Background Paper on the Integration of Oral Cholera Vaccines into Global Cholera Control Programmes

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Executive Summary

Cholera is a rapidly dehydrating watery diarrheal disease transmitted through water or food contaminated with the bacterium, *Vibrio cholerae* O1 (or less frequently, O139), primarily in areas with poor access to safe drinking water and adequate sanitation. If not treated with intravenous or oral rehydration, the disease can lead to death within 24 hours.

The cholera disease burden consists of both cholera outbreaks – including large, explosive epidemics, such as occurred in Zimbabwe in 2008/09 – and endemic cholera. While epidemic cholera attracts most of the attention and accounts for most of the cases reported to WHO each year, endemic cholera continues to exact an unacceptable toll in large parts of South and Southeast Asia, as well as in Africa. The disease is greatly under-reported to WHO, due to inadequate disease surveillance and reporting, fear by countries of the macro-economic impact of cholera reports on trade and tourism, poor access to health services among the very poor and marginalized populations – who are most at risk, among other factors. Therefore, while less than 250,000 cases and 2,000-6,000 deaths have been reported each year to WHO during this decade – mostly from Africa, it is estimated that the actual annual incidence is ≈3-5 million cases and 100,000-130,000 deaths.

The provision of safe drinking water (including “point-of-use” water disinfection and safe storage methods at the household level) and adequate sanitation, along with health education, food safety measures, and strong disease surveillance remain the mainstays of preventing both endemic and epidemic cholera. However, water and sanitation improvements require very large investments and therefore will not likely reach large, poor populations in Africa and Asia, such as those living in slums and remote rural areas, in the foreseeable future. And while the oral rehydration therapy (ORT), along with IV rehydration, can reduce cholera case fatality from around 20% in a good health facility to less than 1%, if patients receive prompt and appropriate treatment, cholera case fatality rates remain high (e.g., >4%) in many countries, especially in Africa, even among patients who reach a treatment center.

Two oral cholera vaccines became available in the 1990s and have shown to have strong safety profiles. The killed whole-cell B subunit (WC-rBS) vaccine, sold as Dukoral® and licensed in persons two years and older, is administered in two doses given one to two weeks apart (three doses for 2-5 year olds) and contains a buffer that is mixed with the vaccine in water. The vaccine, which has been WHO pre-qualified since 2001, conferred 85% protection for four to six months and ≈60% protection at two years of follow-up in a large clinical trial in Bangladesh, with dwindling protection after two years and shorter term protection in children less than six years old. The live attenuated CVD 103-HgR vaccine is provided in a single dose for persons two years and older, also mixed with a buffer in water. The vaccine, sold as Orochol®, was licensed as a traveler’s vaccine on the basis of challenge studies in U.S. volunteers, but it failed to show protection in a large efficacy trial conducted in a cholera-endemic population in Indonesia. The manufacturer stopped production of the vaccine voluntarily in 2004, due to business considerations.

The development of these oral cholera vaccines and a study demonstrating the feasibility of vaccination using Dukoral® in a refugee population in Uganda prompted WHO in a Position Paper in 2001 to issue recommendations for the pre-emptive use of oral cholera “for high-risk populations [including refugees in crowded camps and residents of urban slums] in conjunction with other prevention and control measures.” Despite these recommendations and additional calls for the use of cholera vaccines in “certain endemic and epidemic situations” during WHO meetings of experts in 2002 and 2005, their use is largely limited to travelers in developed countries. No developing country has yet introduced oral cholera vaccines to control endemic or epidemic cholera, except for Vietnam, which conducts yearly vaccination campaigns in high-risk areas.
New developments and trends in the epidemiology of the disease; the development of a lower-cost cholera vaccine developed specifically for use in developing countries; as well as recent evidence of the continual disease and economic burden of cholera and the effectiveness, feasibility and cost-effectiveness of oral cholera vaccination in both endemic and crisis situations make this an opportune time for the SAGE to revisit, update and strengthen the recommendations for the use of oral cholera vaccines.

Recent developments, trends and evidence regarding the disease burden and epidemiology of cholera

Major new developments and data concerning cholera include the following:

- Recent population-based prospective disease surveillance studies reveal the continued high incidence of cholera in several sites in Asia and Africa (up to 4/1,000 per year), with the highest rates by far in children under five years of age (up to 9/1,000 per year).

- Cholera epidemics in sub-Saharan Africa are becoming more frequent, larger and longer-lasting (e.g., 11 months for the 2008/09 Zimbabwe epidemic and 15 months for the 2006/07 outbreak in Angola), with persistently high overall case fatality rates of 4% or more. The disease is also spreading to more countries and becoming more entrenched as endemic disease on the continent. These trends suggest that vaccination, even with a two-dose vaccine, should be considered in countries experiencing ongoing cholera outbreaks.

- New variant strains of *V. cholerae* O1 El Tor that produce the classical cholera toxin are replacing the original El Tor in parts of Africa and Asia and evidence suggests that these new strains cause more clinically severe disease.

- High rates of antibiotic resistant strains of *V. cholerae*, including multi-drug resistant strains, have been found to be common in the highly-endemic countries of Bangladesh and India. These include strains with reduced sensitivity to ciprofloxacin, which is used as the drug of choice in areas where resistance to first-line antibiotics is common. Antibiotic resistance, which can fluctuate unpredictably in countries, can increase the duration of the illness, complicate treatment, and increase treatment costs.

- There is growing concern that increases in water temperatures and in sea levels, due to global climate change, will increase the risk of cholera, since coastal and brackish water in warm climates are important reservoirs of toxigenic forms of *V. cholerae*.

- New evidence of the economic burden of cholera include cost-of-illness estimates from field studies in Asia and Africa – showing average costs of hospitalized cases ranging from $27-208 and a substantial burden of costs borne by patients and their families – as well as estimated macro-economic costs from losses in food exports and tourism that can be substantial.

New developments and data regarding oral cholera vaccines

A new killed whole-cell bivalent (O1/O139) cholera vaccine without the B subunit of the cholera toxin (“whole-cell only”) has been developed by modifying a vaccine produced locally in Vietnam. The new vaccine, developed specifically for use in developing countries, is administered in two doses given two weeks apart, but requires no buffer or water, and is thus easier to administer in developing country settings. Because it lacks the B subunit, it is also relatively low cost to produce. At the same time, the
vaccine meets good manufacturing practice (GMP) standards and WHO guidelines for the production of oral killed whole-cell-based cholera vaccines. The vaccine was licensed in India in 2009 for persons one year and older, and the producer has applied to WHO for pre-qualification of the vaccine to allow its purchase by UN agencies.

The modified whole-cell only vaccine (Shanchol™), which contains the same mix of *V. cholerae* O1 strains as Dukoral®, but has double the LPS content and also contains O139 whole cells, was shown in Phase I/II trials in Vietnam and India to induce strong immune responses in adults and children. It is now being evaluated in a randomized placebo-controlled trial involving more than 67,000 children and adults. Interim results show a protective efficacy rate of 67% against *V. cholera* O1 over two years of follow-up and sustained protection for at least two years. Estimates of protection over three years will be analyzed in late 2009.

A number of studies of oral cholera vaccines have been conducted since the 2001 WHO Position Paper to inform their use in both endemic and post-crisis situations. These include the following:

- The first demonstration project using an oral cholera vaccine (Dukoral®) in a cholera-endemic setting in Africa (Beira, Mozambique) showed the feasibility of cholera vaccination using a two-dose vaccine and considerable demand for the vaccine in this population.

- A case-control study conducted following the demonstration project in Beira revealed a protective efficacy rate of 84% over five months – the first evidence of its protection in an African population with a high prevalence of HIV, and the first evidence of its effectiveness against a new variant strain of *V. cholerae*.

- Cholera vaccination using Dukoral® in two post-crisis situations (Darfur, Sudan and Aceh, Indonesia following the tsunami) has been shown to be feasible and well-accepted by the populations – with overall coverage rates of 69-88% for two doses, although the logistical requirements of the vaccine posed some challenges in these situations.

- A re-analysis of data from the original trials of oral killed whole-cell-based cholera vaccines (Dukoral® and a whole-cell only version) conducted in Bangladesh in the 1980s revealed strong herd protection from the vaccines. These herd effects, which also provided protection to children too young to be vaccinated (<2 years of age), could substantially increase the public health impact of oral cholera vaccines.

- A new analysis of the cost-effectiveness of cholera vaccination, assuming use of the new whole-cell only vaccine and a price/dose of $1.00, and based on site-specific epidemiological and economic data, shows vaccination of children to be “very cost-effective” in high incidence endemic areas when herd effects are taken into account.

The *ad hoc* Cholera Vaccine Working Group has proposed criteria for the performance and characteristics of cholera vaccines for use in public health settings in developing countries. These criteria include an efficacy rate of at least 50% at two years of follow-up, a maximum of two doses for initial vaccination, and effectiveness in children from the age of two years. Both oral killed whole-cell-based vaccines (Dukoral® and Shanchol™) meet these criteria, while the old injectable killed vaccine, which provided 50% protection for only three to six months, does not.

Several cholera vaccines are under development, including oral live attenuated vaccines to be given in a single dose and that have the promise of providing greater and longer-term protection than the current vaccines. However, the most advanced candidates are at least five to ten years away from
becoming available. Therefore, the Working Group recommends that the currently-available two-dose killed whole-cell-based vaccines be used now to control endemic cholera and to be considered for use in areas at risk for cholera outbreaks. To guide vaccine policy, the Working Group has proposed the following practical definition of endemic cholera: the occurrence of fecal culture-confirmed cholera diarrhea in a population in at least three of the past five years.

Proposed Recommendations

General:

1. Given the current availability of two oral cholera vaccines (one pre-qualified and the other pending pre-qualification) and new data on their efficacy, field effectiveness, feasibility and acceptance in cholera-affected populations, immunization using these vaccines should be used in areas with endemic cholera and should be considered for use in areas at risk for cholera outbreaks, in conjunction with other cholera prevention and control strategies.

2. Vaccination against cholera should be considered as synergistic and not in competition with water and sanitation improvements and other traditional means of controlling cholera.

3. WHO should prioritize the evaluation for pre-qualification of the modified whole-cell only vaccine and other future cholera vaccines as they become available.

4. While specific cholera surveillance studies are not recommended for every country and setting, it is strongly recommended that surveillance for microbiologically-confirmed cases of cholera be instituted (e.g., via regional or sub-regional networks) to measure the burden of disease and impact of vaccination and other interventions.

Control of endemic cholera:

5. Specific cholera vaccination strategies regarding whether, when, where and how to vaccinate against cholera should not be prescribed to countries, since the appropriate strategies will differ by country, depending on its epidemiological pattern of cholera, capacity of the immunization program and health system, and other local factors. The ad hoc Working Group instead suggests that countries consider the following options for strategies to control endemic cholera through vaccination:

   - **Scope of vaccination:** Universal vaccination (throughout a country) is not warranted in most countries, with some exceptions. Therefore, cholera vaccination can primarily be targeted to high-risk areas and populations.

   - **Where to vaccinate:** Vaccination should be targeted to areas where two of the following criteria are met: a) culture-confirmed cholera has been detected in at least three out of the last five years; b) an incidence rate of cholera of at least 1/1,000 in any of these years has been recorded; or c) if population-based incidence rates are not available, high-risk areas or groups have been identified, based on information collected from local public health officials.

   - **Age groups to target:** Although all age groups are vulnerable to cholera, priority should be given to high-risk groups, if resources are limited. The primary targets for cholera vaccination in many countries will therefore be pre-school and school-aged children. Other groups that are especially vulnerable to severe disease and for which the current vaccines are not
contraindicated, can also be targeted, such as pregnant women and HIV-infected individuals. Countries should also consider vaccination of older age groups if funding is available.

- **Vaccine delivery strategies**: Periodic mass vaccination campaigns are usually the most practical option for delivering oral cholera vaccines. Schools, religious institutions and other community settings can be appropriate venues for vaccination campaigns. Incorporating cholera vaccination into routine vaccination schedules can be an alternative or complementary strategy to mass vaccination campaigns (for instance, to reach young children between campaigns).

- **Frequency of vaccination**: Since the documented duration of significant protection for the currently-available oral cholera vaccines is two years, it is currently recommended that initial vaccination with two doses be followed by revaccination every second year. Once data on the longer-term efficacy of any oral cholera vaccine becomes available, the recommended interval between initial and booster vaccinations could be extended.

**Control of cholera outbreaks:**

6. Pre-emptive vaccination should be considered by local health authorities to help prevent potential outbreaks or the spread of current outbreaks to new areas.

7. The development of predictive risk assessment tools to help countries determine when pre-emptive cholera vaccination could be used is an urgent need and should be made available and field-tested as soon as possible.

8. Given recent large prolonged outbreaks of cholera (e.g., in Angola and Zimbabwe), reactive vaccination could be considered by local health authorities as an additional control measure, depending on the local infrastructure and following a thorough investigation of the current and historical epidemiological situation and a clear identification of geographical areas to be targeted. Given the lack of experience with reactive vaccination against cholera, the feasibility and impact of vaccination in halting ongoing outbreaks should be documented and widely disseminated.

9. Appropriate treatment of cholera cases, water and sanitation interventions, and community mobilization should remain the mainstays of control measures during ongoing cholera epidemics.

10. Pre-emptive or reactive cholera vaccination should cover as many people eligible to receive the vaccine as possible (e.g., ages ≥ 1 or 2 years, depending on the vaccine), and should be conducted as quickly as possible.

11. Vaccination should not disrupt the provision of other priority health interventions to control or pre-empt cholera outbreaks.

**Research needs:**

12. Further research is recommended in a number of areas to guide policy for the use of oral cholera vaccines, including improved methods of cholera surveillance, operations research to evaluate different vaccination strategies, the testing of reactive vaccination using the currently available oral killed whole-cell-based vaccines to evaluate its impact and feasibility in halting ongoing outbreaks, and research to improve the logistics of using oral cholera vaccines (e.g., new formulations). Suggested research needs are listed in Section VII.
I. Introduction

Key Points:

1. WHO recommended in a 2001 Position Paper that the pre-emptive use of oral cholera vaccines for high-risk populations, e.g., in crowded refugee camps and urban slums, should be considered to complement the provision of safe water, sanitation and other control measures. Reactive vaccination, once an outbreak has begun, was not recommended.

2. In WHO meetings of experts in 2002 and 2005, pre-emptive cholera vaccination was again recommended “in certain endemic and epidemic situations” to complement other control strategies. Recommendations were also made to strengthen cholera surveillance; define cholera endemicity; conduct a series of studies to determine the feasibility, best timing for and impact of vaccination; and develop low-cost cholera vaccines.

3. Only one country (Vietnam) has to date introduced oral cholera vaccines into its immunization program to control endemic or epidemic cholera.

4. Since 2001, concerns within WHO and the global health community about cholera have grown, due to the advent of large, protracted outbreaks in several countries; the emergence of new variant El Tor strains of V. cholerae O1, which appear to cause more clinically severe disease; and the growing incidence of antibiotic resistance.

5. A new, low-cost oral killed “whole-cell only” cholera vaccine that meets WHO guidelines for the production of killed whole-cell-based cholera vaccines and GMP requirements, has been licensed, and application for WHO pre-qualification of the vaccine has recently been submitted.

6. New data have also become available on the disease and economic burden of endemic cholera; the feasibility, acceptability, effectiveness and herd protective effects of oral cholera vaccination; and the demand for and cost-effectiveness of cholera vaccines.

7. These new developments and data make this an opportune time for the WHO SAGE to revisit and update its recommendations for the use of oral cholera vaccines.

Cholera is a rapidly dehydrating watery diarrheal disease that can lead to death in less than 24 hours if untreated, making it, “one of the most rapidly fatal infectious illnesses known” [1]. The disease, transmitted through water or food contaminated by one of the two serogroups of the bacterium Vibrio cholerae (O1 and O139), proliferates in areas where populations have poor access to safe drinking water and sanitation, as a result of poverty (e.g., in urban slums), war and other crisis situations (e.g., in crowded refugee camps).

WHO and the global health community have voiced increasing concerns about cholera in recent years, due especially to the growing number and frequency of large cholera outbreaks with case fatality rates (CFRs) as high as 30% in under-served parts of certain countries, especially in sub-Saharan Africa [2]. According to WHO, “almost every developing country is facing either a cholera outbreak or the threat of an epidemic” [3, p. 305/6]. The prolonged epidemic in Zimbabwe, as well as other recent large,
protracted outbreaks in Angola, Ethiopia, Sudan, Somalia, Northern Vietnam and elsewhere, bring these concerns to the forefront. The epidemic in Zimbabwe lasted around 11 months and spread to all of the country’s provinces, as well as to Zambia and South Africa. As of July 27, 2009, 98,592 cases and 4,288 deaths have been reported, for a case fatality rate of 4.3%.

According to WHO, “concerns are heightened for the growing proportion of vulnerable populations living in unsanitary conditions who are at risk for outbreaks of cholera and other epidemic-prone diarrhoeal diseases. The high number of verified outbreaks and high CFRs reported suggest the activities to control cholera should be strengthened.” [4]. Concerns about cholera have also been heightened in recent years due to the emergence of new, apparently more virulent variant strains of V. cholerae O1 that now predominate in parts of Africa and Asia; the spread and unpredictable emergence of antibiotic resistant strains; and the potential increase in cholera outbreaks due to rising sea levels and water temperatures resulting from climate change, since brackish water and estuaries are natural reservoirs of V. cholerae. Furthermore, while cholera outbreaks attract most of the attention, endemic cholera continues to exact an unacceptable toll in large parts of South and Southeast Asia, as well as in Africa. Thus, while 178,000 – 237,000 cases and 4,000 – 6,300 deaths from epidemic and endemic cholera have been reported each year to WHO in the past three years, the actual disease burden has been estimated to be 3-5 million cases and 100,000 – 130,000 deaths per year [5,6].

