intestine and then produces an enterotoxin that induces voluminous diarrhea containing water and electrolytes. The toxin is composed of A and B subunits. The cholera toxin B-subunit (CTB) binds to GM1 ganglioside receptors on the epithelial cell surface. The CTB is immunogenic, and a recombinant form has been added to some vaccines. The A subunit is released into the cell, where it activates adenylate cyclase, which stimulates fluid loss.[8]

The principle treatment for cholera is to replace lost fluids and electrolytes using oral and intravenous fluids.[9] *V. cholerae* can resides in brackish water and estuaries in association with zooplankton and shellfish and can infect residents in those areas.[10] It is transmitted through the fecal-oral route primarily by water and less so by food. Person-to-person transmission is documented among household members.[11] In endemic areas, defined as *V. cholerae* culture positivity in a community in three of the last five years,[12] cholera incidence is highest among children less than five years old.[13] When *V. cholerae* is introduced into a non-endemic area as in Haiti, all ages may be attacked.

Cholera prevention and oral cholera vaccines

In 1854, John Snow mapped the distribution of cholera cases during an epidemic in Soho, London, and identified water from the Broad Street pump as the source of infection.[14] It was subsequently recognized that improvements in water

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supply and sanitation could reduce cholera morbidity. As a result, many nations adopted water systems, sanitation, and improved hygiene practices that eliminated cholera transmission. Unfortunately, the universal availability of potable water and sanitation has not been achieved, particularly in sub-Saharan Africa and Asia. In 2015, an estimated 844 million people retrieved water directly from surface water sources or used unprotected wells and springs. In addition, 2.3 billion people still lack facilities for the safe disposal of excreta, and 892 million people practice open defecation.[15] While achieving universal access to potable water and sanitation is a long-term goal, the development and use of cholera vaccines have become an additional tool for cholera prevention.[16]

There are three oral cholera vaccines (OCVs) licensed by national regulatory authorities (NRAs) and prequalified by the World Health Organization (WHO) (Table 1). Dukoral, the first prequalified OCV, contains CTB and heat- or formalin-inactivated whole-cells of serogroup O1, which includes classical and El Tor biotypes including Ogawa and Inaba. Dukoral is given with sodium bicarbonate buffer as the CTB is acid-labile, and the buffer protects from gastric acid degradation. In the 1980s, Swedish researchers transferred the strains and technology for this vaccine to the Vietnamese government, and they manufactured a modified vaccine similar in composition but without CTB.[18] Without CTB, the vaccine does not require co-administration of buffer, which greatly eases administration. In 1997, the Vietnamese NRA licensed the vaccine as mORC-Vax. mORC-Vax could not be prequalified for use by the UN as WHO had not approved the Vietnamese NRA. Therefore, the International Vaccine Institute (IVI) acquired the process from Vietnam, improved the formulation, and then transferred the process to Shantha Biotechnics, Ltd., an Indian manufacturer in a country with a WHO-approved NRA. Shantha's vaccine, Shanchol, was prequalified in 2011. IVI also transferred the manufacturing process to Eubiologics Co., LTD., South Korea, and they produced a vaccine called Euvichol. Early-phase and non-inferiority trials demonstrated that Euvichol's safety and immunogenicity was similar to Shanchol's, and it was prequalified in 2015.[19,20]

Vaccine efficacy and effectiveness

Three key field trials established protection afforded by the above vaccines (Table 2).

The first efficacy trial was a study of the whole-cell strains given with B-subunit (CTB-WC or Dukoral) and without the B-subunit (WC only). The trial was conducted in Matlab, Bangladesh, between 1985 and 1988.[21] This individually randomized, placebo-controlled trial included children ages 2 to 15 years old and non-pregnant women more than 15 years old. More than 62,000 residents received three doses given six weeks apart. Over the course of the trial, there were a mixture of *V. cholerae* O1 El Tor and Classical episodes (CTB-WC: 131 episodes, WC:127 episodes, and placebo: 266 episodes). The per-protocol CTB-WC efficacy during the first, second, and third year was 62% (Lower Limit:50), 57% (LL:42), and 17% (LL: −15%), respectively. The WC efficacy for the same periods were: 53% (LL:38), 57% (LL:42), and 43% (LL:19). While, there was a noticeable decrease in efficacy for CTB-WC in the third year, the protective efficacy over three years of follow up was similar for both vaccines: 50% (LL: 39) for CTB-WC and 52% (LL: 41%) for WC. As would be found in later trials, protection among children ages two to five years was significantly less ($p < .05$) than for ages six years and older for both vaccines (CTB-WC: 26% vs. 63% and WC: 28% vs. 68%).

