SUPPLEMENT ARTICLE

The Value of and Challenges for Cholera Vaccines in Africa

Lorenz von Seidlein,[1] Mohammad Jiddawi,[2] Rebecca F. Grais,[3] Francisco Luquero,[3] Marcelino Lucas,[4] and Jacqueline Deen[1]

[1]Menzies School of Health Research, Casuarina, Australia; [2]Ministry of Health, Zanzibar, Tanzania; [3]Epicentre, Paris, France; and [4]Ministry of Health, Maputo, Mozambique

The 21st century saw a shift in the cholera burden from Asia to Africa. The risk factors for cholera outbreaks in Africa are incompletely understood, and the traditional emphasis on providing safe drinking water and improving sanitation and hygiene has proven remarkably insufficient to contain outbreaks. Current killed whole-cell oral cholera vaccines (OCVs) are safe and guarantee a high level of protection for several years. OCVs have been licensed for >20 years, but their potential for preventing and control cholera outbreaks in Africa has not been realized. Although each item in the long list of technical reasons why cholera vaccination campaigns have been deferred is plausible, we believe that the biggest barrier is that populations affected by cholera outbreaks are underprivileged and lack a strong political voice. The evaluation and use of OCVs as a tool for cholera control will require a new, more compassionate, less risk-averse generation of decision makers.

Keywords. cholera; vaccine; OCV; Africa; review.

Cholera control programs have traditionally focused on the provision of safe drinking water and improved sanitation. During the 20th century, when the major cholera burden was in tropical Asia, the major breakthrough in the treatment of cholera—oral rehydration therapy—was conceived and evaluated in India and Bangladesh [1–5]. Other cholera control strategies, including health education, routine hand washing, and improved food preparation, helped to contain major outbreaks in Asia, as well as a large cholera outbreak in South America, which started in 1991 in Peru and quickly spread to many neighboring countries [6, 7]. In the 1970s, *Vibrio cholerae* O1 spread to sub-Saharan Africa, and the 21st century has been notable for horrendous cholera outbreaks on the African continent [8]. In July 1994, an estimated 12 000 refugees in the Goma refugee camp of the Democratic Republic of the Congo died of cholera, despite the efforts of international organizations in setting up treatment centers [9]. More recently, from August 2008 to July 2009, cholera spread throughout Zimbabwe and spilled into neighboring South Africa and Mozambique [10]. Aside from these large outbreaks, endemic cholera is widespread, with seasonal outbreaks documented in East, Central, South, and West Africa. Control activities based on the provision of safe drinking water and improved sanitation have failed to contain the spread of cholera, and outbreaks are now common in sub-Saharan Africa. The risk factors for cholera outbreaks in Africa are incompletely understood, and it remains challenging to predict outbreaks reliably [11–15].

Cholera vaccines have evolved from injectable vaccines with side effects and questionable protective efficacy to the current state-of-the-art killed whole-cell oral cholera vaccines (OCVs), which are safe and guarantee a high level of protection for several years. OCVs have been licensed and prequalified for purchase by United Nations agencies since the early 1990s, but they have been mostly ignored for public health purposes and are marketed for affluent tourists who perceive themselves at risk for cholera. The purpose of this article is to review the potential and the obstacles for the use of cholera vaccines on the African continent.

Correspondence: Lorenz von Seidlein, MD, PhD, Menzies School of Health Research, John Mathews Building (Bldg 58), PO Box 41096, Casuarina, NT 0810, Australia (lseidlein@gmail.com).

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CHOLERA VACCINE TYPES

Up to the 1990s, the only available cholera vaccines were made from phenol-killed whole cells of *V. cholerae* O1 organisms and administered by injection as 2 doses given 2 weeks apart. The vaccine offered around 50% protection for a short duration, was associated with painful local inflammatory reactions, and is no longer recommended for use [16]. Parenteral cholera vaccines have been replaced by orally administered vaccines: killed whole-cell vaccines and genetically modified live attenuated vaccines.