Two oral cholera vaccines became available internationally in the 1990s: 1) a two-dose vaccine consisting of killed whole cells of V. cholerae O1 (including classical and El Tor biotypes and Inaba and Ogawa serotypes) and the B subunit of the cholera toxin (WC-rBS), produced by SBL Vaccin in Sweden13 and sold as Dukoral®; and 2) a single-dose live attenuated vaccine derived from the classical Inaba 596B strain (CVD 103-HgR), produced by Berna Biotech (now Crucell) and sold as Orochol® or Mutacol®. Both were licensed in a number of developed countries as travelers’ vaccines. However, a feasibility study using the WC-rBS vaccine preemptively in a stable refugee population in Uganda in 1997 demonstrated that cholera vaccination was feasible and acceptable in this setting. WHO subsequently recommended in a meeting in 1999 and in a Position Paper on Cholera Vaccines in 2001 the pre-emptive use of oral cholera vaccines “for high-risk populations, [including refugees in crowded camps and residents of urban slums] in conjunction with other prevention and control measures.” [1]. Dukoral® has since been pre-qualified by WHO and has been used pre-emptively in some crisis situations (e.g., in Darfur, Sudan and Aceh, Indonesia) with WHO assistance, but it has not been readily adapted by the international health community due to its high cost, as well as its two-dose regimen and the need for a buffer, both of which may pose logistical challenges in difficult crisis situations. The CVD 103-HgR vaccine, which was licensed on the basis of challenge studies in U.S. volunteers, failed to demonstrate protection in a large trial in a cholera-endemic population in Jakarta, Indonesia in the late 1990s. While it provided an estimated 79% protection during a cholera outbreak in Micronesia in 2000, as assessed in a non-blinded retrospective analysis, its producer suspended manufacture of the vaccine in 2004, due to limited market potential.

No country has yet introduced oral cholera vaccines to control endemic or epidemic cholera, with the exception of Vietnam, which, following technology transfer from Sweden, has produced a low-cost, killed “whole-cell only” vaccine (without the cholera toxin B subunit) for use in high-risk populations since 1997. Among the reasons commonly cited for the lack of uptake of cholera vaccines in cholera-affected countries are the unknown and unappreciated cholera disease burden in many countries; the moderate levels and duration of protection of oral cholera vaccines; the relatively high cost of the one vaccine available internationally (Dukoral®); the preference among some policymakers for water and sanitation improvements over vaccination to prevent cholera and other enteric diseases; the existence of oral and intravenous rehydration therapy, which if used broadly and correctly, can significantly reduce

13 Now Crucell/SBL Vaccines.
mortality from cholera-related dehydration; and the fact that the disease predominately strikes the very poor, who lack a strong political voice. The lack of adoption of oral cholera vaccines in endemic countries continues despite additional calls during meetings of WHO expert groups in 2002 and 2005 for their use in “certain endemic and epidemic situations” to complement the provision of safe water, sanitation, case management and other cholera control strategies. These meetings also recommended strengthening surveillance of acute diarrhea and cholera; additional studies to demonstrate the feasibility, optimal timing for, and impact of cholera vaccination in endemic and epidemic situations; the establishment of a definition of endemicity for cholera; the development of low-cost cholera vaccines and vaccines that include the O139 strain; and the development of a decision-making tool to help determine when cholera vaccination should be used in complex emergencies [7,8]. The 2005 meeting specified that the decision to use cholera vaccines in complex emergencies must be made in light of other public health priorities, and identified exclusion criteria for their use in these situations, including the existence of a current outbreak and possible interference with other critical public health interventions [8].

Many of the studies and developments recommended during these meetings have come to fruition in the last few years, making this an opportune time for the WHO SAGE to update and strengthen the recommendations for the use of oral cholera vaccines, based on these new data and developments. These advances include the development and licensure of a new low-cost bivalent (O1/O139) killed whole-cell only vaccine, which is based on the Vietnamese vaccine, but has been substantially modified to meet WHO pre-qualification and good manufacturing practice (GMP) requirements. Field trials of the vaccine in India are providing data on its field effectiveness in endemic populations, and the producer has applied for WHO pre-qualification of the vaccine. Field studies have also provided among the first data on the incidence, age distribution patterns and economic burden of cholera in endemic settings outside of Bangladesh. Vaccination demonstration projects in endemic and crisis situations (Beira, Mozambique; Darfur, Sudan; Aceh, Indonesia) have yielded important information on the feasibility, acceptability and costs of cholera vaccination using Dukoral®. And a re-analysis of data from the original trials of killed whole-cell-based cholera vaccines conducted in the 1980s in Bangladesh has provided the first estimates of indirect (herd) protection of these vaccines – which, if found to occur in other countries, greatly increase their estimated impact in controlling the disease in cholera-affected communities. Evidence from multiple settings is also now available on the demand for and cost-effectiveness of oral cholera vaccines.

This document provides an update on new developments and data concerning cholera and oral cholera vaccines to inform discussions and recommendations by the WHO SAGE during its meeting in October 2009.
II. Magnitude of the problem of cholera

Key points:

1. Cholera is an acute rapidly-dehydrating diarrheal infection caused by *Vibrio cholerae* O1 or less frequently O139, which is spread through contaminated water and food, and which, if not treated rapidly with rehydration therapy, can cause death within a matter of hours.

2. Risk factors for cholera include unsafe water and inadequate sanitation, factors that lead to these conditions (e.g., poverty and over-crowding), ingestion of undercooked or leftover food (especially seafood), and a lack or shortening of breastfeeding in infants, among others.

3. Coastal and brackish water in the tropics and subtropics are important reservoirs of toxigenic forms of *V. cholerae*, and rises in water temperatures and in sea levels due to global climate change could increase the risk of cholera.

4. The world has been experiencing the seventh cholera pandemic in modern history for the past 49 years, caused by the El Tor biotype of *V. cholerae* O1.

5. While the serogroup O139 first emerged in Bangladesh and India in the early 1990s, the great majority of cholera currently throughout the world, including the subcontinent, is due to *V. cholerae* O1.

6. There is evidence that *V. cholerae* O1 is becoming more virulent – due to the emergence of new variant strains of O1 El Tor that produce the classical cholera toxin – and more resistant to antibiotics.

7. The cholera disease burden includes both endemic and epidemic disease. The *ad hoc* Working Group has proposed the following as a practical, working definition for endemic cholera: “the occurrence of fecal culture-confirmed cholera diarrhea in a population in at least three of the past five years.”

8. The number of cases and deaths reported to WHO is a substantial underestimate of the global disease burden, which has been estimated to be around six million cases and 120,000 deaths per year, primarily in Asia and Africa.

9. While it draws much less attention than cholera outbreaks, endemic cholera has been shown in recent population-based surveillance studies to exist at high rates in selected Asian and African countries.

10. Contrary to previous thinking, it is becoming clear that children under two years of age are at particularly high risk of cholera illness in endemic settings.

11. Whereas cholera in the past was unpredictable and sporadic in sub-Saharan Africa, outbreaks are becoming more frequent and long-lasting, with persistently high case fatality rates, and the disease is becoming more entrenched as endemic disease on the continent.

12. The economic burden of cholera includes both the cost of illness to governments and families and the macroeconomic costs from losses in tourism and trade.
A. Background on the disease, routes of transmission, treatment and risk factors

Cholera is an acute diarrheal infection caused by ingestion of toxigenic serogroups of V. cholerae (O1 and, less frequently, O139) through direct fecal-oral contamination or ingestion of contaminated water or food, including seafood from estuaries where the pathogen resides. Direct person-to-person transmission is rare without the intervening contamination of food or water, due to the large inoculum required to produce the disease [9]. While only around 25% of persons infected develop symptoms (with an illness to infection ratio ranging from 1:3 to 1:100) [6], 10-20% of those who do become symptomatic experience severe disease, after an incubation period of two hours to five days [10]. The risk of severe illness is increased by the size of the dose ingested, the lack of immunity from prior exposure to the disease or through vaccination, reduced ability to produce gastric acid (which neutralizes the pathogen), and having blood group O [9,11].

Symptoms of severe cholera are profuse watery diarrhea and usually vomiting, leading to rapid dehydration. Ten or more voluminous stools can be passed within a few hours, with a rate of one-half to one liter per hour [11]. If untreated, the severe dehydration and resulting complications, such as renal failure, shock, hypokalemia, and pulmonary edema, can lead to death in more than 50% of cases, with most deaths occurring during the first day. Unlike most other diarrheal diseases, cholera can be severe and even fatal in both adults and children.

The symptoms of severe cholera are primarily due to the production of cholera toxin. Upon arrival in the small intestine, V. cholerae “switches on” its virulence genes. The binding (B) subunit of the cholera toxin attaches to the mucosal surface of the intestine and releases the active (A) subunit, which enters the host cell. This activation of the cholera toxin results in a massive loss of fluids and electrolytes, especially sodium, potassium, and bicarbonate through the stool and vomitus. The stools and often the vomitus of these patients contain high concentrations of cholera vibrios, which can then contaminate water and food sources when passed back into the environment, with the potential for causing cholera outbreaks. Recent findings suggest that human colonization of V. cholerae creates a hyperinfectious state of the bacteria that is maintained after shedding, and that may contribute to the epidemic spread of the disease [12].

Treatment of cholera largely consists of rapid rehydration, either through oral rehydration therapy (ORT) or the administration of intravenous (IV) fluids to replace the loss of fluids and electrolytes. Patients with no or moderate dehydration are usually treated with oral rehydration salts (ORS); WHO and UNICEF now recommend a low osmolarity solution that reduces the incidence of vomiting over the original ORS formulation. Rice-based ORS is especially effective in cholera patients, as it has been shown to reduce the purging rate more than traditional glucose-based solutions [11]. The 10-20% of cholera patients who develop severe dehydration must be rehydrated rapidly with IV fluids, preferably Ringer’s lactate solution, followed by ORT, once the patient is able to drink.

WHO also recommends treatment with antibiotics for severe cases of cholera, since antibiotic therapy reduces by around 50% the volume of diarrhea, the duration of illness and time spent in the hospital, as well as the length of time the pathogen is excreted in the stool, thereby potentially reducing transmission of the infection to others [13]. During epidemics in poor countries, antibiotics to treat cholera can actually save lives [13]. WHO recommends doxycycline or tetracycline for treating cholera, with erythromycin as an alternative in areas known to have strains resistant to these first-line drugs [14]. If patients have access to appropriate care for cholera, the case fatality rate should be 1% or less [10].
Resistance to first-line antibiotics, as well as multiple-drug resistant (MDR) *V. cholerae*, is a frequent occurrence in cholera-endemic parts of the world and can complicate the treatment of cholera and increase treatment costs. Studies in Bangladesh have shown that drug-resistant strains cause longer-lasting, more severe illness and higher rates of secondary infection than sensitive strains [13]. There is also some evidence that resistance to tetracycline and doxycycline may have contributed to the high death rates during the 1994 cholera epidemic in refugee camps in Goma, Zaire, where nearly 24,000 Rwandan refugees died from cholera within a month [13,15]. In some countries, including Bangladesh, where MDR strains have emerged, only fluoroquinolones (e.g., ciprofloxacin) and other more expensive antibiotics are often effective. Resistant *V. cholerae* strains can lose their resistance over time and become sensitive again, resulting in unpredictable fluctuations between resistance and sensitivity to any given drug over time and from place to place, thereby complicating treatment regimens and protocols [6].

While there are more than 200 serogroups of *V. cholerae*, only two – O1 and O139 – cause epidemic disease. The O139 serogroup first emerged as a cause of epidemics in 1992 in India and Bangladesh, and now accounts for 2-9% of cases in Bangladesh [16]. This serogroup has since spread elsewhere in Asia, but has not yet been found outside of the continent. There is no proven cross-protection between O1 and O139, and thus vaccines should be bivalent to protect against both serogroups. However, given the current infrequency of O139, a monovalent *V. cholerae* O1 vaccine should be adequate in controlling the disease in most of the cholera-endemic world, as long as ongoing surveillance monitors the occurrence of O139.

The serogroup O1 has two biotypes – El Tor and classical (Figure 1). El Tor, the cause of the world’s seventh cholera pandemic, which began in 1961 and is still ongoing, has replaced classical strains, which are thought to have been responsible for the six previous pandemics in modern history. El Tor infections have a greater rate of asymptomatic or mild cases than the classical O1 – 75% of El Tor infections are inapparent (vs. 59% for classical) and only 2% become severe as compared to an estimated 11% of infections with the classical biotype [17]. El Tor strains are also excreted from infected persons for longer periods of time, multiply more rapidly in food, and persist longer in the environment than classical strains [9]. In addition, while natural infection with classical cholera results in nearly complete protection against subsequent infections with any *V cholerae* O1, infection with El Tor strains provide only 60-70% protection against infections with either biotype [9]. All of these factors favor the spread of El Tor infections and may help explain why the seventh pandemic has lasted for nearly 50 years – twice as long as any prior pandemic. Both El Tor and classical biotypes can further be classified into two serotypes – Ogawa and Inaba [14]. New variant strains of El Tor that produce the classical cholera toxin have emerged in recent years in Asia and Africa, as discussed in Section B below.

Humans are the only known vertebrate hosts of *V. cholerae* O1 and O139. However, the bacteria are native to coastal waters, especially in the tropics and subtropics. They thrive in warm, brackish water, such as estuaries, attaching themselves to and deriving nutrients from zooplankton, including copepods (tiny crustaceans), crabs and other crustaceans. Algae blooms also promote the growth of *V. cholerae*, since they provide food for the zooplankton. Such waters can therefore constitute important environmental reservoirs of *V. cholerae*, which can remain for long periods of time in environmental waters. When humans ingest water contaminated with *V. cholerae*, the bacteria multiplies rapidly in the intestine, making humans an amplifying host of the pathogen [18]. Contamination of the environment, including surface water, with the feces of these infected individuals further promotes the bacteria’s growth and can lead to epidemics. Floods are an important cause of outbreaks in endemic countries like Bangladesh, due to contamination of surface and well water [19]. There also appears to be a close association between cholera infection and the ingestion of untreated surface water full of copepods. Each

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14 There is a third serotype, Hikojima, but it is rarely found and unstable.
year in Bangladesh, blooms of copepods – which can carry a high dose of *V. cholerae* – and other zooplankton in the rivers and ponds are followed by cholera outbreaks [20].

**Figure 1. Types of toxigenic forms of *V. cholerae***

Risk factors for endemic cholera include the use of contaminated water for drinking and bathing and poor sanitation, as well as socio-demographic variables that correspond to poor water and sanitary conditions. These include poverty, low educational level, and high population density. A study of cholera in the Americas in the 1990s found a strong correlation between cholera incidence and infant mortality rates (IMRs), an indicator of poverty and poor access to clean water and sanitation [21]. Countries with IMRs of more than 40 per 1,000 live births had markedly higher cumulative rates of cholera compared to countries with IMRs of less than 20 per1,000 live births. Other risk factors found in recent studies include: having a household member with cholera [22]; eating contaminated food, especially seafood, that is undercooked or has stayed for several hours at ambient temperatures [9]; no previous exposure to the pathogen – placing young children particularly at risk; a lack or shortening of breastfeeding in infants; reduced ability to produce gastric acid (hypochlorhydria); infection with *H. pylori* (which reduces stomach acid production); having blood group O; and heavy rainfall [23]. The risk for cholera epidemics is increased in an area where *V. cholerae* is circulating when there are sudden disruptions to water and sanitation systems, as a result of natural or man-made disasters. Rapid displacements of people into crowded areas like refugee camps unable to suddenly handle their water and sanitary needs can further increase the risk of explosive outbreaks in cholera-endemic areas. Gatherings of people during funerals and feasts in Africa have also been shown to increase the risk of cholera outbreaks. The most common risk factors for cholera outbreaks reported to ProMED were water source contamination, rainfall and flooding, and refugee settings [24].

There have been suggestions that HIV infection may increase the risk of clinical cholera, since HIV is known to affect gut-associated immunity. However, only preliminary data are currently available on the link between HIV and cholera illness.

**B. The global burden of cholera, disease patterns and trends**

**B.1. Definitions of endemic and epidemic cholera proposed by the ad hoc Working Group**
The cholera disease burden is characterized by both endemic disease and epidemics. In this section, the *ad hoc* Cholera Vaccine Working Group has made an effort to define endemic and epidemic cholera, as recommended in the 2005 WHO meeting on oral cholera vaccines held in Cairo, Egypt (WHO 2006a). The definitions of “endemic” and “epidemic” cholera have both biological and practical dimensions.

Biologically, a population is considered to have endemic cholera when cholera vibrios reside in the local environment and the occurrence of cholera in humans does not depend on exogenous introduction of cholera into the population. The mechanism by which cholera becomes endemic is the environmental reservoir of cholera. The bacterium, *V cholerae* O1 or O139, can survive in the environmental waters indefinitely. While brackish waters of estuaries are the ideal site for such persistence, the bacterium can also survive in fresh water. Depending on climatic conditions as well as the conditions of water and sanitation, the bacterium can infect persons who drink the contaminated water, and these infected persons can then spread cholera to others by way of fecal-oral contamination. Thus, the epidemiology of cholera is dependent both on climatic factors and conditions of water and sanitation. Major outbreaks usually result from a confluence of both factors (permissive climate conditions and poor sanitation). Conversely, epidemic cholera occurs when a population is infected by cholera vibrios that are introduced from the outside, carried by infected humans or other vehicles, and when poor sanitary conditions are conducive to transmission.

For several practical reasons, however, this biological definition does not permit a useful public health definition of endemic vs. epidemic cholera, especially one that could guide the use of cholera vaccines. First, most areas of the world have not been studied to ascertain whether *V. cholerae* O1 or O139 resides as an environmental pathogen. Secondly, from a public health prevention perspective, the differentiation between the two rests on the repeat occurrence of cholera as a public health problem in a particular setting, rather than on the mechanism of transmission. Accordingly, endemic cholera should refer to cholera that occurs recurrently in time and place, whereas epidemic cholera should denote cholera that occurs unpredictably with respect to these variables.

**Therefore, to the ad hoc Working Group suggests the following as a definition for endemic cholera: the occurrence of fecal culture-confirmed cholera diarrhea in a population in at least three of the past five years.** Cholera not meeting this definition would be termed epidemic. In addition, even in endemic settings there may be surges in cholera incidence for which intensive public health interventions are required. While such surges might be termed endemic in biological terms, in public health terms it often is treated as epidemic cholera.

**B.2. History and overview**

The world is currently experiencing its seventh cholera pandemic since the disease first left the Indian subcontinent and spread worldwide in 1817. This pandemic started in 1961 in Indonesia and is thought to be the first one caused by the El Tor biotype of O1 (as opposed to classical O1 strains). It spread throughout Asia and was first reported in Africa in 1971. By 1991, the disease reached Latin America (initially Peru) and rapidly spread to 12 countries, causing a reported 400,000 cases and 4,000 deaths within a year of its arrival on the continent [25]. However, the disease was contained relatively quickly in the Americas, due to concerted efforts to build piped water and sanitation systems, improve water chlorination, prohibit unsanitary agricultural practices (e.g., using sewage water for irrigation), and educate the public and promote ORS. Since 2001, no deaths from cholera have been reported to WHO in the Americas and the last reported cases in the region were five cases in Brazil in 2005. However, low levels of the disease may still be present on the continent. The great majority of cholera cases now occur
in large swaths of sub-Saharan Africa, and in Asia, especially the Bay of Bengal (India, Bangladesh), Central Asia (Pakistan, Tajikistan, Afghanistan), the Middle East (e.g., Iraq), and Southeast Asia.