In a second trial, Vietnamese scientists evaluated the whole-cell vaccine without CTB in Hue, Vietnam. This was an open-label trial where more than 67,000 participants one

Table 1. Characteristics of WHO Prequalified Oral Cholera Vaccines*.

Type	Inactivated whole cell with recombinant B-subunit (CTB-WC)	Inactivated whole cell (WC)
Name	Dukoral (Valneva Sweden AB)	Euvichol and Euvichol-Plus (Eubiologics, S. Korea) Shanchol (Shantha, India)
Vaccine strains	O1 (El Tor and Classical Biotypes)	O1 (El Tor and Classical Biotypes), O139
B-subunit added	Yes	No
Buffer required	Yes	No
Packaging	Single-dose vial and sachet for buffer	Euvichol-Plus: plastic tube (fill-seal) Euvichol and Shanchol: 1.5 ml glass vial with rubber stopper and aluminum lid
Doses available per annum for public health use	Not applicable, travelers' vaccine	Euvichol: will discontinue in 2018 Euvichol-Plus: 25 million (50 million if demand increases) Shanchol: 2 million
Dosing regimen	2 doses given 2 to 6 weeks apart 3 doses for children 2 to 5 years	2 doses given 14 days apart but comparable immunogenicity and safety when given 28 days apart
Age-range at vaccination	≥ 2 years	≥ 1 year
Pregnancy	Not contraindicated	Not contraindicated
Length of protection	Recipients > 5 years of age: 2 years Recipients 2 to 5 years of age: 6 months	Up to 5 years
Storage temperature	2° to 8°C	Euvichol and Euvichol-Plus: 2–8°C Shanchol: 2–8°C, 14 days at temperature of up to 40°C prior to administration
Shelf-life	3 years	2 years
Price per dose	Negotiated for public health use	Shanchol: US$1.85 Euvichol: US$1.85 Euvichol-Plus: US$1.30
Herd protection	Yes	Yes

*Adapted from Clemens 2017[9] and Desai 2017[17]

Table 2. Key investigations documenting the protection afforded by oral cholera vaccines including whole cell with B-subunit and whole cell only vaccines.

Vaccine	Brand	Study	Location	Design	Length of follow up	Cholera Cases		% Efficacy or Effectiveness
						Vaccine Recipients	Placebo Recipients/ Controls	
B-subunit and whole cells	Dukoral	Clemens 1990[20]	Matlab, Bangladesh	Double-blind, placebo-controlled, Individually randomized	3 years	6.1 cases per 10^6 person-years of follow up	12.4 per 10^6 person-years of follow up	50% (LL[a]: 39%)
Whole cell only	Unbranded					5.9 cases per 10^6 person-years of follow up		52% (LL: 41%)
Modified whole cell only	mORC-Vax	Trach 1997[16]	Hue, Vietnam	Unblinded, convenience sample	10 months	5.5 cases per 10^4 population	13.7 cases per 10^4 population	60% (95% CI[b]: 40 to 73)
Modified whole cell only	Shanchol	Bhattacharya[21] 2013	Kolkata, India	Double-blind, placebo-controlled, cluster randomized	5 years	2.2 cases per 10^3 population	6.3 cases per 10^3 population	65% (95% CI: 52 to 74)

LL = Lower Limit
CI = Confidence Interval

year of age and older received two vaccine doses, and about the same number received no vaccine. During a cholera outbreak about 8 to 10 months after vaccination, 37 cases of *V. cholerae* O1 El Tor biotype occurred among vaccine recipients and 92 cases among placebo recipients, demonstrating 60% (95% Confidence Intervals [CI]: 40–73) efficacy. Among those who received two full doses, the effectiveness was 66% (95% CI: 46–79), and results were similar for children ages one to five years (68%, 95% CI: 14–88) and older volunteers (66%, 95% CI: 42–80).[18]