Killed Whole-Cell OCVs

The first internationally licensed OCV, Dukoral (Crucell, the Netherlands), contains several *V. cholerae* O1 strains and the recombinant cholera toxin B subunit (WC/rBS). A trial conducted in 90 000 people aged >2 years in Matlab, Bangladesh, between 1985 and 1989 found 85% protection in the first 6 months after vaccination and 50% protection over the 3-year follow-up period [17]. A reanalysis of this trial in 2005 discovered that a high level of protection against cholera was conferred by the vaccine, even among people who had not been vaccinated but lived in communities with high vaccine coverage [18]. The WC/rBS vaccine has been assessed in several African settings. The effectiveness of the WC/rBS vaccine was evaluated following a large mass vaccination campaign in Beira, Mozambique, in 2004 [19]. Using a case-control approach, the investigators found that the vaccine afforded about 80% protection in the year after the vaccination campaign. The findings from Mozambique are of particular importance for 2 reasons. First, the circulating *V. cholerae* strains in the setting were genetic variants of the El Tor strain, with a classic *V. cholerae* toxin cassette [20]. Second, the prevalence of human immunodeficiency virus (HIV) infection in Beira was very high, as indicated by the 20%–30% prevalence among women of child-bearing age [21]. The results from the Mozambique study showed that the WC/rBS vaccine protected against this new variant *V. cholerae* strain, which is spreading throughout Africa, even in environments with a high HIV prevalence. Subsequently, the feasibility of mass vaccination campaigns was evaluated in Aceh, Indonesia, following the Asian tsunami, in 2004, and in a refugee camp in Darfur, western Sudan. These studies demonstrated that mass vaccination campaigns with the WC/rBS vaccine can be successfully completed in complex emergencies [22]. In the beginning of 2009, a mass vaccination campaign with the WC/rBS vaccine, conducted in Zanzibar, found protection similar to that in the earlier study in Mozambique. The study in Zanzibar suggested that, in addition to direct protection of vaccinated individuals, the vaccine also afforded herd immunity to nonvaccinated people, similar to the Matlab trial. A distinct disadvantage of the WC/rBS vaccine is its high price, which is due at least in part to the production cost of the recombinant B subunit and the need for a buffer.

The next generation of killed whole-cell OCV no longer contains WC/rBS. The first of these new vaccines was produced in Vietnam, following a technology transfer from Sweden to VaBiotech, Vietnam [23]. The Vietnamese vaccine producers replaced several of the original *V. cholerae* strains and added the O139 strain, resulting in a bivalent vaccine containing *V. cholerae* O1 and O139. Field testing of the Vietnamese vaccine protected 66% of recipients for 10 months after vaccination [24]. The vaccine was licensed in Vietnam and widely used in the country's public health program to control cholera —the only country to create such a program. The vaccine was not prequalified for purchase by United Nations agencies. During the last decade, the Vietnamese vaccine production protocol was slightly revised, and its technology was transferred to an Indian vaccine producer (Shantha Biotechnics, Hyderabad, India). A large, 3-year field trial of this Indian vaccine, Shanchol, in Kolkata, India, found that the vaccine was safe and afforded 66% protection [25]. Shanchol received prequalification for purchase by United Nations agencies in September 2011. The second-generation killed whole-cell OCVs have 2 advantages over the first-generation WC/rBS vaccine: affordability and ease of administration. Shanchol is sold for $1.85 per dose, while Dukoral is sold to the public sector for $4.70 or more per dose [26] (Table 1).

The Chinese vaccine producer Shanghai United Cell Biotechnology also produces a WC/rBS vaccine, OraVacs, which has been licensed in China and the Philippines [30]. Reports on the safety and efficacy of this vaccine have yet to be published in peer-reviewed international journals. In contrast to the products listed above, OraVacs does not have to be reconstituted because it is formulated as an enteric coated capsule. The vaccine has been made available to the Chinese government for emergencies, such as the earthquake that affected eastern China in May 2008 [31]. Considering the increasingly prominent role of China in Africa, a broader use of this vaccine in African settings could become possible. Evaluation of the safety and protection afforded by OraVacs according to international good clinical practices standards is highly desirable prior to widespread use.