This seventh pandemic, now in its 49th year, has lasted twice as long, spread further and infected more persons than any previous pandemic, and has shown no signs of abating [26]. Reasons given for the persistence of this current cholera pandemic are the characteristics of the El Tor strain of *V. cholerae* O1 (which persists longer in the environment, causes more asymptomatic cases and sheds in excreta, even in asymptomatic cases, for longer periods of time than classical strains), and the increased density and mobility of the world’s population in the modern era [9].

Every year since 2000, a total of approximately 50 countries have reported between 95,000 and 237,000 cholera cases and between 1,900 and 6,300 cholera-related deaths to WHO. The proportion of total reported cases and deaths that are from sub-Saharan Africa has been increasing; while 76% of all reported cases were from Africa in 1996, they accounted for 94% in 2007, following the sharp reduction of the disease in Latin America. The disease appears to be spreading on the African continent; while only 17 African countries, on average, reported cholera cases to WHO between 1971 and 1993, the average increased to 28 countries between 1994 and 2005 [26]. The highest reported incidence in recent years has been in the Democratic Republic of the Congo (DRC), Angola, Somalia, Ethiopia, Sudan, Zimbabwe, and Mozambique.

These figures reflect not only the increasing frequency of large cholera epidemics in Africa, but also inadequate or non-existing reporting from Asia, where the disease is endemic in many countries. Several Asian countries known to be cholera-endemic report no cases or only a small number of cases to WHO each year. India – the birthplace of cholera along with Bangladesh – reported only 2,635 cases and three deaths in 2007, but the Infectious Disease Hospital in Kolkata alone reports around 4,000 inpatient cases per year (D. Sur, personal communication), and according to one estimate, there were 400,000 cases in the state of West Bengal alone in 2004 [8]. Similarly, while Bangladesh has reported no cases of cholera to WHO since 1993, continual surveillance in Matlab district by icddrb has shown the area to be highly endemic for cholera since surveillance began in the 1960s. In addition, the icddrb hospital in the capital of Dhaka estimated that it had more than 38,000 cholera patients pass through this one hospital alone in 2006, and up to 50,000 in peak years (D. Sack, personal communication; 27). It has been estimated that Bangladesh has around 300,000 cases of cholera per year, based on an assumed average rate of 2 per 1,000 population – a number greater than all cases reported globally to WHO in any given year in the past decade [6].

Research has also shown cholera to be endemic in Pakistan – where a study showed a rate of 1/1,000 in squatter settlements in Karachi [8]; in Thailand, which experienced an epidemic in the South in 1997/8 and where more than five percent of cases of bacterial diarrhea in children in a Bangkok hospital from 1995-2000 tested positive for cholera [5]; and in Indonesia. Yet, all three countries report no cases or only a handful of cases to WHO each year.

There are a number of reasons for poor reporting of cholera in Asia and elsewhere (Table 1). Many are related to limited disease surveillance and reporting capacity and infrastructure in countries, including inadequate compliance among health facilities and local governments in completing routine disease reports; the lack of facilities to diagnose cholera vs. other causes of acute watery diarrhea in many health centers and hospitals in cholera-endemic countries; and the reliance of the population in some countries, such as India and Pakistan, on private health providers, who do not contribute to government reporting systems. The “unmet cholera burden” due to patients never reaching health facilities for

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15 Based on 2 million cases of diarrheal disease reported locally and data from the Infectious Disease Hospital in Kolkata showing that more than 20% of diarrheal patients had laboratory-confirmed cholera.
appropriate care in the poorest areas where access to health services is lacking is another factor. A study in Kenya demonstrates the under-reporting of cholera that is likely indicative in many developing countries. When active surveillance of cholera involving household visits was implemented, there was a 37% increase over the passive surveillance system in reported cases among survivors and a 200% increase in the number of deaths, resulting in an increase in the case fatality rate from 5.5% to 11.4% [28]. In addition, endemic disease – the predominant pattern in Asia – tends not to attract the attention of the local media and governments, contributing further to under-reporting of cholera. Even if reports of the disease reach the central government, they are often not reported to WHO, owing to concerns by many national governments, especially in Asia, of the negative impact of cholera reports on tourism and trade.

Table 1. Factors contributing to the under-reporting of cholera to WHO

<table>
<thead>
<tr>
<th>Health systems factors</th>
<th>Inadequate access of the very poor and marginalized populations to health services (“unmet burden”), thereby forgoing cholera treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health facilities lack the facilities, equipment, supplies and training to conduct laboratory diagnosis of cholera among acute watery diarrhea cases.</td>
<td></td>
</tr>
<tr>
<td>Health facilities and local governments do not submit complete or on time routine disease reports to government authorities.</td>
<td></td>
</tr>
<tr>
<td>Heavy use of private providers and facilities in many countries for treatment, who do not participate in government disease reporting systems</td>
<td></td>
</tr>
<tr>
<td>The lack of accessible rapid diagnostics for cholera</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Poverty-related and cultural factors</th>
<th>Reluctance of national governments to report cholera cases to WHO due to the potential impact on export industries (especially food-related) and tourism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inadequate access of the very poor and marginalized populations to health services (“unmet burden”), thereby forgoing cholera treatment</td>
<td></td>
</tr>
<tr>
<td>Lack of social access to allopathic health facilities (such as, social taboos preventing women from seeking health care in some societies (e.g., rural Bangladesh) and a preference for traditional healers)</td>
<td></td>
</tr>
</tbody>
</table>

As a result, WHO estimates that only around 5-10% of clinical cases of cholera are reported to the agency each year [26]. The U.S. Institute of Medicine made an estimate of six million cases, more than 600,000 hospitalizations, and 120,000 deaths per year from cholera in 1986 – before the disease struck and then abated in Latin America and before large epidemics were reported regularly from Africa. This estimate is still widely quoted in the cholera literature. Another analysis made in 2001 estimated 11 million cases of cholera per year in children [29]16. An updated detailed analysis of the global cholera morbidity and mortality has yet to be undertaken and is sorely needed.

Since the 2001 WHO Position Paper was published, a number of studies and analyses have yielded new data on the disease burden and epidemiological patterns of endemic cholera; cholera epidemics; antibiotic resistance; the emergence and global spread of new, more virulent variant strains of *V. cholerae* O1; the potential effects of climate change on the spread and incidence of the disease; and the economic costs of cholera. These new data are presented in the following sections to update the SAGE on the current situation and trends regarding the burden and epidemiology of cholera.

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16 Based on the estimated global incidence of diarrheal diseases in children and an estimated proportion of 0.6% due to cholera.
B.3. New evidence regarding endemic cholera

New data have become available on the magnitude, age-specific risk and cyclical patterns of endemic cholera in Asia and Africa. A hospital-based surveillance study conducted in four widely-separated rural areas of Bangladesh from 1997-2001 showed the disease to be endemic throughout the country – beyond the much-studied district of Matlab [30]. Among patients hospitalized with acute watery diarrhea, 4-20% tested positive for cholera, with an average of 14% across sites. Very young children seemed disproportionately affected; 38% of patients under the age of two years with acute watery diarrhea tested positive for cholera, with a range of 30-45% across sites. Of cholera patients, 27% had the O139 biotype and the remainder tested positive for O1 El Tor. As previously shown in Matlab, cholera incidence is very cyclical, with peaks occurring every year before and after the monsoons.

Recent population-based prospective surveillance studies have provided incidence rates in cholera-endemic countries. Long-term surveillance in Matlab district, Bangladesh shows a high overall incidence of cholera (1.5/1,000), but considerable variability from year to year – from a peak of 3.5/1,000 population in 1994 to a low of 0.45/1,000 in 2001\(^\text{17}\). Children under five years of age have by far the highest rates, ranging from 3 to 9/1,000 from 1994 to 1999. And while cholera is often not suspected in infants, the rates in children less than one year old were extremely high in certain years – between 6.7 and 9.5/1,000 from 1994 to 1997 – and averaged 4.6/1,000 over the 10-year period from 1994 to 2003.

Prospective cholera surveillance was conducted in the early-mid 2000s by the Diseases of the Most Impoverished (DOMI) Program in three cholera-endemic areas – selected slums of Kolkata, India; the coastal city of Beira, Mozambique; and selected slum areas in North Jakarta, Indonesia. Surveillance involved passive surveillance in public health centers and hospitals, including clinics set up in the study site in Kolkata specifically for the study. The results showed overall annualized incidence rates of culture-confirmed cholera of 1.6/1,000 in Kolkata, 4.0/1,000 in Beira (which did not include children less than two years old), and 0.5/1,000 in North Jakarta (Figure 2) [31]. Only \textit{V. cholerae} O1 was found in any of the sites. As was seen in Bangladesh, very young children were most affected by the disease. Children 2-4 years of age had annualized rates of 8.8/1,000 in Beira, 6.2/1,000 in Kolkata, and 1.2/1,000 in North Jakarta. These rates were two to four times higher than those found in the overall population in these sites. In the two study sites where children under two years old were included in the surveillance, they had by far the highest incidence rates (8.6/1,000 in Kolkata and 3.2/1,000 in North Jakarta).

Seasonal outbreaks often occur in cholera-endemic areas, such as in the Kolkata study site before and during the monsoons in 2004 (Figure 3). Large outbreaks of cholera are a frequent occurrence during floods in Bangladesh. During periods of flooding from 1998 to 2007, \textit{V. cholerae} O1 became the most common pathogen identified in patients hospitalized with diarrhea at the ICDDR,B Hospital in Dhaka, accounting for 33-40% of all cases in which the pathogen was detected, as compared to an average of 23% during non-flood years [16,19]. Figure 4 shows the dominance of cholera over other enteric diseases during a period of flooding in 2007. \textit{V. cholerae} O1 became the most common cause of diarrhea among children and adults combined. Among children under five, cholera became the second most identified cause of diarrheal disease, after rotavirus. Patients during floods had very high rates of severe dehydration – especially in recent years, with 78% of laboratory-confirmed cholera patients requiring IV rehydration [19].

\(^{17}\) Data provided by the ICDDR,B.
Figure 2. Incidence of culture-confirmed cholera per 1,000 population per year in study sites in three countries

*Surveillance did not include pregnant women and children <2 years of age. Rates were corrected for direct protection from cholera vaccination.  
Source: Diseases of the Most Impoverished Program [31]

Figure 3. Cholera cases by week in the DOMI surveillance site in Kolkata, India, May 2003 – April 2004

Source: [22].
Figure 4. Cases per month of selected enteric pathogens among all patients (children and adults) with diarrheal illness seen at the Dhaka Hospital of the ICDDR,B in 2007

Note: All values are estimated based on surveillance data in 2% of total cases.

Source: [19].

Evidence from Africa shows that cholera is spreading and has become endemic in several regions, with 18 countries reporting cases to WHO every year from 2000 to 2005 [26]. Endemicity is highest in the Lake Region (DRC, Uganda, Rwanda, Kenya), Southern and West Africa and lowest in Southwest Africa. A retrospective analysis of surveillance records and WHO reports of culture-confirmed or suspected cholera cases in Zanzibar found 12 major outbreaks from 1978 to 2006/7, with increasing frequency over time (IVI/WHO unpublished report). While no cases or only minor local outbreaks were reported in Zanzibar over the 13-year period from 1984 to 1997, outbreaks have occurred every year since 2001, sometimes three in a single year, indicating increasing endemicity on the islands. Surveillance data from the Eastern part of the Democratic Republic of the Congo (DRC) also show an endemic pattern of cholera from 2000 to 2007, with seasonal peaks and periodic epidemics (Figure 5).

Figure 5. Cholera cases by week in the East of the Democratic Republic of Congo, 2000 – 2007

Source: Dr. Didier Bompangue, Ministry of Health, Democratic Republic of Congo
B.4. Recent patterns and trends in antibiotic resistance

A series of studies conducted this decade in India has shown high rates of *V. cholerae* strains resistant to several commonly-used, inexpensive antibiotics. Hospital-based surveillance in Kolkata from 2002-2003 and in Delhi from 2003-2005 both found nearly 100% resistance to three drugs – furazolidone (often given to pregnant women with cholera), co-trimoxazole (TMP-SMZ) and nalidixic acid [32,33]. Nearly 100% of the isolates (both O1 and O139) were sensitive to the first-line drug, tetracycline. However, of concern is the fact that the O139 strains found in Kolkata were “uniformly resistant” to ciprofloxacin and norfloxacin – fluoroquinolones that have become the drugs of choice in areas where resistance to tetracycline and other first-line antibiotics is common [32].

Results from the prospective community-based cholera surveillance study conducted by DOMI in Kolkata from 2003 to 2005 also found high rates of resistance to furazolidone (59%) and co-trimoxazole (57%) among O1 isolates\(^\text{18}\) (Figure 6). In addition, 30% of isolates tested were resistant to erythromycin, which WHO recommends as an alternative drug for treating cholera in areas with tetracycline-resistant strains [14]. As seen earlier, the *V. cholerae* strains found in Kolkata were still largely sensitive to tetracycline and doxycycline, with resistance rates of 1% and 2%, respectively, although these drugs are contraindicated for use in children and for women in their first trimester of pregnancy. As shown in Figure 7, resistant strains of these drugs can appear suddenly – as happened in Kolkata in 2007, where 68% of isolates tested were resistant to tetracycline. The strains can also become sensitive again when use of the drug declines, as apparently has happened in the past two years in the case of erythromycin-resistant O1 strains in Kolkata.

![Figure 6. Antibiotic resistance rates of *V. cholerae* O1 isolates of patients found in cholera surveillance in Kolkata, India, May 2003 – December 2005 (n=290)](source: DOMI Program)

\(^{18}\) No isolates of O139 were found in the Kolkata surveillance study.
In contrast to the findings in India, strains found in the DOMI surveillance study in North Jakarta, Indonesia were still largely sensitive to most antibiotics. The rates of resistance were five percent or less to most drugs, including co-trimoxazole, tetracycline, and nalidixic acid, and were highest for cefotaxime (12% of isolates) and ampicillin (8%). Low rates of antibiotic resistance in Indonesia have also been observed for typhoid fever.

Of growing concern is the fact that multi-drug resistant strains – that are resistant to tetracycline, as well as to furazolidone, co-trimoxazole and erythromycin – can very suddenly appear in a country and become dominant. This was the case in Bangladesh in 2004-6, where O1 Ogawa strains resistant to all four drugs emerged suddenly in Dhaka and Matlab, and within a few months accounted for 100% of Ogawa strains tested [34]. This MDR strain was also less sensitive to ciprofloxacin. While a single one-gram dose of the drug has been successful in treating the disease in Bangladesh, only 68% of patients treated during the period when the MDR strain was dominant had resolution of diarrhea within 48 hours after a 500 mg dose of ciprofloxacin given every 12 hours for three days [34]. The MDR strain subsided in the country within two years and by August 2006, 90% of stains were again sensitive to tetracycline, continuing the fluctuating patterns of drug resistance and sensitivity seen in the past with V. cholerae O1.

B.5. Cholera outbreaks: recent developments and data

This decade has seen the phenomena of large, protracted cholera outbreaks, especially in sub-Saharan Africa. Cholera outbreaks appear to be increasing in frequency, duration and size of the population affected (Table 2). The years 2006 and 2007 alone saw major widespread outbreaks with tens of thousands of reported cases and thousand of deaths each in five African countries: Angola, Ethiopia, Sudan, Somalia and the DRC.
Table 2. Information on selected cholera outbreaks in the 2000s

<table>
<thead>
<tr>
<th>Location</th>
<th>Year(s)</th>
<th>Duration</th>
<th>Number of Reported Cases</th>
<th>Case Fatality Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Madagascar</td>
<td>2000</td>
<td>12 months</td>
<td>37,000</td>
<td>6%</td>
</tr>
<tr>
<td>S. Africa</td>
<td>2000/01</td>
<td>8 months</td>
<td>116,000</td>
<td>0.22%</td>
</tr>
<tr>
<td>Liberia</td>
<td>2003/04</td>
<td>8 months</td>
<td>34,000</td>
<td>N/A</td>
</tr>
<tr>
<td>Afghanistan</td>
<td>2005</td>
<td></td>
<td>155,000</td>
<td>N/A</td>
</tr>
<tr>
<td>Angola</td>
<td>2006/07</td>
<td>15 months</td>
<td>&gt;86,000</td>
<td>4%</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>2006/07</td>
<td>1 ¾ years</td>
<td>54,000</td>
<td>1%</td>
</tr>
<tr>
<td>Sudan</td>
<td>2006/07</td>
<td>8 months</td>
<td>44,000</td>
<td>3.3%</td>
</tr>
<tr>
<td>Somalia</td>
<td>2006/07</td>
<td>8 months</td>
<td>41,600</td>
<td>2.8%</td>
</tr>
<tr>
<td>Vietnam (Northern, Hanoi, other areas)</td>
<td>2007 - 2009</td>
<td>≈ 3 years</td>
<td>6,573 in 2007/08 (reported as acute watery diarrhea)</td>
<td>N/A</td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>2008/09</td>
<td>≈11 months</td>
<td>98,592*</td>
<td>4.3%</td>
</tr>
<tr>
<td>India (Hyderabad, Kerala, areas affected by Aila cyclone)</td>
<td>2009</td>
<td>Hyderabad: 10 days</td>
<td>Hyderabad: 2,950</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Kerala: 20 days Areas affected by Aila cyclone: 4 months to date</td>
<td>Kerala: 478 cases admitted</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>since May 2009</td>
<td>Aila cyclone areas: 700,000 cases of cholera and acute water diarrhea</td>
<td>Hyderabad and Kerala: 0.4 – 0.54; Unknown for Aila</td>
</tr>
</tbody>
</table>

* Up to July 27, 2009

Note: The definition of cholera cases is left up to the country reporting and can include clinical diagnoses, laboratory-confirmed cholera cases and cases of acute watery diarrhea.

Source: WHO Cholera Task Force

The explosive potential of cholera outbreaks, especially in areas in economic or political crisis, is well illustrated by the curve of the epidemic in Zimbabwe, which, according to conservative estimates, caused nearly 100,000 reported cases and nearly 4,300 deaths over 11 months (Figure 8). The rapid spread and magnitude of this outbreak were facilitated by an economic collapse, leading to widespread poverty, food shortages, a breakdown in potable water and sewerage systems, as well as a collapse in the public health system. Little ORS was initially available to the public and the government encouraged people to make home-made solutions of sugar and salt, which many could not afford [35]. The outbreak, which began in Harare, spread to 85% of the country’s districts, although only four provinces account for 78% of cases. The disease has already affected nearly one percent of Zimbabweans. The case fatality rate (CFR) was as high as 7% early in the outbreak, but then declined due to a major international response, and remains at 4.3% overall since the outbreak began.