The third trial evaluated Shanchol (WC) over five years in Kolkata, India, in a double-blind, placebo-controlled, cluster-randomized trial among children one year of age and older.[18] Two doses of Shanchol were given 14 days apart. All episodes were *V. cholerae* O1 El Tor. In a per-protocol assessment, 69 cases occurred among nearly 32,000 vaccine recipients and 219 cases occurred among almost 35,000 participants for an adjusted protective efficacy of 65% (95% CI: 52–74) over five years. Efficacy was lower among children aged one to five years (42%, 95% CI:11–66) than among children aged 5 to 15 years (68%, 95% CI: 41–83) and those 15 years of age and older (74%, 95% CI: 58–84). There was no statistically significant difference detected for efficacy by year of study.

A meta-analysis estimating OCV efficacy was conducted with the results of these three trials and including two other trials.[22] The first was a trial of a two-dose regimen conducted in 1,426 adult Peruvian military recruits (efficacy 86%; 95% CI: 37–97%).[23] The second, the only trial to suggest a lack of two-dose efficacy (−3.6%; 95% CI: −88–43%), was conducted among ages 2 to 65 years in Peru with slightly more than 9,000 vaccine recipients who experienced 17 events and 8,800 placebo recipients who experienced 16 events.[24] Concerns were raised regarding the results of this trial, and it was proposed by other investigators that outcome events may have been misclassified.[25] The meta-analysis suggested that the average efficacy for a two-dose regimen is 58% (95% CI: 42–69%) over three years. Among studies providing age-stratified results, children one to less than five years old had a 30% (95% CI: 15–42%) vaccine efficacy. The meta-analysis also calculated effectiveness for five observational studies that were conducted in Mozambique (78%; 95% CI: 39–92%), Zanzibar (79%; 95% CI: 47–92%), Guinea (87%; 95% CI: 57–96%), Haiti (63%; 95% CI: 8–85%), and India (69%; 95% CI: 15–89%).[26–30] Mean effectiveness was 76% (95% CI: 62–85%).[22]

Herd protection

Herd protection is the reduction in incidence resulting from reduced transmission after immunizing a portion of the target population.[31,32] Herd protection reduces disease in the unimmunized and may increase protection for the vaccinated. Several field trials have explored OCV herd protection. A reanalysis of the 1985–89 trial in Bangladesh found cholera incidence among placebo recipients was inversely correlated to OCV coverage. Incidence among placebo recipients was 7.0 cases per 1,000 population in the lowest-coverage quintile (< 28%) versus 1.47 cases per 1,000 population in the highest quintile (> 51%).[33] Herd protection lasted three years. Similar results were seen in a Dukoral study (CTB-WC) comparing immunized to unimmunized individuals in Zanzibar.[27] Another analysis used data from the three-year Shanchol trial in Kolkata.[34] In this analysis, researchers did not detect indirect protection from a cluster-randomized analysis possibly due to high levels of inter-cluster transmission. However, using a geographic information systems (GIS) approach that identifies cluster by level of coverage, an inverse correlation between coverage and cholera risk was observed in placebo recipients. Cholera risk decreased systematically for each step-increase in vaccine coverage from 5.54 cases per 1,000 placebo recipients in areas with the lowest coverage (≤ 25%) to 1.93 cases per 1,000 placebo recipients among those with the highest coverage (≥ 34.01%).

The above results imply that increasing the level of coverage positively correlates with increases in levels of herd protection. Mathematical modelers have further proposed that transmission can be interrupted when the appropriate level of vaccine coverage is reached. Using an age-structured mathematical model of endemic cholera transmission calibrated to reproduce cholera dynamics of Matlab, Bangladesh, maintaining 70% OCV coverage of residents one year and older can

interrupt cholera transmission.[35] These results are consistent with an earlier model from Bangladesh suggesting that 50% coverage was sufficient to stop transmission.[36] As cholera dynamics (e.g., age-specific incidence, proportion of water-to-person transmission, degree of endemicity) can vary across nations and subnationally, these results from Bangladesh may not be straightforwardly generalizable to other nations or subnational areas.[37] Fortunately, as OCV vaccines become widely deployed preemptively and reactively, field data will become available that further informs policymakers on the levels of population coverage necessary to interrupt transmission.