Live Attenuated OCV

In addition to the killed whole-cell OCVs, a genetically modified live attenuated OCV, CVD 103-HgR, has been licensed. The vaccine was safe and afforded promising protection in North American volunteers [32] but was likely underpowered to show protection during any of the 4 years of follow–up in a large trial in Jakarta, Indonesia [33]. The vaccine, Orachol or Mutachol, was used in a mass vaccination campaign in Micronesia, where a retrospective case-control study estimated 79% protection [34]. The vaccine is administered as a single dose with a buffer. Production of the vaccine was stopped by the producer (Crucell, Switzerland), most likely because of business

Table 1. Comparison of 2 Currently Licensed Oral Cholera Vaccines (OCVs)

Characteristic	Whole-Cell rBS OCV	Killed Whole-Cell OCV
Trade name	Dukoral	Shanchol
Composition [1, 2]	• *V. cholerae* O1 Inaba classic strain, heat-inactivated vibrios • *V. cholerae* O1 Inaba El Tor strain, formalin-inactivated vibrios • *V. cholerae* O1 Ogawa classic strain, formalin-inactivated vibrios • *V. cholerae* O1 Ogawa classic strain, heat-inactivated vibrios • Recombinant *V. cholerae* toxin B subunit 1 mg	• *V. cholerae* O1 Inaba classic strain Cairo 48, heat-inactivated vibrios • *V. cholerae* O1 Inaba El Tor strain Phil 6973, formalin-inactivated vibrios • *V. cholerae* O1 Ogawa classic strain Cairo 50, formalin-inactivated vibrios • *V. cholerae* O1 Ogawa classic strain Cairo 50, heat-inactivated vibrios • *V. cholerae* O139 strain 4260B, heat-inactivated vibrios
Producer	Crucell, a subsidiary of Johnson and Johnson	Shanta Biotechnics, a subsidiary of the Sanofi group
Buffer requirement	Yes, to stabilize the B subunit	No
Efficacy [3]	60% efficacy over 2 y	67% vaccine efficacy over 3 y
Price [3]	$4.70/dose (discounted for public health use/ emergencies)	$1.85/dose
Dosing	• 2-dose requirement for individuals aged ≥5 y • 3 doses for children aged <5 y	2-dose requirement
Minimum age	≥2 y	≥1 y
Administration during pregnancy	No data; thus, not recommended	No data; thus, not recommended
WHO prequalified	Yes	Yes

Data are from [27, 28, 29].

Abbreviations: rBS, recombinant cholera toxin B subunit; *V. cholerae, Vibrio cholerae*; WHO, World Health Organization.

considerations. PaxVax, of Menlo Park, California, is working toward the reintroduction of an improved, new-generation version of CVD 103-HgR [35].

In addition to the licensed OCVs mentioned above, there are several promising vaccine candidates in development. Genetic modification of *V. cholerae* O1 El Tor strains isolated in Peru has resulted in the vaccine candidate Peru 15. Current phase 2 studies suggest that it has a promising safety and immunogenicity profile [36]. Other candidates, such as *V. cholerae* 638, VA 1.3, and IEM 108, are currently undergoing clinical evaluation [37–40].

USE OF VACCINES IN CHOLERA EPIDEMICS AND CHOLERA-ENDEMIC SETTINGS IN AFRICA

In general cholera comes in two varieties in Africa: (1) an endemic distribution, with seasonal variations and peaks every 1–3 years that result in a steady flow of hospital admissions; and (2) an acute-onset epidemic distribution, which may affect hundreds of thousands of individuals at the same time and overwhelm existing healthcare systems. The latter distribution tends to occur in areas with infrastructure breakdown, such as Haiti and Zimbabwe, and often where cholera has been absent for many years, resulting in a large pool of susceptible individuals.