Two salient points can be made about these large cholera outbreaks in recent years. First, case fatality during these outbreaks, especially in Africa, is often quite high – 4% or greater, especially early on in the outbreaks, although they have declined from higher levels in the 1990s. The actual rates are likely higher, since some people may die before reaching a health facility, especially in remote, impoverished areas. In some provinces in Angola, the CFR reached 30% during its large outbreak in 2006/07 [18]. Among cases reported to WHO from African countries for both endemic disease and outbreaks, the mean CFR was more than 5% in eight countries, including 10% in Cameroon, around 9.5% in Guinea and Swaziland, and 8% in Niger and Mali [26]. The experience in South Africa during its outbreak in 2001/02 demonstrates that, with good access to health care, health education campaigns to raise awareness of the outbreak and encourage people to seek health care, coupled with a strong disease surveillance and reporting system, the CFR could be kept at a low 0.22% – the lowest rate ever observed in such a large outbreak [25]. Unfortunately, very few countries in sub-Saharan Africa have a health care infrastructure that comes close to approximating that of South Africa.
Figure 8. Cumulative cholera cases and deaths in Zimbabwe, November 20, 2008 – February 12, 2009

Second, unlike in self-contained communities like refugee camps, the duration of many of these outbreaks within a country appears to be increasing (Table 2). They tend to start in cities and spread to large parts of the country over a period of several months. The 2006/07 outbreak in Angola lasted for 15 months and the Zimbabwe outbreak lasted from August 2008 to July 2009. An outbreak in a district in Northeast Kenya in 2001 persisted for four months [36]. The argument that all cholera epidemics are short-lived; thus making cholera vaccination with a two-dose vaccine ineffective and impractical, is becoming less tenable in areas with large, protracted, uncontrolled epidemics, such as in large parts of sub-Saharan Africa.

An analysis of cholera outbreaks reported through the Program for Monitoring Emerging Diseases (ProMED) – a passive reporting system that relies on reports from governments, international agencies, the media and local observers – identified 632 unique outbreaks over an 11-year period (1995-2005), for an average of more than 60 per year and five times more than reported to WHO [24]. Two-thirds of the epidemics were reported from sub-Saharan Africa and 20% from South or Southeast Asia, though outbreaks in Asia could have been under-reported. The average outbreak affected more than 38,000 people and caused 1,555 deaths, with Africa accounting for 88% of the cases and deaths. The highest concentration of multiple epidemics in Africa was along the border between the DRC and Uganda, other parts of the Lake Region (Rwanda, Tanzania, Kenya), Mozambique and along the Mozambique-South Africa border, and other countries in Eastern and Southeastern Africa (Figure 9). High numbers of outbreaks were also reported in parts of West Africa and the Horn of Africa.
B.6. Emergence of new variant strains of V. cholerae O1

In 1992 a new variant strain of V. cholerae O1 was identified in Bangladesh. This new strain is of the El Tor biotype, but it produces the cholera toxin formerly produced only by classical strains. By 2001, the new strain had completely replaced the original El Tor strain of the seventh pandemic in Bangladesh [37] and now accounts for all V. cholerae strains isolated in Kolkata, India [K. Nair, personal communication]. A study of isolates collected during the cholera surveillance study in Beira, Mozambique found that all specimens tested contained a strain that similarly had traits of El Tor, but produced the classical cholera toxin, though it was genetically distinct from those found in Bangladesh [38, 39]. A similar variant strain was found to be the cause of the 2007-09 cholera outbreaks in Northern Vietnam [40].

These variant strains now predominate in parts of Africa and South and Southeast Asia and are spreading globally [40]. They also appear to be more virulent and to cause a more severe clinical illness than the original El Tor strains [4, 41]. The proportion of cholera patients seen at two sentinel surveillance hospitals in Southern Bangladesh with severe dehydration was 70-79% in 2006, compared to an average of 40% from 1998 to 2000 before the variant strain replaced the original El Tor strain in the country [41]. It is not yet known if the greater virulence of these variant strains as compared to the original El Tor strains is due to the classical cholera toxin, the quantities of toxin produced, or other virulence factors. In any event, these variant strains are raising concerns among scientists and physicians dealing with cholera.
B.7. Potential effects of global climate change on the prevalence of cholera

Research in Bangladesh and elsewhere has found that increases in the temperature of sea and surface water can lead to plankton blooms and increases in the growth of *V. cholerae* [42]. One study found that a 5°C rise in the water temperature of a lake in rural Bangladesh increased the risk of cholera cases appearing in the area by more than three times [43]. Increases in water temperature as a result of climate change may therefore increase the prevalence of vibrios in surface water, increasing the risk of cholera in areas where untreated water is used for drinking and household use [44]. In addition, the rise in sea levels predicted to result from global climate change will lead to greater salt water intrusion inland, which in turn should favor the growth of *V. cholerae*, including toxigenic forms, since salinity is believed to enhance the survival of the bacteria and the expression of cholera toxin [42]. However, the increased risks of cholera from rising water temperatures and sea levels could be mitigated by improvements in sanitation and other public health measures, including vaccination.

B.8. The economic costs of cholera

Relatively little data are available on the economic costs of cholera – either at the macro or micro level. An analysis by Médecins sans Frontières (MSF) in the late 1990s estimated that it cost US $52-61 to treat a cholera patient in three refugee settings in Africa [45]. These estimates are conservative, since they include only direct costs of treatment and do not include national government, MSF headquarters or indirect costs. Detailed cost-of-illness studies conducted by the DOMI Program of the International Vaccine Institute (IVI) among culture-confirmed cholera cases estimated the cost of illness for hospitalized patients in endemic situations (in contrast to the outbreak data cited above by MSF) to average $26-47 per patient in Kolkata, India; Matlab, Bangladesh and Beira, Mozambique, and $208 in North Jakarta, Indonesia (Figure 10) (DOMI Program, unpublished data). These estimates include the costs of medical treatment (incurred by both institutions and patients or their families), transportation and lodging costs of family members, and indirect costs of lost wages from missed work. The low costs in Kolkata are partly due to the establishment of free clinics in the study site and thus are artificially low. Much of the costs was borne by families, and consequently, 13-17% of families in Matlab, N. Jakarta and Kolkata and 27% in Beira had to borrow money to pay for cholera treatment. In North Jakarta, the only site for which complete public and private cost information for hospitalized and outpatient cases are available, the average cost of illness for hospitalized and outpatient cases combined was $67, based on a hospitalization rate of 22%. Families bore 60% of these costs on average (Table 3).

**Figure 10. Estimated cost of culture-confirmed cholera illness for hospitalized cases (US$2007) in four study sites**

![Cost of Cholera Illness](image)
Table 3. Weighted average cost of stool-culture confirmed cholera illness per case (hospitalized and outpatients) in North Jakarta, Indonesia (US $2007)

<table>
<thead>
<tr>
<th>Rate of hospitalization</th>
<th>22%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Private costs:</td>
<td></td>
</tr>
<tr>
<td>• Direct</td>
<td>$31.00</td>
</tr>
<tr>
<td>• Indirect (lost wages)</td>
<td>9.40</td>
</tr>
<tr>
<td>• Total private costs</td>
<td>40.40</td>
</tr>
<tr>
<td>Costs to the public sector (public health facilities)</td>
<td>26.20</td>
</tr>
<tr>
<td>Total costs</td>
<td>$66.60</td>
</tr>
</tbody>
</table>

Source: DOMI cost-of-illness studies

At the national level, Mozambique estimated in 2002 that it spends $145 million per year to respond to cholera outbreaks [7]. The most detailed analysis of the macro-economic consequences of cholera in a country has come from Peru. In one year alone (1991), the cholera epidemic was conservatively estimated to cost the country $530–$715 million, including $175 million in lost revenues from reduced tourism and exports [7]. When the European Union restricted the importation of fish from four African countries (Kenya, Uganda, Tanzania and Mozambique) in 1998, in response to cholera outbreaks in 1997, the result was an estimated loss in trade of more than $1 billion for the five-year period of 1998-2002, or $212 million per year for the four countries combined [46]. This loss grew to more than 10% of the total value of exports from these countries in 2002.
III. Cholera prevention and control measures

Key points:

1. The establishment of piped water, water treatment and sewerage systems played a key role in eliminating cholera as a public health problem in industrialized countries in the 19th and 20th centuries and helped to halt the 1990s cholera epidemic in several Latin American countries.

2. Various point-of-use interventions and materials to improve water quality at the household level (e.g., safe water storage containers, chlorine solutions) have been shown to be effective in reducing the risk of diarrheal disease and cholera when implemented in pilot programs.

3. All established public health interventions that are effective in preventing cholera, including water and sanitation infrastructure improvements, have not been implemented on an adequate scale in major parts of Africa and Asia.

4. Treatment, including IV and oral rehydration, while life-saving, is still not being implemented on-time, fully or adequately in many cholera-endemic areas and often does not reach the most vulnerable.

5. Vaccination against cholera can create synergies with safe water and sanitation programs in at least two ways: a) vaccination reduces the number of people who can contaminate the environment; and b) improved water and sanitation may increase the vaccine’s effectiveness by reducing the amount of bacteria that people ingest in contaminated water or food.

Like other diseases spread by the fecal-oral route, improvements in sanitation and access to clean water remain the mainstays of preventing both endemic cholera and cholera outbreaks. Also important to contain transmission of the disease are health education to promote handwashing with soap, safe food handling and breastfeeding; strong disease surveillance and reporting systems; and the establishment and enforcement of basic sanitation laws for food industries, including food vendors. As discussed below, vaccination can also play an important role in preventing the disease, especially as a short to medium-term solution before a country can make significant improvements to its water and sanitation infrastructure. In addition, proper case management is vital in reducing mortality from the disease and limiting its spread (see box).

Industrialized countries controlled cholera and other diseases transmitted through contaminated water or food through the “sanitary revolution”, which involved the development of piped water, water treatment (i.e., chlorination systems), and sewerage systems. Cholera outbreaks and their threat in the U.S. and Europe in the mid-late 19th century actually prompted efforts to improve municipal water supply and sewer systems and to establish Boards of Health in U.S. cities, which likely prevented large-scale epidemics during the 5th and 6th cholera pandemics [9].
Methods to Prevent and Control Cholera

- **Provision of clean water and safe water storage:**
  - Piped water systems
  - Treatment (chlorination at the municipal level)
  - Point of use household interventions:
    - Filtration with saris placed over water collection pots (where vibrio-bearing copepods proliferate in water), ceramic filtration
    - Chlorine solutions
    - Boiling water
    - Solar or heat disinfection using clear bottles
    - Flocculant disinfectants
    - Provision of improved water storage containers (e.g., with narrow mouths or spigots)

- **Improvements in sanitation and waste disposal:**
  - Construction of sewerage systems
  - Latrine construction

- **Appropriate case management:**
  - Rapid and appropriate rehydration with oral rehydration salts (ORS) or IV fluids
  - Antibiotic therapy for severe cases

- **Health education:**
  - Promotion of handwashing with soap
  - Promotion of safe preparation and storage of food
  - Promotion of breastfeeding
  - Promotion of domestic and personal hygiene
  - Awareness campaigns during outbreaks to encourage people with symptoms to seek immediate health care

- **Improvements in food safety:**
  - Enactment of food safety laws for restaurants, food vendors and food processing factories
  - Banning of unsafe agricultural practices (e.g., use of residual or sewerage water to irrigate crops)

- **Strengthening of disease surveillance/reporting and early warning systems:**
  - Strengthening of disease and environmental surveillance
  - Establishment or strengthening of diagnostic laboratories
  - Establishment of an alert and response mechanism (e.g., during outbreaks)

In more recent times, cholera outbreaks were halted the 1990s in Santiago, Chile after a sewage treatment plant was built, and typhoid fever incidence declined by 83% in two years [26]. Mexico launched a massive, comprehensive effort to control cholera once the disease arrived in the country in 1991. The government’s multi-disciplinary response involved a series of programs to improve water quality through large-scale water chlorination in urban areas, which reached an estimated 95% of the population; by disinfecting high-risk areas; and through the promotion of household chlorination and boiling of water [47]. Sanitation was improved through large-scale latrine building projects in rural areas, improved waste disposal, and laws that banned the use of waste water to irrigate vegetables. Strong disease surveillance and active case finding to control local cholera outbreaks were also critical and included the establishment of a network of more than 200 laboratories capable of identifying *V. cholerae*. The country’s response also involved multi-faceted educational campaigns for the public, health professionals, teachers and others; efforts to promote the use of ORS; monitoring of food vendors’
compliance with sanitation laws; and training of health providers in cholera case management. Through these efforts, the epidemic subsided within six years and the last case found in the country was in 2001. The case fatality rate during the Mexico epidemic was 1.2% and diarrheal disease mortality in children under five declined on average 18% each year between 1990 and 1993 [47, 48].

Such efforts require massive investments, which countries less developed than Mexico are unlikely to carry out, especially in rural areas and in growing urban slums. It has been estimated that the investment required just to meet the Millennium Development Goal of increasing the number of people with access to safe water by 50% by 2015 will cost $37.5 billion international dollars [49]. In sub-Saharan Africa an estimated 45% of the population does not have access to safe water for drinking and 68% lack adequate sanitation [50]. Such large-scale programs are unlikely to reach these populations in Africa or the slums and poor rural areas of Asia in the foreseeable future.

In recent years, especially since the cholera epidemics in Latin America, attention has turned to alternative, lower-cost, and more decentralized approaches to preventing cholera and other diarrheal diseases. Various health education programs have shown to be effective, especially when tested on a small scale in research studies. Studies in Bangladesh have shown that handwashing promotion can lead to changes in handwashing practices and can reduce diarrheal disease incidence in young children (e.g., by 26% in one study) [51, 52]. A pooled analysis of programs promoting handwashing with soap found that they reduced diarrheal disease incidence by 42-47%, though most of the studies were not randomized and the specific effect on cholera was not examined [53]. Breastfeeding has been shown to protect against cholera – even into the second and third year of life – and to reduce the severity of infection. Studies in Bangladesh showed breastfeeding to be associated with a 70% reduction in the risk of clinically severe cholera and exclusive breastfeeding was associated with a 100% reduction [54]. Therefore, breastfeeding promotion should have a significant impact on reducing cholera morbidity and mortality in very young children, as it has had on diarrheal diseases in general [55].

A number of programs to improve the quality of water within the home have been implemented in Latin America, prompted by the cholera epidemic in the 1990s, and in a number of African countries [106]. These “point-of-use” programs often involve disinfecting water through the use of packaged chlorine solutions (sodium hypochlorite), through solar disinfection in clear bottles, through flocculant disinfectants packaged in sachets that clear up turbid water; through the use of ceramic filters, or through a combination of methods. Since water is often contaminated in the home from infected persons dipping their hands into water storage containers, many point-of-use programs also involve the use of safe water storage vessels with narrow mouths or spigots. Many programs involve the sale of disinfectants and storage containers through social marketing programs.

Several of these programs have been shown to be effective in reducing the overall rates of diarrhea when tested on a pilot basis, though only a few have been evaluated for their specific effect on cholera. A cluster-randomized control study in Northern Kenya involving the weekly distribution of flocculant disinfectant sachets to villagers using untreated surface water found a 25% less incidence of diarrheal disease in children under two years of age and 53% fewer deaths overall in villages using the disinfectant vs. control villages [56]. A meta-analysis of such household point-of-use water programs found that, among high quality studies that included “adequate” control groups, they were associated with a 39% reduced risk of diarrheal diseases overall [57]. A study that distributed safe water storage containers in Calcutta, India in the 1980s was associated with a significant decrease in cholera risk when evaluated in an observational study [58]. The use of a sodium hypochlorite solution sold through a social marketing program in Madagascar to control cholera was shown in a case-control study to be highly protective against clinical cholera, though the results were not statistically significant due to small numbers [59].
Another simple, culturally-appropriate means of reducing cholera incidence was found in Bangladesh, using a common household item. An educational program in rural villages conducted in 1999 and the early 2000s promoted the use of sari cloth, which when folded several times and placed over water collection pots, filtered out the copepods carrying *V. cholerae* in untreated surface water [20]. The study found strong compliance (≈90%) and a cholera incidence rate of 52% less in the intervention vs. the control villages. As the study site for this trial was a rural area of Bangladesh, where sari filtration may have filtered out vibrio-bearing zooplankton from water sources in canals, it remains to be seen whether this intervention would be effective in urban areas, where it is presumed that water sources may be less contaminated by zooplankton.

While all of these interventions have been shown to be effective on a small scale, few have been demonstrated to be feasible and scalable on a programmatic basis, or shown to confer substantial protection over time. This is a potential concern in view of their dependence on behavioral changes.

Vaccination using oral cholera vaccines offers another prevention strategy that is becoming more feasible in cholera-endemic countries with the advent and licensure of a new low-cost vaccine that was specifically developed for use in public health programs in endemic countries (discussed in detail in Section IV below). It is generally accepted that cholera vaccines should not be used as a sole intervention, but as an additional cholera prevention tool, along with efforts to improve access to safe water and adequate sanitation, health education programs, and other traditional cholera control strategies. Vaccination can, in fact, create synergies with safe water and sanitation programs to reduce the risk of infection in two important ways: 1) vaccination will result in fewer people contaminating the environment with *V. cholerae*, and 2) safer water may increase the effectiveness of the vaccine by reducing the amount of bacteria that people ingest in contaminated water or food [27].

The use of oral rehydration salts (ORS) revolutionized the treatment of cholera in the 1970s. Prior to the advent of ORS, all patients with cholera had to be rehydrated with IV fluids until cessation of diarrhea. This limited the number of patients who could be effectively treated and was in part responsible of case-fatality rates or up to 20% observed even in good health facilities. Now, the majority of cholera cases, presenting with moderate dehydration or less, can be treated effectively with ORS by low level health workers. Even those with severe dehydration, who require IV fluid infusion, can be switched to ORS as soon as the severe dehydration has been corrected [14]. With ORS and IV rehydration, it is now estimated that case fatality due to cholera in patients arriving at a health facility should not exceed 1%, provided that patients are treated properly and rapidly.

However, use of ORS solution is still quite low in most developing countries. Only an estimated 32% of children under five years of age with diarrhea in developing countries as a whole, and 28% in sub-Saharan Africa receive ORS packets to treat their illness [50]. There has been very little or no progress in increasing the use of ORS packets among children with diarrhea over the last 10 years. In fact, one study that examined data from Demographic and Health (DHS) surveys found that among 34 countries that had conducted DHS surveys in both 2000 and 2005, declines in the use of ORS or other fluids to treat children with diarrhea were seen in 23 countries (68%) from 2000 to 2005 [60].
IV. The case for cholera vaccination using oral cholera vaccines

Key Points

1. The only WHO pre-qualified oral cholera vaccine at present is the oral killed whole-cell B subunit two-dose vaccine sold as Dukoral®, which is used primarily as a travelers vaccine since it was first licensed in 1991.