Operational enhancements to OCV use

Several operational improvements are likely to enhance vaccine deployment. In August 2017, Euvichol-Plus was prequalified by the WHO.[38] Euvichol-Plus is the whole-cell vaccine packaged in plastic tubes rather than the small 1.5 ml glass vials with rubber stoppers and aluminum lids. The lid and stopper must be removed by hand before administering Euvichol or Shanchol.[39] The new packaging makes vaccine easier to open and administer. Euvichol-Plus costs US$1.30 per dose, which is 25% less than Euvichol. It also reduces the vial storage volume by nearly 30% and weight by 50%, allowing for easier shipping, distribution, and waste management.[40] The vaccine was shipped to Zambia and Somalia for outbreak control in 2018.

Shanchol is now easier to store and transport. In February 2018, WHO permitted a change to the storage label, reflecting that the vaccine can remain unrefrigerated for up to 14 days at temperatures up to 40°C prior to administration.[41] This minimizes the requirements for refrigeration, cold boxes, and ice packs before administration. Eubiologics is expected to obtain the same label change for Euvichol-Plus.

Shanchol and Euvichol have not been recommended during pregnancy. However, clinical data suggests that cholera during pregnancy increases fetal distress and death.[38,41] In a systematic analysis of seven studies, fetal death among pregnant women with cholera from Haiti, Senegal, and Peru was 3.8 (95% CI: 2.1–7.1) times higher compared to national stillbirth estimates.[42] The Haiti study, conducted with 263 women with cholera-like illness, also suggested that severe maternal dehydration (risk ratio = 9.4; 95% CI: 2.5–35.3) and severe vomiting (5.1; 95% CI: 1.1–23.8) were risk factors for fetal death.[43,44] These data imply that an OCV should not be counter-indicated during pregnancy, and studies conducted in Guinea,[45] Zanzibar,[46] Malawi,[47] and Bangladesh[48] have not observed statistically significant adverse outcomes to fetus, newborn, or mother from OCV exposure. Given the risk to the fetus from maternal cholera and the excellent vaccine safety record, there is no scientific basis to withhold OCVs from pregnant women.[49]

Single dose

Manufacturers recommend that two doses of OCV be given 14 days apart for residents one year of age and older. This is applicable to reactive or preemptive vaccination. However, a single OCV dose, rather than two doses, appears to provide a modicum of protection for two years. In an efficacy trial conducted in Dhaka, Bangladesh, 102,552 persons one year and older received a single dose of Shanchol and had 38 cholera episodes and 102,148 received placebo and had 63 episodes over six months. The vaccine protective efficacy was 40% (95% CI: 11 to 67%) for all ages, but protection was not afforded to children 1 to less than 5 years of age (16%, 95% CI: −49 to 53%).[50] Follow up at two years had a protective efficacy similar to the six month results (i.e., 39%, 95% CI: 23 to 52) and again protection was not provided to children (−13%, 95% CI:-68 to 25%).[51] In a single dose, case-cohort study in Juba, South Sudan data suggested better protection than that seen in clinical trials. Protective efficacy was 87% (95% CI: 70 to 100%) over two months among 87 suspected cholera cases (34 positive) and 858 cohort members, none of whom developed cholera.[52,53] Vaccine indirect effects and the short period of follow up, 2 months, may explain the greater efficacy in South Sudan than observed in other trials. Regardless, more data is needed to evaluate if a single dose administered to ages one year and above provides indirect protection to children ages one to less than five years.