In settings where cholera is endemic, improvements in infrastructure—specifically, drinking water supply and sanitation—are the long-term solutions, but in the medium term, vaccines could reduce the cholera burden. Endemic cholera tends to be highly heterogeneous in distribution, sparing certain communities. Ideally, vaccination campaigns would target geographically well-defined high-risk areas. In practice, it is very difficult to identify such hot spots. Furthermore, targeting high-risk groups and withholding the vaccine from other population groups can result in political tension. Thus, it is more promising to vaccinate the affected areas, with a wide safety margin, or to vaccinate the whole city.

In areas of cholera epidemics, the priority is to reduce cholera-related deaths, and the focus of outbreak response is to ensure proper case management. At the extreme end of the spectrum are outbreaks such as that in Zimbabwe, during 2008–2009, which resulted in 98 591 cases and 4288 deaths [10]. In the Haiti outbreak, which began in 2010, 515 699 cases have been reported, with 6942 deaths by November 2011 [41]. In both instances, a combination of critical factors provided the ideal conditions for continued propagation of the outbreak, including the prolonged deterioration of infrastructure. Both areas had large cholera-naive populations, a health system unprepared to respond to the outbreak, and the introduction of a highly infectious strain of *V. cholerae*. The intense effort in providing proper treatment and the classic prevention strategies—provision of safe drinking

water and improved sanitation and hygiene—were insufficient to avoid a high increase in mortality in these countries. It may have been possible to contain outbreaks through a reactive mass vaccination campaign. We calculated that, for a large outbreak like the one in Zimbabwe, 40% of cases and deaths could be prevented if the risk for a large outbreak is recognized early and a vaccination campaign is executed with reasonable speed [42]. Clear advantages of reactive vaccination campaigns are a highly motivated population and the assurance of political support, which are likely to result in high vaccine coverage. In October 2009, the Strategic Advisory Group of Experts advised the World Health Organization to consider reactive vaccination campaigns in response to large cholera outbreaks [43].

OCVs have been considered useful tools for avoiding outbreaks in complex emergencies. The cholera outbreak in Goma, in 1994, showed the catastrophic consequences of cholera outbreaks in such contexts. But not all areas of disaster are affected by cholera. Models to predict cholera outbreaks tend to be based on climate, the presence of endemic cholera cases, and poor water supply and sanitation and can be quite sensitive yet not specific [13, 15, 44]. Frequently, one critical variable, the size of the susceptible population, is unknown. Individuals in many at-risk locations would have to be preemptively vaccinated to prevent a limited number of actual outbreaks. Mass vaccination campaigns require large amounts of resources that, consequently, will not be available for other healthcare services. The value of preventive mass vaccination campaigns will be difficult to predict until sensitive and specific tools for risk assessment have been developed.

STOCKPILING CHOLERA VACCINES

To contain large outbreaks of cholera, a large number of immediately available OCV doses will be required. Scaling up production takes 1–3 years and depends on the commitment of prospective buyers. The international community has long delayed putting in place a mechanism to ensure the availability of cholera vaccines when needed. The epidemiology of cholera is not unique: cases of meningococcal meningitis and yellow fever also tend to occur as epidemics. For the latter diseases, the international donor community has established large stockpiles of vaccines [35]. Both stockpiles make use of revolving vaccine doses managed by 4 partners, UNICEF (the United Nations Children's Fund), Médecins Sans Frontières, the International Federation of Red Cross and Red Crescent Societies, and the World Health Organization, through an international coordinating group. When a country requests vaccines, the coordinating group promises to come to a decision within 48 hours and to deliver the vaccine within a maximum period of 7 days. The decision whether to approve a request is based on predetermined criteria: epidemiological evidence for an outbreak, which includes laboratory confirmation; availability of an action plan for mass vaccination; and adequate storage conditions. There is an urgent need for a similar cholera vaccine stockpile [45]. Much can be learned from the experience of running the meningitis vaccine and yellow fever vaccine stockpiles, which have been in existence since 1997 and 2001, respectively. In addition to the similarities between meningococcal disease, yellow fever, and cholera, there are differences, not least in the risk groups. Considering the vulnerability of the populations at risk for cholera, there is a need to ensure equitable access to vaccines and to minimize the potential for implementing organizations to abuse the process. Major challenges for the meningitis and yellow fever vaccine stockpiles involve how to ensure continued financing for the stockpile program and how to use vaccines with limited remaining shelf life if no requests for them have been made during the year. Cholera vaccines that have not been used in outbreaks and approach the end of their shelf-life could be used for disease control in cholera-endemic settings.