2. Dukoral® has been shown to confer an estimated 78-84% protection over at least five months in an African population against one of the new variant strains of V. cholerae El Tor that are becoming dominant in parts of Africa and Asia.

3. There is now a new low-cost, easier-to-administer oral killed “whole-cell only” cholera vaccine (without the B subunit) that will soon become available for use in cholera endemic settings in developing countries and for which WHO pre-qualification is being sought.

4. The new whole-cell only vaccine, now produced in India (Shanchol™) and Vietnam (mORCVAX®), does not require administration with a buffer, provides sustained protection over at least two years, and is licensed for use in children as young as one year of age.

5. Dukoral® has the added advantage of providing short-term protection against enterotoxigenic E. coli (ETEC), a common cause of diarrhea and cholera-like disease in developing countries.

6. The oral killed whole-cell-based vaccines (both with and without the B subunit) were shown to confer considerable herd protection in a re-analysis of data from the Bangladesh clinical trials, including in children too young to be vaccinated.

7. Cholera vaccination using oral killed whole-cell-based vaccines has been shown to be feasible and well accepted by populations when used to control endemic disease in Vietnam and Mozambique and in several post-crisis situations in Africa and Asia (using Dukoral®), though the logistical requirements of Dukoral® posed a number of challenges.

8. The two available oral killed whole-cell-based cholera vaccines meet the criteria established by the 2009 ad hoc Cholera Vaccine Working Group for acceptable cholera vaccines for use in public health settings in developing countries.

9. A new analysis of the cost-effectiveness of cholera vaccination, assuming use of the new whole-cell only vaccine and a price/dose of $1.00, and based on site-specific epidemiological and economic data, shows vaccination of children to be “very cost-effective” in high incidence endemic areas when herd effects are taken into account.
**A. Criteria proposed by the *ad hoc* Cholera Vaccine Working Group for features and performance of cholera vaccines for use in cholera-affected countries**

The *ad hoc* Cholera Vaccine Working Group has identified criteria for the characteristics and performance of cholera vaccines for use in cholera-affected countries in order to assist the SAGE in providing guidance to policymakers and program managers concerning whether currently available oral cholera vaccines should be used and under what circumstances. Following these criteria, shown in Table 4, cholera vaccines must, at a minimum, protect against both serotypes (Ogawa and Inaba) of *V. cholerae* O1 El Tor – the only O1 biotype currently circulating – and provide at least 50% sustained protection for two years in cholera-affected countries. The vaccines should be safe and able to be used in persons as young as two years old, as well as in pregnant women and HIV positive and other immuno-compromised individuals. Other proposed criteria for use in endemic or epidemic settings include a maximum regimen of two doses for the primary series, and the need for booster doses no more frequently than every two years (and every one year for young children). The need for a buffer and local water for administration also meet the criteria set by the Working Group. The vaccines should also have a shelf life of at least two years and not require storage below freezing.

The old parental killed vaccine that provided at most 50% protection after two doses for only three to six months were never recommended by WHO and clearly do not meet the criteria of at least one year of sustained protection of 50% or more [9].

Three orally-administered cholera vaccines have now been licensed. These include a live attenuated single-dose vaccine (CVD 103-HgR), licensed as a traveler’s vaccine, but no longer being produced. The other two are killed whole-cell-based vaccines requiring two doses. The WC-rBS (Dukoral®) vaccine, which includes the B subunit of the cholera toxin, along with killed whole cells of *V. cholerae* O1, is also sold primarily as a traveler’s vaccine and is the only WHO pre-qualified cholera vaccine to date. A killed whole-cell vaccine that lacks the B subunit (“whole-cell only”) and is considerably less expensive to produce, and which is now bivalent (O1/O139), was produced and used exclusively in Vietnam from 1998 to 2008, making it the first oral cholera vaccine used primarily for endemic populations. This vaccine was reformulated by the International Vaccine Institute, in cooperation with the Vietnamese producer, VABIOTECH, in the mid-2000s to meet WHO and Good Manufacturing Practice (GMP) requirements and has recently been licensed in Vietnam (to replace the original vaccine). The reformulated vaccine was also licensed in India in February 2009, where it will be produced for both domestic and international use. The producer has recently applied to WHO for pre-qualification of the vaccine.

The main features and performance of these vaccines, using the criteria proposed by the *ad hoc* Working Group, are shown in Table 5 and summarized below. The results of pre-licensure clinical trials of the vaccines are shown in Table 6.

**B. Key characteristics, safety and efficacy of licensed oral cholera vaccines**

**B.1. WC-rBS (Dukoral®) vaccine**

The WC-rBS vaccine was developed at the University of Gothenburg, beginning in the 1970s, and was first licensed in 1991[9]. The vaccine, produced by Crucell/SBL Vaccines in Sweden and

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[9] The original version was made with chemically-produced cholera toxin B subunit and later the B subunit was purified using recombinant technology, hence the rBS. Both forms are nearly identical.
marketed as Dukoral®, consists of a mix of killed cells of both classical and El Tor biotypes and Inaba and Ogawa serotypes that are heat or formalin killed, plus a recombinant B subunit of the cholera toxin (Table 5). The vaccine stimulates the production of both antibacterial and anti-toxin antibodies, including IgA antibodies produced locally in the intestine.

Table 4. Criteria for cholera vaccines proposed by the ad hoc Cholera Vaccine Working Group for use in cholera-affected countries

<table>
<thead>
<tr>
<th>Feature/Characteristic</th>
<th>Criteria for use in endemic and crisis or post-crisis situations</th>
</tr>
</thead>
<tbody>
<tr>
<td>What it protects against</td>
<td>O1 El Tor (Inaba and Ogawa)</td>
</tr>
<tr>
<td>Maximum number of doses required for protection</td>
<td>2 doses</td>
</tr>
<tr>
<td>Need for booster doses acceptable and how often?</td>
<td>Booster dose every 2 years for &gt; 5 year olds and every year for &lt; 5s acceptable for use in endemic settings</td>
</tr>
<tr>
<td>Target age groups</td>
<td>2 years and above</td>
</tr>
<tr>
<td>Safety/tolerability profile</td>
<td>Only mild, short-term side effects are acceptable</td>
</tr>
<tr>
<td>Can pregnancy be contraindicated?</td>
<td>No</td>
</tr>
<tr>
<td>Can immuno-compromised status (including HIV positive) be contraindicated?</td>
<td>No</td>
</tr>
<tr>
<td>Do we need immune response surrogates?</td>
<td>Yes</td>
</tr>
<tr>
<td>Maximum time of onset of protection after full vaccination</td>
<td>2-4 weeks</td>
</tr>
<tr>
<td>Minimum efficacy rates at two years following vaccination in cholera-affected countries</td>
<td>50%</td>
</tr>
<tr>
<td>Minimum duration of sustained protection</td>
<td>1 year</td>
</tr>
<tr>
<td>Must confer herd protection?</td>
<td>Not necessary</td>
</tr>
<tr>
<td>Formulation</td>
<td>Any formulation(s) appropriate for all ages, including very young children</td>
</tr>
<tr>
<td>Buffer is acceptable?</td>
<td>Yes</td>
</tr>
<tr>
<td>Can be to administered with local water (with or without chlorination)?</td>
<td>Yes</td>
</tr>
<tr>
<td>Presentation and packaging</td>
<td>Multi-dose or single dose packaging</td>
</tr>
<tr>
<td>Cold chain requirements</td>
<td>2-8°C</td>
</tr>
<tr>
<td>Minimal shelf life</td>
<td>2 years</td>
</tr>
<tr>
<td>Need for WHO pre-qualification?</td>
<td>Not if specific country wants to use and is willing to pay for it (pre-qualification required for donor funding and UN procurement)</td>
</tr>
</tbody>
</table>
Table 5. Key features and performance of licensed oral cholera vaccines against criteria for cholera vaccines proposed by the *ad hoc* Cholera Vaccine Working Group for use in cholera-affected countries

<table>
<thead>
<tr>
<th>Feature/Characteristic</th>
<th>WC-rBS</th>
<th>CVD 103-HgR</th>
<th>Modified WC-only vaccines</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Basic Information:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Producer</td>
<td>Crucell/SBL Vaccines</td>
<td>Crucell/Berna Biotech</td>
<td>Vietnam: VABIOTECH (Hanoi)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>India: Shantha Biotechnics (Hyderabad)</td>
</tr>
<tr>
<td>Commercial name</td>
<td>Dukoral®</td>
<td>Orochol® or Mutachol®</td>
<td>Vietnam: mORCVAX</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>India: Shanchol™</td>
</tr>
<tr>
<td>Year first licensed</td>
<td>1991</td>
<td>1993</td>
<td>Vietnam: 1997 (original vaccine – ORCVAX) and 2009 for new formulation (mORCVAX)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>India: 2009 (Feb)</td>
</tr>
<tr>
<td>Vaccine type/composition</td>
<td>Killed whole cells of <em>V. cholerae</em> O1 (Inaba and Ogawa, classical and El Tor) plus recombinant cholera toxin B subunit (monovalent)</td>
<td>Live attenuated <em>V. cholerae</em> O1 classical Inaba strain 596B (monovalent)</td>
<td>Killed whole cells of <em>V. cholerae</em> O1 (Inaba and Ogawa, classical and El Tor) and O139 (bivalent)</td>
</tr>
<tr>
<td>Current availability and use</td>
<td>Sold mainly as a traveler’s vaccine in developed countries (~6 million doses sold)</td>
<td>Production was voluntarily suspended by the producer in 2004.</td>
<td>Vietnam: ~20 million doses of the original ORCVAX vaccine used by the National Immunization Program from 1998 to date in high-risk areas and during floods</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>India: Production has begun</td>
</tr>
<tr>
<td>Price to the public sector per dose</td>
<td>Will depend on production volume (2008 negotiated price to WHO: €3.57/dose (~US $5.25) for small quantity of 250,000 doses)</td>
<td>Vaccine not currently available</td>
<td>Vietnam: ~$0.75 for the modified WC vaccine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>India: $1.85 or less, depending on volume</td>
</tr>
<tr>
<td><strong>Features and performance against <em>ad hoc</em> Cholera Vaccine Working Group criteria for cholera vaccines:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>What it protects against</td>
<td>O1 classical and El Tor (Ogawa &amp; Inaba)</td>
<td>O1 classical and El Tor (Ogawa &amp; Inaba) (in North American volunteers only)</td>
<td>O1 classical and El Tor (Ogawa &amp; Inaba); possibly O139 (no clinical evaluation to date)</td>
</tr>
<tr>
<td>Number of doses required for protection</td>
<td>2 doses given 7-14 days apart (3 doses for children 2-5 years old)</td>
<td>1 dose</td>
<td>2 doses given 14 days apart</td>
</tr>
<tr>
<td>Need for booster doses and frequency</td>
<td>After two years (every six months for 2-5 year olds)</td>
<td>Unknown (serological data indicates persistent immunity for at least up to 2 years)</td>
<td>After two years (according to current data; may be longer once data from Kolkata efficacy trial become available for longer duration)</td>
</tr>
<tr>
<td>Minimal age of use according to license</td>
<td>2 years old</td>
<td>2 years old</td>
<td>Vietnam: 2 years old</td>
</tr>
<tr>
<td>Safety/tolerability</td>
<td>High, including in HIV+ individuals</td>
<td>High, including in HIV+ individuals</td>
<td>High, presumably including in HIV+ individuals, given</td>
</tr>
<tr>
<td>Feature/Characteristic</td>
<td>WC-rBS</td>
<td>CVD 103-HgR</td>
<td>Modified WC-only vaccines</td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>-----------------------------</td>
<td>--------------------------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>Is pregnancy contraindicated?</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Is use in immuno-compromised (including HIV positive) individuals contraindicated?</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Are there immune response surrogates?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Time of earliest onset of protection after full vaccination</td>
<td>1 week</td>
<td>8 days</td>
<td>Unknown</td>
</tr>
<tr>
<td>Efficacy rates at two years of follow-up in cholera-affected countries</td>
<td>58%</td>
<td>2.3% cumulative over 2 years</td>
<td>77% (67% cumulative over 2 years)</td>
</tr>
<tr>
<td>Duration of sustained protection</td>
<td>6 months in children ≤5 years of age; 2 years in persons &gt;5 years old</td>
<td>At least 6 months in N. American volunteers. Not found to be protective in endemic populations</td>
<td>At least 2 years in children and adults (3-5 years for the original Vietnamese vaccine)</td>
</tr>
<tr>
<td>Confers herd protection?</td>
<td>Yes (see section C.2. below)</td>
<td>Unknown</td>
<td>Likely, since WC vaccine in Bangladesh was found to confer herd protection (see Section C.2. below). Currently being evaluated for the modified WC vaccine in Kolkata.</td>
</tr>
<tr>
<td>Formulation</td>
<td>Liquid</td>
<td>Lyophilized</td>
<td>Liquid</td>
</tr>
<tr>
<td>Requires buffer?</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Water requirements</td>
<td>Vaccine and buffer are mixed in 150 ml of water (chlorinated or not) for persons &gt;5 years old (75 ml for 2-5 year olds).</td>
<td>Vaccine and buffer are mixed in 100 ml of non-chlorinated water</td>
<td>No water is required</td>
</tr>
<tr>
<td>Presentation and packaging</td>
<td>Single-dose vial with oral suspension (vaccine) and bicarbonate buffer in effervescent granules in sachet. Two vials/sachets per box</td>
<td>Single-dose sachets containing vaccine and bicarbonate buffer</td>
<td>mORCVAX (Vietnam): single and five-dose vials. Shanchol (India): single-dose vial. Plan to use blister pack or blow-filled seal containers</td>
</tr>
<tr>
<td>Cold chain requirements</td>
<td>License requires 2-8°C, but remains stable for 1 month at 37°C</td>
<td>2-8°C</td>
<td>License requires 2-8°C. Stability tests at ambient temperatures being studied.</td>
</tr>
<tr>
<td>Shelf life</td>
<td>3 years</td>
<td>2 years</td>
<td>2 years</td>
</tr>
<tr>
<td>WHO pre-qualified?</td>
<td>Yes</td>
<td>No</td>
<td>Application to WHO submitted in September 2009.</td>
</tr>
</tbody>
</table>
Table 6. Results of pre-licensure efficacy trials of oral cholera vaccines

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Type of Trial</th>
<th>Study Population</th>
<th>No. Participants</th>
<th>Doses and Schedule</th>
<th>Follow-up Period</th>
<th>Protective Efficacy (95% CI) at follow-up period</th>
<th>Annual Incidence in Control Group</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>WC-rBS vaccine (Dukoral®)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Matlab, Bangladesh (1985-1989)</td>
<td>Randomized placebo-controlled double blinded study (with WC-BS and WC only vaccines as study agents)</td>
<td>Children 2-15 years old and women 16 and older</td>
<td>89,596 (62,285 completed 3 doses)</td>
<td>3 doses as 6 week intervals</td>
<td>4-6 months 1 year 2 years 3 years</td>
<td>All ages (2+)* 85% (56) 62% (50) 58% (44) 18% (-14) 2-5 year olds 100% (80) 38% (7) 47% (13) Nil</td>
<td>2.7 – 5.2/1,000</td>
<td>WC-BS rather than WC-rBS was tested in this trial. The cholera detected included both El Tor and classical. Two doses were found to be as effective as three in all age groups except 2-5 year olds.</td>
</tr>
<tr>
<td>Peru (military training centers near Lima) (1994)</td>
<td>Randomized placebo-controlled double blinded study</td>
<td>Military recruits aged 16-45</td>
<td>1,426</td>
<td>2 doses given 7-27 days apart</td>
<td>4-5 months</td>
<td>86% (37-97)</td>
<td>28/1,000 attack rate over 3-6 months</td>
<td>Only El Tor cholera detected. High percent of study participants had blood type O (76%)</td>
</tr>
<tr>
<td>Peru (outskirts of Lima) (1994/5)</td>
<td>Randomized placebo-controlled double blinded study</td>
<td>2-65 year olds</td>
<td>17,799 received 2 doses (14,997 received booster dose)</td>
<td>Primary series: 2 doses 2 weeks apart. Booster dose given 10 months after 2nd dose</td>
<td>1 year 2 years</td>
<td>-3.6 (-88 – 43) 60.5 (28-79)</td>
<td>1.8 – 4.3/1,000</td>
<td>Only El Tor cholera detected. First year results excluded by EMEA due to methodological problems.</td>
</tr>
<tr>
<td>CVD 103-HgR (Orochol®)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>North Jakarta, Indonesia (1993-1997)</td>
<td>Randomized placebo-controlled double blinded study</td>
<td>2-41 year olds</td>
<td>67,508</td>
<td>1 dose</td>
<td>1 year Cumulative over 2 years Cumulative over 3 years Cumulative over 4 years</td>
<td>18% (-89 lower CI) 2.3% (-50 lower CI) 19.1% (-28 lower CI) 13.5% (-24 lower CI)</td>
<td>0.4/1,000 (average annual rate over 3 years)</td>
<td>No significant efficacy was seen at one year of follow-up, although there were too few cases to determine 6-month efficacy.</td>
</tr>
<tr>
<td>Vietnamese whole-cell only vaccine (ORCVAX) (original vaccine)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hue (1992-3)</td>
<td>Open controlled trial (no placebo and not randomized)</td>
<td>1 year and above</td>
<td>134,453</td>
<td>2 doses 2 weeks apart</td>
<td>8-10 months</td>
<td>All ages 66% (46-79) 1-5 year olds 68% (14-88)</td>
<td>1.4/1,000 (in non-vaccine group)</td>
<td></td>
</tr>
<tr>
<td>Modified whole-cell only vaccine (Shanchol™ (India) and mORCVAX (Vietnam))</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kolkata, India (2006-2009)</td>
<td>Cluster randomized placebo-controlled double-blinded study</td>
<td>1 year and above</td>
<td>66,360 (completed 2 doses)</td>
<td>2 doses</td>
<td>1 year 2 years Cumulative over 2 years (interim results)</td>
<td>45% 77% 67%</td>
<td>1.1/1,000 (1.6/1,000 in population prior to vaccination)</td>
<td>Three years of surveillance will be completed in late 2009 and efficacy results over 3 years will follow.</td>
</tr>
</tbody>
</table>

* Against El Tor and classical cholera combined. Figure in parentheses is the lower boundary of the 95% confidence interval. Source: [63].
Dukoral® has been licensed for persons two years and above. The manufacturer recommends that the vaccine be given in two doses 7-14 days apart for adults and children six years and older, and in three doses for children 2-5 years old\(^\text{20}\). Boosters are recommended every two years for persons six and above, and every six months for 2-5 year olds. To protect the cholera toxin B subunit from being destroyed by gastric acid, the vaccine must be given with a bicarbonate buffer, consisting of effervescent granules dissolved in 150 ml. of water (75 ml. for children less than six years olds) and mixed with the vaccine. The vaccine is in liquid form in a 3 ml. suspension in single-dose vials. The current packaging consists of boxes containing two single-dose vials and sachets containing the buffer salts.