Outbreaks, endemic disease, and stockpiling OCVs

Cholera outbreaks continue globally. In addition to outbreaks in Yemen and Haiti cited earlier, in recent years, Somalia[54], Democratic Republic of the Congo (DRC)[55], and South Sudan[56] have also experienced significant cholera outbreaks. This list is not inclusive of all affected countries. In 2013, to assist affected countries, an OCV stockpile was established. After country application and approval[57], doses are sent from the stockpile to countries for emergencies including reactive response to an outbreak or for preventive vaccination as part of a humanitarian crisis.[58] Release of vaccine for emergencies is managed by the International Coordinating Group (ICG) comprised of the International Societies of the Red Cross and Red Crescent, UNICEF, WHO, and Doctors without Borders. Doses from the stockpile are also deployed for preventive vaccination in sites with recurrent cholera outbreaks (i.e., hotspots). This use is managed by the Global Task Force on Cholera Control. The WHO is the secretariat for the ICG and Task Force. The stockpile is funded by Gavi, the Vaccine Alliance. In 2013, Gavi made a time-limited investment to the global cholera stockpile to be revisited in 2018. However, in 2016, the Gavi Board shifted its approach to give more stability to the supply and manufacturers by agreeing to continue funding the emergency response of the stockpile for as long as needed. In 2018, they will consider expanding OCV use to hot spots (personal communication, Melisa Ko, Senior Programme Manager, Vaccine Implementation, Gavi).

In 2017, the Global Task Force on Cholera Control (GTFCC) reported on the use of the stockpile.[59] From 2013 to July 2017, countries and other agencies requested more than 25 million OCV doses. Of these doses, nearly 18 million (71%) were approved and nearly 13 million were shipped in 46 deployments. The number of doses shipped has roughly doubled annually from about 200,000 (2013) to 1.5 million

(2014), 2.5 million (2015), 4.6 million (2016), and 4 million (until July 2017). OCVs were deployed to 15 countries: Cameroon, DRC, Ethiopia, Guinea, Haiti, Iraq, Malawi, Mozambique, Nepal, Niger, Somalia, South Sudan, Sudan, Tanzania, and Zambia. The largest number of doses were shipped to Haiti (2,517,815), Somalia (2,101,400), and South Sudan (1,969,660). Of the shipped vaccines, 37%, 36%, and 27% were for humanitarian crises, outbreaks, and endemic areas.

The deployment of OCVs from the stockpile offers an opportunity to study the effectiveness, coverage, acceptability, feasibility, safety, costs, and cost-effectiveness in a diverse populations residing in different geographic settings. The GTFCC are addressing these needs using a rigorous system for monitoring and evaluating OCV use.[60]

For estimating vaccine effectiveness during a deployment simple and low cost study designs are required and several study designs (e.g., case-control, cohort, GIS, before-after) have been suggested[61]. Of potential benefit to the study of vaccine effectiveness is the use of case-negative design. This design is logistically less complicated than other study designs as the test-negative study can be incorporated into high-quality clinic-based cholera surveillance.[30] In this design, all patients in a geographic area designated for vaccination and seeking medical care with acute diarrhea are enrolled. Acute diarrhea patients are tested for *V. cholerae*, and positive patients are cases, and negative cases are controls. Vaccine effectiveness is estimated from the ratio of the odds of vaccination among subjects testing positive to the odds of vaccination among residents testing negative. One other benefit is the design minimizes putative bias due to differences in health-seeking behavior that can occur when the vaccinated and unvaccinated have differential health-seeking behaviors.[30] Test-negative results have been validated against the results of observational studies and randomized controlled OCV trials.[62]

For cholera diagnosis, the use of polymerase chain reaction (PCR) has been shown to be more sensitive than culture methods.[63,64] A reanalysis of the GEMS data shows that more cases of cholera were identified in those populations using PCR than those using standard fecal culture, although the increased detection did not appear as dramatic as observed with Shigella (2 times the number from culture) and ETEC results (1.5 times the number). Still, the use of PCR in endemic disease surveillance could increase the number of cholera cases identified and better estimate the impact of disease control measures.

Targeted control

As noted earlier, an estimated 1.3 billion residents in endemic areas are at risk of cholera.[1] Clearly, providing universal OCV coverage to a global population would require a massive investment of several billion dollars to cover vaccine costs alone. Therefore, strategies are needed to prioritize populations so that policymakers have a rational and cost-effective basis for deploying OCVs.