BARRIERS TO USING CHOLERA VACCINES IN AFRICA: LOGISTICS AND OTHER CONSIDERATIONS

The single biggest barrier to the use of cholera vaccines could be the financial investment required to vaccinate millions of people. But cost has not prevented widespread use of other vaccines. Large mass vaccination campaigns are major logistical undertakings, a further barrier against the widespread use of cholera vaccines. The success of a mass vaccination campaign is measured in terms of the vaccine coverage achieved by the vaccination team. Cholera mass vaccination campaigns cannot rely on a preexisting infrastructure because in most cases it is the very absence of an infrastructure that has resulted in an outbreak. While vaccination campaigns in cholera-endemic settings are challenging, reactive vaccination campaigns are a daunting task even for hardened logisticians. The healthcare system is already stretched, and the most experienced staff who, under normal circumstances, would work on a vaccination campaign are either treating cholera cases or have been affected by the disease. A major reason why cholera vaccines have found so little public health use are these technical barriers [46]. In the past, the World Health Organization has failed to support or has advised against the use of cholera vaccines, citing a catalogue of technical arguments [46, 47]. It seems likely that a list of these arguments will be rolled out each time a mass vaccination campaign is considered. We believe that a closer look at these technical barriers of a reactive mass oral cholera vaccination campaign is necessary.

Water Provision and Cholera Treatment Measures Take Priority Over Vaccination

There should never be a competition between mass vaccinations and safe drinking water and sound sanitation. Experience in recent decades has amply demonstrated that activities to

procure safe drinking water and improve sanitation are insufficient to prevent cholera on the African continent. Cholera vaccinations should by no means replace safe drinking water and sound sanitation. Instead, vaccination campaigns must be included among efforts to improve the supply of safe drinking water and sound sanitation.

Convincing Modeling Data on the Benefit of Vaccination Campaigns Are Nonexistent

Models have to make assumptions. To predict the benefit of mass vaccination campaigns, it is essential to know not only the peak but also the duration of an outbreak, which is highly variable. From our knowledge, it is impossible to predict (during the early days of an outbreak) the characteristics of the entire epidemic curve and, thus, the overall number of cases and deaths preventable by early mass vaccination campaigns. Estimating the benefit of a mass vaccination campaign is only possible with hindsight.

Mobile Populations Cannot Be Relied on to Take 2 Doses

The uptake of the second dose of cholera vaccine is likely to be determined by the ease of vaccine access and the level of motivation of the participant. If the participants understand that 2 vaccine doses are required to confer immunity and know that they are at high risk for cholera, a high uptake of the second dose is quite likely. In a recent mass vaccination campaign in Zanzibar, 86% of the campaign participants (23 921/27 678) who received the first dose also received the second dose. The corresponding percentage in Mozambique was 78% [19].

Immunity Is Not Generated Until 1 Week After the Second Dose

This argument is frequently followed by the suggestion to wait until a single dose becomes available. A single dose prevents significantly more cases during very short cholera outbreaks, for which the use of mass vaccination campaigns may be questionable in the first place. During extended large outbreaks, such as those in Zimbabwe and Haiti, a delay in full immunity by 2 weeks would make an insignificant difference in the number of cases prevented [42]. Research is ongoing to understand the short-term effectiveness of a single dose of Shanchol.