Dukoral® has been shown in both pre-licensure studies and post-marketing surveillance to have a strong safety profile. In clinical trials involving around 240,000 participants, adverse effects were no more common in vaccinees than in placebo recipients (0-24%) and consisted primarily of mild abdominal discomfort or pain or diarrhea, attributed mainly to the buffer solution given to both groups [61]. While more than one million doses were sold between 1992 and 2003 in Sweden and Norway to travelers, only 63 adverse reactions were reported [61].

The oral killed whole-cell B subunit cholera vaccine was tested in randomized, placebo-controlled double-blinded efficacy trials in both Bangladesh and Peru (Table 6). The Bangladesh trial, using the WC-BS version of the vaccine in which the cholera toxin B subunit was chemically extracted, was conducted from 1985 to 1990 in Matlab district and enrolled around 90,000 children 2-15 years old and women 16 and above [62]. During the trial, both El Tor and classical cholera co-circulated in the study population. The results showed protective efficacy against El Tor and classical cholera combined at 4-6 months following vaccination of 85%, dropping to 62% at one year of follow-up, 58% during the second year of follow-up, and 18% during the third year [63]. The cumulative efficacy of the two doses of the vaccine over three years was 64% against El Tor and classical cholera combined [64]. Protection was slightly lower against El Tor than against classical cholera – 61% at one year, 38% during the second year and 19% during the third year.

The results differed considerably between young children, on the one hand, and older children and adults on the other hand. While 100% of 2-5 year olds were protected at 4-6 months following vaccination against El Tor and classical cholera combined, the level of protection dropped to 38% at the end of one year, 47% at the end of the second year and to 0% thereafter [63]. The protective efficacy for persons older than five years, including adults, on the other hand, was 78% at one year and 63% at two years. The Matlab trial also evaluated an oral whole-cell only (WC) vaccine, which showed a lower protective efficacy rate at four to six months than the WC-BS vaccine (58% vs. 85%), but a similar rate at two years of follow-up (58% vs. 57%), and a higher rate at three years of follow-up (42% vs. 18%) [63].

It therefore appeared that the B subunit significantly increases the protection of the vaccine, especially in young children, but its effect lasts only for the first nine months [65]. Two doses of the WC-BS vaccine were found to be as protective as three doses in persons six and older and thus it became a two-dose vaccine in this age group in later trials and when licensed.

The practical impact of the WC-BS vaccine was illustrated by the fact that during the first year of surveillance in Matlab, recipients of this vaccine experienced 26% fewer visits for treatment of diarrhea due to any cause, and also had a 26% lower rate of mortality from all causes [66].

Two trials of the oral WC-rBS vaccine (identical to the vaccine tested in Bangladesh except that the B subunit was produced by recombinant technology) were conducted in Peru in the early to mid 1990s during the epidemic. The vaccine conferred 86% protection against El Tor cholera in military recruits

\(^{\text{20}}\) Though the interval between doses can be up to six weeks.
aged 16-45 years old during four to five months after vaccination [67]. In a trial among nearly 18,000 children and adults on the outskirts of Lima, the vaccine showed no protection after two doses during the first year in any age group, but following a booster dose given 10 months after the primary series, the vaccine conferred 61% protection in the second year against cholera and 82% against illness requiring hospitalization [68]. The vaccine following the booster dose was more protective in adults (72% in ≥16 year olds) than in children (≈50%). However, several methodological problems affected this trial, particularly during the first year of surveillance [69], and the European Medicines Agency (EMEA) consequently discarded the first year results in its deliberations about licensing Dukoral®.

The WC-rBS vaccine was also shown to cross-protect against enterotoxigenic E coli (ETEC) in several studies. In the Bangladesh trial, it provided 67% protection against ETEC infection and 86% protection against severe dehydrating ETEC in the first three months following vaccination [61]. In studies in travelers to developing countries, the vaccine provided around 50% short-term protection against ETEC [70, 71].

Dukoral has been licensed to date in more than 60 countries, but is still used mainly as a traveler’s vaccine. It has been pre-qualified by WHO since 2001.

**B.2. CVD 103-HgR (Orochol® or Mutachol®)**

The Center for Vaccine Development (CVD) at the University of Maryland developed a live attenuated cholera vaccine derived from the classical Inaba 569B strain in the 1980s. It was engineered to express the cholera toxin B subunit, with most of the active A subunit deleted to remove its toxicity. The vaccine has the advantage of being administered in a single dose. Protective efficacy was studied in seven experimental challenge studies in North America involving a total of 103 vaccinees and 86 unvaccinated controls. In these studies, vaccinees were challenged with virulent El Tor Inaba (N=34), El Tor Ogawa (N=30) or classical Inaba (N=39) strains at different points in time (varying from 8 days to six months after ingestion of a single oral dose of CVD 103-HgR. Vaccine efficacy in preventing moderate or severe cholera (≥ 3.0 liter purge) was found to be 100% against classical and 95% against El Tor cholera, and 76% in preventing diarrhea of any [72-74]. These studies showed the vaccine to protect North American volunteers against both classical and El Tor strains, beginning as early as eight days following vaccination and persisting for at least six months [75]. The vaccine was shown to be safe and immunogenic in a series of Phase I and II randomized, controlled clinical trials in adults and children in Asia, South America and Africa [76].

Based on the results in U.S. volunteers, the CVD 103-HgR vaccine achieved licensure in 1993 as a traveler’s vaccine in several countries. It was produced by Berna Biotech (now Crucell) and sold as Orochol® (or Mutachol®) in single-dose, double-chambered sachets that contain the freeze-dried vaccine in one chamber and a sodium bicarbonate buffer in the other, which is required to protect the B subunit and live vibrios against gastric acid. The vaccine is reconstituted by mixing it and the buffer in 100 ml of water. Two different dosage amounts were available – one for developed countries and another, with ten times as many organisms, for developing countries [21].

The CVD 10-HgR vaccine was also evaluated in a large randomized, placebo-controlled Phase III trial in North Jakarta, Indonesia in the 1990s, involving more than 67,000 persons aged 2-41 years [76]. The efficacy was shown to be 18% at one year of follow-up, 2.3% over two years, and 14% (not statistically significant) over four years, though the incidence was low. There were too few cases found in the first six months following vaccination to evaluate its short-term efficacy. The vaccine was next used

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21 The higher dose for developing countries is based on immunogenicity studies in Indonesia showing that this dose was required to achieve high seroconversion rates of vibriocidal antibodies in Indonesian children [75].
in a developing country setting in Pohnpei, Micronesia in 2000/01, where it was provided during a cholera outbreak in mass vaccination campaigns in a non-randomized fashion. A retrospective cohort study estimated that the vaccine provided 79% protection (95% CIs: 72-84%) over five months against all suspected cases of cholera (both clinically diagnosed and laboratory confirmed) [77], although the study was not controlled or randomized. Production of Orochol® was suspended by Crucell in 2004 and it is not currently available.

B.3. Killed whole-cell only vaccine (mORCVAX® and Shanchol™)

The Bangladesh trial in the 1980s had also evaluated a whole-cell only vaccine without the B subunit ("WC"), in addition to the WC-BS vaccine, as described above in Section B.1. This vaccine contained the same strains as those in the WC-BS vaccine. The results showed less short-term protection against El Tor and classical cholera combined compared to the WC-BS vaccine (58% vs. 85% at four to six months of follow-up), but over the longer term, the levels of protection of the two vaccines were similar – 53% for the WC vaccine vs. 62% for the WC-BS at one year of follow-up and 57% vs. 58% during the second year of follow-up [63]. Protection of the WC vaccine was somewhat higher than the WC-BS vaccine during the third year of follow-up (42% vs. 18%) [63]. As with the WC-BS vaccine, the WC version was quite protective against El Tor and classical cholera combined in children older than five years and adults (67% and 73% during the first and second years of follow-up, respectively), and considerably less so in children two to five years of age (31% during the first year and 24% during the second year of follow-up) [61]. Against El Tor cholera, which is the only biotype of *V. cholerae* O1 currently detected globally, protection by the WC-BS and WC-only vaccines was also similar at three years of follow-up (≈40% cumulative protection).

Based on this evidence, the Vietnamese government decided to develop a whole-cell only vaccine, with assistance and technology transfer from Sweden, since the omission of the cholera toxin B subunit eliminates the need to administer a buffer and significantly reduces the cost and complexity of production and thus the price of the vaccine. In addition to omitting the B subunit, some other modifications in the mix of strains were made to the vaccine (Table 7). The vaccine is squirted into the mouth via a plastic syringe, followed by a drink of water.

The Vietnamese WC vaccine was evaluated in a large open controlled trial (with no placebo) in 1992/3 among 334,000 residents aged one year and above in the city of Hue. Following a cholera outbreak eight to ten months after the vaccination, the vaccine’s protective efficacy against El Tor cholera was shown to be 66% after two doses for all ages [78]. Unlike the results of the WC-BS vaccine, the efficacy in children one to five years old (68%) was as high as in adults (66%). The longer term protection could not be determined at the time, since cholera disappeared in Hue until several years later (see below). The O139 strain was added to the vaccine and the bivalent version was shown in non-inferiority trials in children and adults in Hanoi comparing the vaccine with Dukoral® and a placebo, to be safe and immunogenic against both O1 and O139, with similar responses to O1 as Dukoral® and stronger responses in children than adults [79]. It should be noted that the vaccine’s efficacy against O139 cholera has never been evaluated in a Phase III trial.

The bivalent WC vaccine was licensed in Vietnam in 1997, and from 1998 to 2009, more than 20 million doses were administered to children in high-risk areas of Vietnam, such as the Mekong Delta and central coastal areas, and to children and adults in pre-emptive vaccination campaigns following floods. The vaccine, produced by the government-owned producer, VABIOTECH, was sold as ORCVAX® in multi-dose vials to the National Immunization Program. Besides its low cost (≈$0.40 at the time) and the fact that no buffer is required, the vaccine also can be given to children as young as one year old – all attributes that increase its attractiveness for use in cholera-endemic countries. However, its potential use
internationally was limited, since the country’s national regulatory authority was not WHO-approved and since the vaccine was not being produced under GMP standards at the time. It also did not comply with WHO guidelines for the production of inactivated oral cholera vaccines, specifically, in the way the antigen content was determined and in the presence of low, but detectable levels of cholera toxin.

With the goal of making available internationally a low-cost oral cholera vaccine appropriate for use in cholera-endemic countries, the International Vaccine Institute (IVI), in cooperation with VABIOTECH, significantly reformulated the Vietnamese O1/O139 whole-cell vaccine in 2004 to comply with WHO guidelines. This involved replacing the high toxin-producing strain (classical Inaba 569B) with two strains (classical Inaba Cairo 48 (heat-killed) and classical Ogawa Cairo 50 (formalin-killed)) contained in the original Swedish vaccine, and doubling the quantities of LPS antigen (Table 7). To comply with WHO guidelines, new ELISA assays were developed to provide greater consistency in the LPS antigen content and to verify the complete removal of cholera toxin. Administration of the vaccine remains the same as with the Vietnamese vaccine, via the use of an oral syringe.

Table 7. Composition of killed whole-cell based oral cholera vaccines

<table>
<thead>
<tr>
<th>Element/Strain</th>
<th>WC-rBS (Dukoral®)</th>
<th>Original Vietnamese WC vaccine (ORCVax®)</th>
<th>Modified WC vaccine (modified ORCVAX® and ShancholTM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O1 strains:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ El Tor Inaba (Phil 6973), formalin-killed</td>
<td>2.5 x 10^10 cells</td>
<td>5 x 10^10 cells</td>
<td>600 EU LPS</td>
</tr>
<tr>
<td>▪ Classical Ogawa (Cairo 50), heat-killed</td>
<td>2.5 x 10^10 cells</td>
<td>2.5 x 10^10 cells</td>
<td>300 EU LPS</td>
</tr>
<tr>
<td>▪ Classical Ogawa (Cairo 50), formalin-killed</td>
<td>2.5 x 10^10 cells</td>
<td>---</td>
<td>300 EU LPS</td>
</tr>
<tr>
<td>▪ Classical Inaba (569B), formalin-killed</td>
<td>---</td>
<td>2.5 x 10^10 cells</td>
<td>---</td>
</tr>
<tr>
<td>▪ Classical Inaba (Cairo 48), heat-killed</td>
<td>2.5 x 10^10 cells</td>
<td>---</td>
<td>300 EU LPS</td>
</tr>
<tr>
<td>O139 (4260B), formalin-killed</td>
<td>---</td>
<td>5 x 10^10 cells</td>
<td>600 EU LPS</td>
</tr>
<tr>
<td>Recombinant cholera toxin B subunit</td>
<td>1 mg</td>
<td>---</td>
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</tr>
</tbody>
</table>

A clinical development plan was then developed for the modified vaccine, with the ultimate goal of attaining WHO pre-qualification to facilitate its acceptance in developing countries and enable its purchase by UN agencies (Figure 11). To make this a reality, a high-quality producer (Shantha Biotechs) in India – a country with a WHO-approved national regulatory authority – was selected to be the first recipient of the technology to produce the vaccine. Shantha meets GMP standards and produces vaccines that have been pre-qualified by WHO. The modified WC vaccine was then evaluated in Phase II double-blinded placebo-controlled randomized trials in Sonla, Vietnam and Kolkata, India to enable its licensure in both countries. The Vietnamese trial, involving 143 adults, showed the vaccine to be safe and highly immunogenic 14 days after the second dose [80]. The seroconversion rate for *V. cholerae* O1 (91%) and the mean rise in vibriocidal O1 antibodies from baseline (27-fold) were considerably higher than the results with the original Vietnamese vaccine (which had a 60% seroconversion rate and a five-fold rise in titers). This is likely due to the increased LPS content of the modified vaccine. The seroconversion rate for O139 was considerably lower (11%), but serum vibriocidal titers to O139 have been shown to be poor predictors of protection against this serotype. On the basis of these results, the modified vaccine was licensed in Vietnam in 2009 to replace the original Vietnamese WC vaccine.
Two similar Phase II trials of the modified WC-only vaccine took place in Kolkata – one among 100 adults and another among 98 children aged 1-17 years. The vaccine was shown to be safe and immunogenic in both groups, though seroconversion rates for *V. cholerae* O1 were lower than in Vietnam (53% in adults and 80% in children), due to the higher cholera endemicity in Kolkata vs. Sonla and thus higher baseline antibody levels in this population [81]. When subjects with only low baseline serum vibriocidal titers were analyzed in the Kolkata trial, seroconversion rates and geometric mean-fold rises of serum vibriocidal antibodies after vaccination were virtually identical in the two sites. The mean increase in serum antibody titres in Kolkata was 4.5-fold in adults and 12.6-fold in children.

**Figure 11. Clinical development plan for the modified oral killed whole-cell cholera vaccine**

Following these studies, the modified WC only vaccine produced in bulk in Vietnam was fill-finished at Shantha and used in a Phase III trial that began in 2006 in two slum areas of Kolkata and is ongoing. In this cluster-randomized, placebo-controlled double-blinded study, more than 67,000 children one year and above and adults received two doses of the vaccine or placebo. Interim results over two years of follow-up after vaccination reveal an overall protective efficacy of 67% against culture-confirmed cholera among those completing two doses [82]. The vaccine was shown to be protective in all age groups, including 1-4 year olds, and protection showed no decline in the second year of follow-up. Results over three years of follow-up, including estimates of herd protection, will be analyzed in late 2009.

At the same time, the technology transfer of the modified WC vaccine from VABIOTECH and the IVI to Shantha has taken place. The vaccine was licensed in India in February 2009 as a two-dose vaccine for persons one year of age and older. It will be sold under the name, Shanchol™, at a price to the public sector of $1.85 per dose or less, depending on the production volume. Shantha applied to WHO for pre-qualification of the vaccine in September 2009. Other high-quality vaccine producers are also being explored as possible recipients of the technology for the vaccine.

A study in Kolkata was recently conducted to measure the serum vibriocidal antibody response to the modified WC vaccine both after a single dose and after two doses [83]. A randomized, placebo-controlled trial among 80 children (aged 1-17) and 80 adults compared the serum antibody responses to *V.
*cholerae* O1 between subjects given the two-dose vaccine 14 days apart and those given a placebo prior to vaccination (baseline), two weeks after the first dose, and two weeks after the second dose. The results showed that the second dose did not improve immune responses in children or adults, suggesting that a single dose of the vaccine is as immunogenic as two doses. To determine if a single dose of the vaccine is protective against cholera, however, will require that it be evaluated in a Phase III trial, which is currently being planned.

**B4. Conclusions on the attributes and acceptability of currently-licensed oral cholera vaccines**

Both the oral killed WC-rBS (Dukoral®) and modified whole-cell only (Shanchol™) vaccines meet the criteria developed by the *ad hoc* Cholera Vaccine Working Group for acceptable cholera vaccines for use in cholera-affected countries, including their safety and eligibility profile, their proven efficacy, and their administration and storage requirements. Both vaccines have a strong safety profile, induce an immune response relatively quickly, and provide sustained protection of >50% over two years in endemic populations. The modified WC-only vaccine has demonstrated longer term protection in children less than five years of age, as compared to Dukoral®, and therefore does not require booster doses every six months in this age group, as does Dukoral®. On the other hand, Dukoral® has been shown in Bangladesh to provide strong short-term protection against cholera (100% for 2-5 year olds and 85% overall at 4-6 months of follow-up) and also confers significant short-term protection against ETEC, a major cause of diarrhea in crisis situations, such as floods. These two attributes may make Dukoral® a preferred choice in some crisis or post-crisis situations. There is also evidence that both vaccines confer significant herd protection, although the evidence for the modified WC only vaccine is based on an earlier version used in the Bangladesh trial, and new evidence from the Kolkata study is not yet available.