To this end, investigators have suggested an approach using five scenarios by which to prioritize populations for cholera vaccination.[65] Scenario 1 and 2 concerns vaccination in areas having humanitarian emergencies as a result of natural or man-made disasters and with or without cholera transmission, while scenario 3 and 4 include endemic areas again with or without cholera transmission. Vaccines would be deployed either reactively if an outbreak is ongoing or preemptively if at high risk due to recent cases or outbreak in a geographically adjacent area. Scenario 5 covers populations with adequate sanitation and access to water and vaccination would not be required. The authors note that use of vaccines preemptively or reactively as described above requires, among other things, reliable epidemiological data, prompt reporting, and laboratory case confirmation. Such data is not normally available in resource-limited areas where cholera is found. Investments should be made to strengthen surveillance.

In keeping with areas experiencing endemic cholera (scenario 3 above), cholera cases due tend to cluster, allowing the targeting of vaccines to specific subpopulations in high-incidence areas (i.e., hotspots).[66] In a study of sub-Saharan Africa, investigators using multiple data sets covering 2,283 locations identified 4.0% of districts, including 87.2 million people, as having a high cholera incidence. Data suggest that by focusing on districts with the highest incidence, targeted interventions including vaccines given to persons one year of age and older every three years and improvements WASH could eliminate 50% of the region's cholera, covering 35.3 million persons.[67] Similarly, a study exploring the spatial distribution of cholera using GIS and identifying associated risk factors could pinpoint high-risk areas for vaccination and WASH. A study in Uganda using a similar approach demonstrated that high-risk districts were along the border with DRC and Kenya, covering a population of 7 million or about 20% of the Ugandan population.[68]

Conclusions

Clearly, WASH strategies and OCVs can significantly reduce the global cholera burden. Trials and observational studies have shown that two OCV doses offer substantial direct protection for up to five years. Data further suggests that OCVs can induce herd protection among the unimmunized. OCVs are also easier to use given reduced costs with improved presentation and packaging including maintenance for 14 days at ambient temperatures. Given the safety record, these vaccines can be administered to pregnant women providing protection to mother and fetus. More than 50 million OCV doses per year can be produced given sufficient demand. The global stockpile have ensured that OCVs are deployed where needed. Attention is turning now to control of endemic cholera.

In addition to these advances, improved vaccine efficacy for preschool children needs to be addressed as efficacy data suggests that two OCV doses provides moderate protection and one dose may not provide direct protection to these children. The lower efficacy in children may be due in part to inadequate immunity due to a lack of prior exposure, poor vaccine response due to environmental enteropathy, a disorder marked by intestinal inflammation and impaired gut

immune function, microbiota dysbiosis, malnutrition, and others clinical factors.[69,70] Regardless of the lower performance, given the high disease burden in preschool children, even a modicum of protection can be extremely beneficial to children and children should be actively sought for vaccination.

When doses are limited during an outbreak, it would seem reasonable to provide a single dose for persons five years and older, but still provide two doses to children one to less than five years old.[51] In the future, it may be necessary to consider other strategies for children, for example, by providing two doses followed by a booster dose one month or later as suggested by a study of killed vaccines that supports use of three doses to build high affinity lymphocytes in the lamina propria.[71] While concerns could be raised about adding adjuvant dmLT (double mutant of ETEC heat-labile toxin) because it would require co-administration with a buffer, for this youngest group, it would be worthwhile to explore its adjuvant effects on protection.[72] Finally, for children and adults, a simpler vaccine consisting of a single inactivated Hikojima strain that expresses Ogawa and Inaba serotypes is in development.[7,73] As the vaccine includes a single strain, the manufacturing costs would likely be less than for current OCVs. This vaccine, Hillchol, has been shown to be safe in a phase 1/2 trial and non-inferior when compared to Shanchol.[74]

The GTFCC has established a goal to reduce global cholera deaths by 90% and eliminate transmission in 20 countries by 2030, thereby reducing the global burden from cholera until it is "no longer a threat to public health."[75] This strategy is based on early detection and response to outbreaks, a multisectoral approach to prevent case recurrence in high-risk areas, and mechanisms for local and global coordination. Many of the outlined control activities have been known for many decades, but the inclusion of OCVs offers a new and significant opportunity to attain global cholera control.

Disclosure of potential conflicts of interest

No potential conflict of interest was reported by the author.

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