Logistics Are Challenging in Settings of Inadequate Infrastructure and Human Resources

The logistical challenges of mounting a cholera vaccination campaign can be daunting. But the logistical challenges associated with a reactive influenza mass vaccination campaign will also be of an enormous scale. Yet nobody has suggested withholding mass influenza vaccination campaigns because of logistical challenges. The difference between cholera and influenza vaccination campaigns is not the scale of the logistical challenge but the absence of vigorous advocacy for populations at risk for cholera.

Cold-Chain Requirements Cannot Be Met

There is no absolute requirement for the refrigeration of OCV containing killed whole-cell bacteria. Stability tests with Shanchol have indicated that the vaccine can remain outside the cold chain at temperatures up to 37°C for 21 days, although this information is not included in the label [35]. It should be noted that other vaccines, including the universally used vaccines in the World Health Organization's Expanded Programme on Immunization, require refrigeration.

Vaccine Is Too Bulky for Transport

The storage space for 100 000 single doses of cholera vaccine is 9 m^3, but the storage requirement is much smaller for multiple-dose vials [35]. The provision of the vaccine via multiple-dose vials will reduce the storage requirements considerably.

Clean Water Is Needed for the Buffer

The second-generation OCVs, such as Shanchol or the Chinese OraVacs vaccine, do not require the use of a buffer.

Public Response to the Vaccination Campaign Cannot Be Predicted During Civil Unrest

In every community, a small fraction of the population refuses to participate in mass campaigns, irrespective of the intervention. In Mozambique and Zanzibar, people residing outside the targeted areas travelled to vaccination centers, suggesting that, at the other end of spectrum, there is a population of highly motivated individuals who will actively seek to be vaccinated. The shape of the resulting response curve depends on the sensitization campaign preceding the vaccination campaign and on the perception of risk by the population. If the target population is adequately educated about the characteristics of the vaccine and each individual knows $\geq$1 person with cholera, a very high coverage is virtually assured.

Vaccination Campaigns Are Not Cost-effective

Last, concerns about the cost-effectiveness of cholera vaccination campaigns must be addressed. There is a lack of data on the economic benefits of OCVs in severe outbreaks, although their cost-effectiveness in cholera-endemic settings has been demonstrated [48, 49]. A more recent analysis concluded that the use of OCVs is very cost-effective in Africa, regardless of whether herd immunity was taken into account [26]. It is important to keep in mind that the damage to the local economy caused by large cholera outbreaks is compounded by a negative impact on tourism and food, especially seafood exports. This larger economic damage tends to be overlooked in cost-effectiveness studies. Most importantly, we believe that anyone who has lived through the agonizing indignities of a cholera attack, especially one that occurred during a cholera outbreak, would without hesitation dismiss the argument that cholera vaccines may not be cost-effective.

CONCLUSION

The continent most affected by cholera is no longer Asia but Africa and *V. cholerae* has adapted to the new environment. A variant strain of *V. cholerae* O1, El Tor, has successfully spread through the African continent, while control methods have remained the same. The results have been catastrophic, as illustrated by recent massive cholera outbreaks. Yet the international donor community has steadfastly refused to purchase and deploy safe and effective OCVs, even in the face of thousands of deaths in very large outbreaks. Each item in the long list of technical reasons why mass vaccination campaigns have been deferred is plausible—not for one second do we want to belittle the massive challenges of mass vaccination campaigns. But if a catastrophic situation similar to a large cholera outbreak occurred among more-privileged groups, a much more aggressive response from the international community would be likely. The main reason why cholera vaccines have not been used in Africa and countries like Haiti 20 years after they have been licensed and shown to be effective is that people affected by cholera outbreaks are underprivileged, even by the standards of impoverished populations. The evaluation and use of OCVs as a tool for cholera control will require a new, more compassionate, less risk-averse generation of decision makers.

Note

Potential conflicts of interest. All authors: No reported conflicts.

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