In terms of logistics and handling, both vaccines have a two-dose regimen and require a cold chain. However, Dukoral® has been shown to remain stable for a month at ambient temperatures and was not refrigerated for more than one month when used in the refugee camps in Uganda in 1997. Stability tests of the modified WC only vaccine produced in India (Shanchol™) to determine how long it can be kept outside of the cold chain are currently underway. Shanchol™, unlike Dukoral®, does not require a buffer or water for administration, although water may be given. The producer also plans to develop packaging that requires considerably less storage space than either vaccine at present and that simplifies its administration (e.g., blister packs).

The CVD 103-HgR vaccine has the important advantage of a single-dose regimen and has a strong safety profile. However, the vaccine failed to show protection in the only Phase III trial that has taken place to date in a cholera-endemic country. Therefore, further consideration of this vaccine awaits additional data on its protection in endemic populations.

While the *ad hoc* Cholera Vaccine Working Group feels that both oral killed whole-cell-based vaccines are acceptable for use now to control endemic cholera and prevent cholera outbreaks, we recognize that vaccines with improved features and performance, including a single-dose regimen and longer-term protection, would be preferable. Single-dose vaccines could especially be useful in controlling on-going outbreaks when used reactively. Several cholera vaccines are currently under development, mainly live attenuated vaccines that have the promise of providing longer term protection with a single dose. However, the most advanced cholera vaccine candidates, described in Section V. below, are at least five to ten years away from becoming available on the market. It is therefore the opinion of the Working Group that countries make use of the currently-available cholera vaccines, as part of a package of interventions to control cholera, instead of waiting many years for new vaccine candidates to perhaps available.
C. Recent evidence of the field effectiveness, feasibility and population acceptance of and demand for cholera vaccination from post-licensure studies and programmatic use

C.1. Field effectiveness and duration of protection of oral killed whole-cell cholera vaccines

A cholera vaccine demonstration project using Dukoral® was conducted in Beira, Mozambique in 2003/04 by the Ministry of Health, in collaboration with WHO, Epicentre, MSF, the IVI, and other groups [84]. The demonstration followed a recommendation made at the 2002 WHO meeting of experts on the use of oral cholera vaccines and was requested by the Government in response to frequent cholera outbreaks and increasing endemicity of the disease in the country. More than 44,000 persons aged two years and above received two doses of the vaccine, including around 11,000 persons in the target neighborhood of Esturro22. A case-control study conducted in Esturro during a cholera outbreak following the vaccination campaign allowed for the estimation of field effectiveness of the vaccine.

The study compared the cholera vaccination rate of 43 culture-confirmed cholera cases treated at the city’s Cholera Treatment Center with the vaccination rate of sex- and age-matched neighborhood controls (four for every case) [85]. The vaccine’s effectiveness was shown to be 84% for those who received two doses (78% for those who received at least one dose) over a five-month period following vaccination (Table 8). The vaccine effectiveness in 2-4 year olds was 82%. A case-control study in the same population to detect bias by comparing persons treated with non-cholera diarrhea with controls found, as predicted, no protection from cholera vaccination in these patients. The results were therefore similar to those found in the pre-licensure trials in Bangladesh using the same vaccine.

Table 8. Estimates of effectiveness of the WC-rBS (Dukoral®) vaccine over five months of follow-up from a case control study in Beira, Mozambique

<table>
<thead>
<tr>
<th>Persons vaccinated with Dukoral® No./Total No. (%)</th>
<th>Odds Ratio (95% CI)</th>
<th>Vaccine Effectiveness (95% CI) (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>Controls</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persons who received 2 doses (&quot;per protocol&quot;)</td>
<td>8/39 (21%)</td>
<td>80/156 (51%)</td>
<td>0.16 (0.05 – 0.57)*</td>
</tr>
<tr>
<td>Persons who received 1 or 2 doses (&quot;intention to vaccinate&quot;)</td>
<td>10/43 (23%)</td>
<td>94/172 (55%)</td>
<td>0.22 (0.08 – 0.61)*</td>
</tr>
<tr>
<td>2-4 year olds who received 1 or 2 doses</td>
<td>2/9 (22%)</td>
<td>22/36 (61%)</td>
<td>0.18 (0.02 – 1.19)</td>
</tr>
<tr>
<td>≥5 year olds who received 1 or 2 doses</td>
<td>8/34 (24%)</td>
<td>72/136 (53%)</td>
<td>0.33 (0.14 – 0.84)</td>
</tr>
</tbody>
</table>

* Adjusted for consumption of uncooked food, dried fish, food away from home; access to a water tap; residence in a household with electricity and ownership of multiple kitchen implements.

The significance of these results is two-fold. First, although the study was not designed to evaluate the efficacy of the vaccine in HIV seropositive individuals per se, the vaccine was shown to be protective in this population with a known prevalence of HIV infection of 20-30% in women of childbearing age. Second, since all confirmed cases were found to be infected with a variant El Tor strain of V. cholerae that expresses the classical cholera toxin (described in Section II.B.6 above), the results demonstrate that the vaccine protects against these new, increasingly dominant strains of the disease.

22 The remainder were from other parts of Beira, as explained in Section C.3.1 below.
Data on the duration of protection of killed whole-cell cholera vaccines have also become available in Vietnam. Mass vaccination in Hue using an earlier version of the locally-produced bivalent WC only vaccine took place in half of the city in 1998 and in the remaining half in 2000, resulting in nearly 222,000 persons receiving both doses, for a coverage rate of 77% [86, 87]. A cholera outbreak in 2003 in Hue made it possible to measure the long-term effectiveness of the vaccine three and five years following the mass vaccination campaigns. A case-control study was conducted comparing the proportion of vaccinees among culture-confirmed and clinically-suspected cholera cases old enough to have been vaccinated during the campaigns with the proportion of neighborhood age- and sex-matched controls who had been vaccinated. Seventy-five percent of controls had been vaccinated in either 1998 or 2000 vs. 62% of cases, resulting in a statistically significant vaccine effectiveness of 50% at three or five years (95% CI: 9-63%, p=0.023)23. The study suggests that the WC vaccine produced in Vietnam (prior to its reformulation) provided protection for at least three to five years. This is considerably longer than the protection found in the Bangladesh trial with the WC-BS vaccine, which showed only 18% protection during the third year of follow-up.

C.2. **Evidence of herd protection from oral killed cholera vaccines**

Data from the Bangladesh trial of the oral killed whole-cell-based vaccines that took place in the 1980s were recently re-analyzed to determine if the WC or WC/BS vaccines conferred any indirect (herd) protection. This could be manifested by the level of protection of non-vaccinees residing in the neighborhoods of vaccinees and by enhanced protection of vaccinees residing in the same neighborhoods. Herd effects could result from a reduction in the number of infectious persons contaminating water and food sources or from a reduction in infectivity in those vaccinated [88]. Using geographic information system (GIS) methods, family-related clusters of households called baris were grouped by the level of vaccination coverage achieved during the trial, which ranged from 4% to 65% [89]. During the first year of cholera surveillance following vaccination, placebo recipients living in baris with high vaccination coverage rates were found to be at a much lower risk of getting cholera than placebo recipients living in low vaccination coverage baris, suggesting a significant herd effect (Table 9). The incidence rate among placebo recipients in baris where the vaccine coverage was less than 28% was 7/1,000, compared to only 1.47/1,000 among those living in baris with coverage rates of more than 51% – a difference of almost five fold. Vaccine recipients living in more highly vaccinated baris were also found to be better protected than vaccinees residing in low-coverage baris.

Indirect protection was also pronounced in children who were less than two years old during enrollment for the trial and thus too young to be vaccinated [90]. The risk of getting cholera was cut in half if they lived in baris with the highest vaccination coverage vs. those who lived in the lowest coverage baris (Figure 12). The risk in children under two was independently associated with vaccine coverage in adult women, suggesting that women in rural Bangladesh play a key role in the transmission of cholera to young children, and thus could be important targets for vaccination in this setting.

An analysis of these data using a stochastic (probability) model of cholera transmission in Matlab predicted that vaccinating only 50% of the population in Matlab would result in a 93% decrease in cholera incidence in the entire population, taking both direct protection in vaccine recipients and herd protection of both vaccinees and the unvaccinated into account [91] (Figure 13). Herd protection from oral killed cholera vaccines needs to be investigated in other settings, including urban areas, as this type of protection may be affected by the epidemiology of transmission in the study area [88].

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23 The results for the single years 1998 and 2000 were not statistically significant. A bias indicator study of non-cholera diarrheal cases showed no protection from vaccination and thus no bias.
Table 9. Risk of cholera by level of cholera vaccination coverage during the first year of follow-up in the Matlab clinical trials of oral killed cholera vaccines (WC/BS and WC only)

<table>
<thead>
<tr>
<th>Level of vaccination coverage (%)</th>
<th>Vaccine recipients</th>
<th>Placebo recipients</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. Cases Risk/1,000 persons</td>
<td>No. Cases Risk/1,000 persons</td>
<td></td>
</tr>
<tr>
<td>&lt;28%</td>
<td>5,627 15 2.66</td>
<td>2,852 20 7.01</td>
</tr>
<tr>
<td>28-35%</td>
<td>8,883 22 2.47</td>
<td>4,429 26 5.87</td>
</tr>
<tr>
<td>36-40%</td>
<td>10,772 17 1.57</td>
<td>5,503 26 4.72</td>
</tr>
<tr>
<td>41-50%</td>
<td>11,513 26 2.25</td>
<td>5,801 27 4.65</td>
</tr>
<tr>
<td>&gt;51%</td>
<td>12,541 16 1.27</td>
<td>6,082 9 1.47</td>
</tr>
<tr>
<td>Total</td>
<td>49,336 06 1.94</td>
<td>24,667 108 4.37</td>
</tr>
</tbody>
</table>

Source: [88].

Figure 12. Incidence of cholera among children too young to be vaccinated (<2 years) by level of vaccination coverage of the bari during the first year of follow-up in the Matlab clinical trials

Source: [90].

Figure 13. Simulated number of cholera cases per 1,000 over a 180-day period in the Matlab study population using stochastic modeling and epidemiological data from this population
C.3. Evidence of the programmatic and logistic feasibility and population acceptance of oral cholera vaccines in endemic populations and crisis situations

Oral cholera vaccines have now been used in developing countries in several instances, including in endemic settings and among refugees and internally-displaced persons in post-crisis situations. These experiences are described below and summarized in Table 10.

C.3.1. Use in endemic settings

Vietnam (1998 to present)

Mass vaccination in Hue, Vietnam, using earlier versions of the locally-produced oral killed bivalent (O1/O139) whole-cell only vaccine, was conducted in two phases: in one half of the city in 1998 and in the remaining half in 2000. Week-long campaigns took place at schools, community health centers, government buildings and homes of group leaders, all of which were open for 12 hours each day. Ninety three-person teams conducted the campaigns in 1998 and each team vaccinated an average of 130 persons per day [86]. The vaccine was supplied in five-dose vials and the wastage rate was 10% (in 1998). Coverage in 1998 was 84% for the first dose and 79% for the second dose, with a drop-out rate of only 5%. Coverage in 2000 was similar: 76% for the first dose and 75% for the second [87].

Since 1998 cholera vaccine has been provided yearly through the national immunization program in high-risk districts, which are selected each year on the basis of routine disease reports from the districts. The vaccine is delivered through campaigns that target children 1-15 years old and are conducted before the peak cholera season. Data from the national immunization program for 2001-03 show that campaigns took place in 4-18 districts in three to five provinces each year, resulting in 235,000 to 335,000 children being vaccinated and coverage rates of 91-95%24. Pre-emptive vaccination also takes place during natural emergencies, such as floods. Since 1998, more than 20 million doses of cholera vaccine have been administered through this program.

Beira, Mozambique (2003/04)

The first use of oral cholera vaccines in Africa to control endemic disease (i.e., a non-crisis situation) was the demonstration project in Beira, Mozambique described in Section C.1 above. The vaccination was provided in a mass campaign conducted in churches and schools in the neighborhood of Esturro (population: 21,818) during two rounds in December 2003 and January 2004, with an interval of around two weeks between doses. The vaccination campaigns were preceded by multimedia information campaigns that included door-to-door visits during the second round. Dukoral® was used, which required the administration of a buffer diluted in safe water provided in cups. A total of 213 persons were deployed in teams and each team vaccinated an average of 93 persons per hour or 609 per day [84].

More than 98,000 doses of the vaccine were administered during the two rounds, with 53,700 persons receiving the first dose and more than 44,000 receiving the second, for a drop-out rate of nearly 18%. The target population of Esturro had an eligible population of only 19,550, and thus many of the people vaccinated were from outside of the study area, since anyone was allowed to receive vaccine on a

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24 Data from the National Immunization Program in Vietnam.
Table 10. Summary of the past use of oral cholera vaccines in developing countries outside of clinical trials

<table>
<thead>
<tr>
<th>Location/dates</th>
<th>Situation</th>
<th>Target population and ages</th>
<th>Vaccine used</th>
<th>No. persons vaccinated</th>
<th>Vaccination coverage rates</th>
<th>Costs</th>
<th>Overall feasibility and conclusions from experience</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endemic settings</strong></td>
<td></td>
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</tr>
<tr>
<td>Hue, Vietnam (1998 and 2000)</td>
<td>Endemic area (vaccination provided through national immunization program (NIP) in campaigns)</td>
<td>All residents one year old and above (total of 288,308 individuals)</td>
<td>Locally-produced WC-only O1/O139 vaccine (ORCVAX) in 5-dose vials</td>
<td>229,841 received at least 1 dose, 221,929 received 2 doses</td>
<td>80% for at least 1 dose and 77% for 2 doses</td>
<td>$0.89 per fully immunized person, using vaccine price/dose of $0.31</td>
<td>Cholera vaccination was found to be feasible, low cost, and well accepted by the population, with a drop-out rate between doses of around 4%.</td>
</tr>
<tr>
<td>High-risk areas of Vietnam (1998 – present)</td>
<td>Vaccine provided by the NIP in yearly campaigns to control endemic cholera and preemptively during floods</td>
<td>Children 1-15 years old in high-risk areas (Mekong Delta, Central Vietnam), and residents of all ages during floods</td>
<td>ORCVAX</td>
<td>&gt; 20 million doses have been used since 1998</td>
<td>N/A</td>
<td>Cost of the ORCVAX vaccine to the NIP was $0.40/dose</td>
<td>Cholera vaccination provided through yearly campaigns in high-risk areas has become a regular activity of the NIP, similar to yearly targeted campaigns of JE vaccination. Recorded coverage rates are high.</td>
</tr>
<tr>
<td>Beira, Mozambique (2003/04) (demonstration project)</td>
<td>Endemic area with yearly outbreaks</td>
<td>19,550 residents in the neighborhood of Esturro (2 years old and above)</td>
<td>Dukoral® (donated)</td>
<td>53,734 received 1 dose; 44,156 received 2 doses</td>
<td>Esturro population: 54%, but residents from other areas were also vaccinated.</td>
<td>$2.09 per fully immunized person without cost of vaccine (includes air shipping to Beira from Stockholm and extra salary costs)</td>
<td>Vaccination was shown to be feasible in this endemic population. Demand for the vaccine was high, especially for the first dose, illustrated by the fact that many people outside of the study area of Esturro stood in line for and received the vaccine.</td>
</tr>
<tr>
<td><strong>Post-crisis situations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Uganda (1997) (feasibility study)</td>
<td>Stable refugee setting</td>
<td>Around 44,000 Sudanese refugees in 6 camps</td>
<td>Dukoral® (donated)</td>
<td>&gt;35,000 for 1st dose; ≈27,000 for 2nd dose</td>
<td>83% for 1st dose; 76% for 2nd dose</td>
<td>$0.53 per fully immunized person for delivery (without cost of vaccine)</td>
<td>Vaccination was found to be well accepted by the population and feasible in this setting. Logistical challenges included the storage requirements due to bulky packaging of the vaccine, the need to air ship the vaccine from Entebbe due to security problems, and the time required to prepare the buffer solution.</td>
</tr>
<tr>
<td>Location/dates</td>
<td>Situation</td>
<td>Target population and ages</td>
<td>Vaccine used</td>
<td>No. persons vaccinated</td>
<td>Vaccination coverage rates</td>
<td>Costs</td>
<td>Overall feasibility and conclusions from experience</td>
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<tr>
<td>------------------------</td>
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<td>-----------------------------------------------------</td>
</tr>
<tr>
<td>Darfur, Sudan (2004)</td>
<td>Stable refugee setting</td>
<td>&gt;53,000 internally displaced persons 2 years and above in 2 camps</td>
<td>Dukoral®</td>
<td>≈40,000</td>
<td>93% for 1st dose; 88% for 2nd dose</td>
<td>$7.10 per fully immunized person, including $6.40 for vaccine and shipping, and $.70 for delivery</td>
<td>High coverage was achieved due to well-organized camps, strong community support and a relative lack of movement within the camps.</td>
</tr>
<tr>
<td>Aceh, Indonesia (2005) (in 3 phases over 6 months)</td>
<td>Complex emergency following tsunami</td>
<td>≈79,000 persons living in camps</td>
<td>Dukoral® (donated)</td>
<td>54,627</td>
<td>69% for 2nd dose (58% - 90%)</td>
<td>$8.15 per fully immunized person (not including $9.40 for vaccine and shipping costs)</td>
<td>Drop out rate was 12.6%, due to high mobility of the population in some camps. Costs were high due to the cost of the vaccine, international shipping of the vaccine, and the use of WHO consultants.</td>
</tr>
</tbody>
</table>
C.3.2. Pre-emptive use in post-crisis situations

Uganda (1997)

The first use of an oral cholera vaccine outside of vaccine trials or in travelers was a mass vaccination campaign among Sudanese refugees living in Northern Uganda in 1997. Nearly 44,000 refugees living in six settlement and transit camps were targeted for cholera vaccination [92]. The vaccine was provided over a five-week period in two rounds by two NGOs operating the camps, who set up 15 vaccination sites manned by an average of seven persons. Acceptance among this stable refugee population was high, with coverage estimated at 83% for the first dose and 76% for the second dose, for a drop-out rate of 9.5%. Logistical issues included the need to airship the vaccines from Entebbe to the camps due to security problems, and the large amount of cold storage space required, due to the bulky packaging of the vaccines.

Darfur, Sudan (2004)

In reaction to a cholera outbreak in Chad that was moving towards Sudan, cholera vaccination campaigns were conducted, with assistance from WHO and several international partners in two camps for internally displaced persons in Southern Darfur in 2004. The time from initial planning to completion of the second round was only seven weeks, and the organizers received strong support from the residents and community leaders. More than 40,000 people were fully immunized with two doses of Dukoral®, for an estimated coverage rate of 88%, suggesting strong acceptance of the vaccine among the population [93]. The relative stability of the camps (with little in- or out-migration), strong political commitment, the relatively small target population, and widespread community mobilization all contributed to the high coverage rate.

Aceh, Indonesia (2005)

The Indonesian Ministry of Health decided to conduct mass cholera vaccination campaigns in Aceh among internally displaced persons following the tsunami in 2005, using Dukoral® vaccine donated by the Swedish government and with technical support from WHO [94]. Pre-emptive vaccination was conducted in three phases in three areas over a six-month period. A total of around 79,000 people were targeted for the vaccination. Logistics were made difficult by the damaged roads – requiring the vaccine to be sent part of the way by helicopter; depletion of local health workers from death or physical injury caused by the tsunami; security problems; continual aftershocks from the earthquake; and limited cold chain capacity in the area, resulting in a 12% loss of the vaccine. The high level of movement of the population also presented a logistical challenge. The campaigns were delayed due to other competing health priorities, including a measles vaccination campaign, and social mobilization and training of health workers were limited. Despite all of these challenges, more than 54,000 persons received both doses, for an overall coverage rate of 69%, ranging from 58-90% in different areas. The drop-out rate between doses was 12.6%. There were no reported cases of cholera in the area following the vaccination campaigns, but very few cases had been reported from Aceh for several years prior to the tsunami.
These varied experiences have shown that cholera vaccination using a two-dose oral vaccine is feasible in both endemic settings and post-crisis situations. As with any vaccine, it is most feasible when provided to endemic populations, especially through the regular immunization program as in Vietnam, and to stable refugee populations. Coverage rates for the second dose – ranging from a low of 69% in the challenging situation of Aceh to a high of 95% in Vietnam – show that the challenges of using a vaccine with a two-dose regimen provided outside of the infant EPI schedule, including to many adults, can be overcome and that the vaccine is generally well-accepted in communities. For complex emergencies, such as Aceh, where there are many logistical challenges, as well as competing health priorities, WHO has developed a three-step assessment tool to assist governments to decide when cholera vaccination should be implemented, though it has yet to be field tested.

C.3.3. Costs of cholera vaccination

The costs of cholera vaccination have varied considerably (Table 10), from a low of $0.89 per fully immunized person in Vietnam, using a locally-produced vaccine provided through the national immunization program, to as much as $7.10 - $17.55 in situations where the Dukoral® vaccine was used and was shipped by air from overseas and within the country. However, the cost of delivering the vaccine (i.e., not including the vaccine cost itself) can be low even in refugee settings, as it was in Uganda ($0.55) and Darfur ($0.70) for the two doses combined. The use of a low-cost vaccine would substantially reduce the total costs of vaccination further in these and other settings.

D. Potential impact and cost-effectiveness of cholera vaccination

D.1. Impact

The practical impact of the WC-BS vaccine (what became Dukoral®) was illustrated by the fact that during the first year of surveillance in the Bangladesh trial, recipients of this vaccine experienced 26% fewer visits for treatment of diarrhea due to any cause, and also had a 26% lower rate of all-cause mortality [66]. Less information is available on the overall impact of cholera vaccination conducted outside of clinical trials on the incidence and severity of the disease in a community over time and its impact on preventing outbreaks. This is due in part to the relatively few instances where oral cholera vaccination has been used. About one year after the cholera vaccination campaigns among Sudanese refugees in selected camps in Uganda in 1997, a cholera outbreak occurred in the area. Eight percent of the 358 cases occurred among refugees (with the remainder occurring among the local population), but there was not one case in the six camps where vaccination had taken place [95]. Diarrhea rates in the vaccinated camps were also lower than in the other camps (2.8/1,000 vs. 10/1,000) and remained stable during the epidemic, but the differences were not statistically significant. These results were from an observational study that was not randomized or blinded and the field effectiveness of the vaccine could not be evaluated. Nonetheless, they suggest a protective impact of the vaccine in this population.

D.2. Cost-effectiveness

A number of cost-effectiveness analyses of cholera vaccination have been conducted in the past 10 years for both endemic and refugee populations – some based on hypothetical situations and others on real-life situations; some using global estimates of incidence, costs and other variables, and others based on empiric country-specific data from the field. The various analyses also assume the use of different cholera vaccines and different vaccine prices. The measures of cost-effectiveness have also differed across studies, with some using cost per death or case averted, and others also using cost per disability-adjusted life year (DALY) averted. The later has become the standard measure and is then compared to a
country’s GDP per capita to define an intervention’s cost-effectiveness. The results from five cost-effectiveness analyses of oral cholera vaccines are summarized below.

An analysis of vaccine cost-effectiveness in both stable refugee populations and in endemic settings was conducted by the BASICS project in the 1990s, using cholera incidence data from Malawi refugee camps in the 1980s and early 1990s and cost data from various sources [96]. The study compared the cost-effectiveness of cholera vaccination, using the WC-rBS vaccine (Dukoral®) with that of treatment, the provision of safe water, and the provision of sanitation to control cholera and simple diarrhea. The analysis assumes a cost per dose of $1.50 for the vaccine and considerably higher cholera incidence rates among refugees than endemic populations (8/1,000 per year vs. age-specific rates in endemic areas ranging from 0.3-3/1,000). The analysis estimated a cost per DALY averted for cholera vaccination in endemic populations of nearly $3,000 – the least cost-effective of the interventions analyzed – while the cost/DALY averted for vaccination in a stable refugee population declines to $269, on a par with the cost-effectiveness of water and sanitation combined ($276).

Another analysis published in 1998 used a hypothetical refugee camp setting and epidemiological data from the Malawi camps in 1980s and early 1990s [97]. Assuming an 80% probability of a cholera epidemic over two years in a stable refugee population in Africa, an attack rate of 3.65% of the population and a cost/dose of $0.50 for Dukoral®, and using actual treatment costs from Médecins sans Frontières (MSF) in such settings, the analysis estimates that adding pre-emptive vaccination to a strategy of setting up a camp to prepare for cholera case management, including IV rehydration (“pre-emptive treatment”) would cost an additional $71 per case averted and $1,745 per death averted25. However, adding preemptive vaccination to preventive treatment becomes more cost-effective than preventive treatment alone when the cost of the vaccine declines to $0.22/dose. Pre-emptive vaccination also prevents more deaths and costs less than treatment alone once the cost falls below $0.16 per dose.

A cost-effectiveness model of cholera vaccination was developed by ICDDR,B, based on estimated costs and incidence rates from Bangladesh, where cholera is endemic [27]. Based on the data from the Bangladesh trials of whole-cell-based vaccines, the model attempted to determine if the use of the vaccine would save money relative to current costs for treatment. The model estimated that the cost of treatment was approximately US$350 per life saved, and assumed that facilities were already established for treatment of patients with other diarrheal diseases. The model found that the key determinants for cost effectiveness were: a) the incidence of cholera and, b) the cost of the vaccine. While important, the absolute value for protective efficacy had less of an impact on the cost effectiveness than the other two variables. When the incidence of the cholera exceeded three per thousand and the cost of the vaccine was less than US$0.40, the vaccine saved money relative to treatment. The model did not examine the cost per DALY averted, nor did it address the issues of equity of the costs for treatment versus the cost of vaccine. The analysis was also based on cost estimates as opposed to a costing study.

The Disease Control Priorities (DCP) Project, launched in 2001, looked at the cost-effectiveness of diarrhea interventions, including cholera vaccination, in children under five years of age only, assuming the use of a single-dose live vaccine and a cost per vaccination of $3.65 [98]. The analysis, which made broad global assumptions for cholera disease incidence, found cholera vaccination not to be very cost-effective ($2,945/DALY averted), compared to other interventions to reduce mortality in this age group (e.g., breastfeeding promotion, measles vaccination, ORT, water and sanitation improvements in rural areas). However, unlike rotavirus, measles and other childhood diseases, cholera is not a disease that primarily kills children under five and thus an analysis limited to this population underestimates the cost-effectiveness of cholera vaccination in the general population in an endemic or epidemic situation.

---

25 DALYs were not used in this analysis.
The most recent and most comprehensive cost-effectiveness analysis of cholera vaccination was conducted by the Diseases of the Most Impoverished (DOMI) Program [99]. The analysis provides cost-effectiveness estimates for four study sites (Beira, Mozambique; Kolkata, India; Matlab, Bangladesh; North Jakarta, Indonesia), and is based on site-specific data derived from prospective studies of incidence, cost-of-illness and private demand (to estimate vaccine uptake) obtained during several years of field research. The DOMI analysis assumes a 1% case fatality rate; the use of the two-dose oral killed modified whole-cell only cholera vaccine (Shanchol); and a vaccine effectiveness of 60% over three years. It also assumes a vaccine price of $1.00 per dose, based on Shantha’s targeted public sector price for large-scale production; and a vaccine delivery cost of $0.50 per dose in low-income countries and $1.00/dose in middle-income countries. The analysis examines only the costs to the public sector, and thus the costs-of-illness incurred by individuals and families are not taken into account, potentially underestimating the cost-effectiveness from a societal perspective. The analysis also examines the vaccine’s cost-effectiveness with and without herd protection taken into account, using modeling based on estimates of herd protection from the Bangladesh clinical trials described in Section IV.C.2 above. Three vaccination programs were assessed: those for school-aged children only (5-14 years old); those that included both pre-school and school-aged children (1-14 years old); and those that included all persons one year and older, including adults.

The results show that across sites and programs, only the program for 1-14 year olds in Kolkata would be cost-effective (defined as the cost/DALY averted is <3 times the GDP/capita, using the standard WHO definition), if the herd effects of cholera vaccination are not incorporated into the analysis (Table 11). The picture changes considerably once herd protection is taken into account. All programs in all four sites would then be cost-effective, and the programs for children (1-14 and 5-14 years old) would be “very cost-effective” in Beira and Kolkata (defined as cost/DALY averted is < GDP/capita), and cost-effective in Matlab.

E. Considerations regarding the possible use of oral cholera vaccines and vaccination strategies

In deciding whether to use cholera vaccination in a specific setting or circumstance, the magnitude of the incidence of either endemic or epidemic cholera will be an important determinant. For example, there are some areas of the world, such as the Gulf of Mexico Coast of the U.S., where cholera is endemic but, because of a high level of water quality and sanitary conditions, the disease occurs as a minor problem among the human population and vaccination with cholera is clearly not indicated. Even among high incidence populations, it is important to consider two factors. First, even in the most highly endemic settings in the world that have been well characterized for cholera incidence, such as Matlab, Bangladesh, the incidence of cholera can vary by as much as 25-fold from year to year. For example, during the period of 1966-1980, comprehensive, population-based surveillance in Matlab revealed the average yearly incidence to be 2.1 cases/1,000 population. However, from year to year, the annual incidence varied from a low of 0.2 cases/1,000 population to a high of 5.1 cases/1,000 population. Thus, a period of only a few years of surveillance may not be sufficient to define the magnitude of the cholera disease burden affecting a population. Second, most areas of the world with cholera do not have reliable population-based statistics on cholera incidence. For both of these reasons, a threshold incidence of cholera in endemic settings that would trigger vaccination is not easily defined, and the threshold is better assessed by local policymakers in terms of the local public health importance of cholera.

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26 The Jeuland paper assumed a base case price of $0.60/dose. The analysis was revised for this background paper using a base-case price of $1.00 per dose, after obtaining price information from Shantha.
Table 11. Results of the DOMI Program cost-effectiveness analysis of cholera vaccination, assuming use of the modified oral killed whole-cell vaccine ($1.00/dose in 2007 dollars), with and without herd effects.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Matlab, Bangladesh</th>
<th>Kolkata, India</th>
<th>N. Jakarta, Indonesia</th>
<th>Beira, Mozambique</th>
<th>Matlab, Bangladesh</th>
<th>Kolkata, India</th>
<th>N. Jakarta, Indonesia</th>
<th>Beira, Mozambique</th>
</tr>
</thead>
<tbody>
<tr>
<td>Programs targeting school children (5-14 years old)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number vaccinations</td>
<td>21,296</td>
<td>16,036</td>
<td>14,421</td>
<td>65,938</td>
<td>21,296</td>
<td>16,036</td>
<td>14,421</td>
<td>65,938</td>
</tr>
<tr>
<td>Cases avoided over three years</td>
<td>56</td>
<td>60</td>
<td>7</td>
<td>322</td>
<td>341</td>
<td>301</td>
<td>65</td>
<td>651</td>
</tr>
<tr>
<td>% reduction in cases over three years</td>
<td>5%</td>
<td>6%</td>
<td>3%</td>
<td>5%</td>
<td>33%</td>
<td>31%</td>
<td>30%</td>
<td>38%</td>
</tr>
<tr>
<td>Deaths avoided over three years</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>26</td>
</tr>
<tr>
<td>Net public cost per DALY avoided</td>
<td>$4,031</td>
<td>$2,858</td>
<td>$28,851</td>
<td>$2,371</td>
<td>$643</td>
<td>$542</td>
<td>$3,242</td>
<td>$213</td>
</tr>
<tr>
<td>GDP/capita</td>
<td>$486</td>
<td>$871</td>
<td>$1,812</td>
<td>$382</td>
<td>$486</td>
<td>$871</td>
<td>$1,812</td>
<td>$382</td>
</tr>
<tr>
<td>3 times GDP/capita</td>
<td>1,458</td>
<td>$2,613</td>
<td>$5,436</td>
<td>$1,146</td>
<td>1,458</td>
<td>$2,613</td>
<td>$5,436</td>
<td>$1,146</td>
</tr>
<tr>
<td>Cost-effectiveness rating</td>
<td>Not cost-effective</td>
<td>Not cost-effective</td>
<td>Not cost-effective</td>
<td>Not cost-effective</td>
<td>Cost-effective</td>
<td>Very cost-effective</td>
<td>Cost-effective</td>
<td>Very cost-effective</td>
</tr>
<tr>
<td>Programs targeting children 1-14 years old</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number vaccinations</td>
<td>34,475</td>
<td>23,702</td>
<td>19,712</td>
<td>89,282</td>
<td>34,475</td>
<td>23,702</td>
<td>19,712</td>
<td>89,282</td>
</tr>
<tr>
<td>Cases avoided over three years</td>
<td>141</td>
<td>151</td>
<td>21</td>
<td>672</td>
<td>517</td>
<td>448</td>
<td>91</td>
<td>3393</td>
</tr>
<tr>
<td>% reduction in cases over three years</td>
<td>14%</td>
<td>16%</td>
<td>10%</td>
<td>10%</td>
<td>50%</td>
<td>47%</td>
<td>42%</td>
<td>49%</td>
</tr>
<tr>
<td>Deaths avoided over three years</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>7</td>
<td>5</td>
<td>4</td>
<td>1</td>
<td>34</td>
</tr>
<tr>
<td>Net public cost per DALY avoided</td>
<td>$2,544</td>
<td>$1,621</td>
<td>$13,111</td>
<td>$1,479</td>
<td>$689</td>
<td>$534</td>
<td>$3,152</td>
<td>$227</td>
</tr>
<tr>
<td>Cost-effectiveness rating</td>
<td>Not cost-effective</td>
<td>Cost-effective</td>
<td>Not cost-effective</td>
<td>Not cost-effective</td>
<td>Cost-effective</td>
<td>Very cost-effective</td>
<td>Cost-effective</td>
<td>Very cost-effective</td>
</tr>
<tr>
<td>Parameters</td>
<td>Matlab, Bangladesh</td>
<td>Kolkata, India</td>
<td>N. Jakarta, Indonesia</td>
<td>Beira, Mozambique</td>
<td></td>
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<tr>
<td>------------------------------------------------------</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Programs for children and adults (1 year and older)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number vaccinations</td>
<td>72,653</td>
<td>82,796</td>
<td>38,473</td>
<td>257,595</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases avoided over three years</td>
<td>207</td>
<td>244</td>
<td>30</td>
<td>1772</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% reduction in cases over three years</td>
<td>20%</td>
<td>25%</td>
<td>14%</td>
<td>26%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deaths avoided over three years</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>18</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Net public cost per DALY avoided</td>
<td>$3,896</td>
<td>$3,812</td>
<td>$19,199</td>
<td>$1,851</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost effectiveness rating</td>
<td>Not cost-effective</td>
<td>Not cost-effective</td>
<td>Not cost-effective</td>
<td>Cost-effective</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: [99].
Taking all of these considerations into account, it is proposed that cholera vaccination be used pre-emptively for populations in which culture-confirmed cholera has become endemic, as demonstrated by its microbiologically-documented occurrence in at least three of the past five years, and in which public health policymakers consider cholera to be a significant public health problem. For areas or populations at high risk of epidemic cholera due to factors such as climatic conditions or poor sanitation, it is proposed that the vaccine be considered for use to reduce the threat of cholera outbreaks. This recommendation includes the use of the vaccine in endemic settings with unexpectedly high surges in disease incidence.

The most appropriate strategies regarding which geographic areas, ages, and population groups to target for vaccination to control endemic cholera; how to deliver the vaccines (e.g., through mass vaccination campaigns vs. routine immunization); and other issues to consider will differ by country, depending on the epidemiological pattern of cholera in the country, the capacity of the immunization program and health system, the availability of funding and other circumstances. This is especially true since current cholera vaccines can not be given to infants and therefore simply added to the infant EPI schedule. Adults will also be appropriate targets for cholera vaccination in many countries. Therefore, countries will need to consider a variety of delivery strategies and venues – beyond the traditional EPI venues – that are appropriate for the target groups and the specific economic, cultural and other conditions of the country. In countries where booster doses of EPI vaccines are provided to children beyond infancy, for example, it could be appropriate to add cholera vaccine to the routine schedule (e.g., at 18 months or two years of age) as a complement or alternative to mass vaccination campaigns.

Therefore, instead of recommending specific strategies for cholera vaccination for countries to follow, the ad hoc Cholera Vaccine Working Group suggests a series of options for countries to consider that have been shown to be feasible in different cholera vaccine studies and demonstration projects. These options are given in Section VI (Proposed Recommendations) below.
V. Cholera vaccines under development

### Key points:

1. There are several cholera vaccines in development, which aim to improve upon the performance and characteristics of the currently available vaccines.

2. The three most advanced candidate vaccines are all oral, live attenuated mutants of *V. cholerae* that are designed to confer protection in a single dose and have the potential of providing greater and longer term protection than currently available cholera vaccines.

3. However, none of the most advanced candidates has yet gone beyond Phase II testing and thus will not likely be available on the international market for at least another five to ten years.

Several cholera vaccines are in development, which aim to improve upon the performance and characteristics of the currently available vaccines. Many of the vaccine candidates are oral live attenuated mutants of *V. cholerae* that use recombinant techniques to delete or mutate genes that encode virulence factors. These live vaccines theoretically have several advantages over the two-dose killed whole-cell vaccines. First, they can potentially be administered in a single dose, since live organisms could result in intestinal colonization, eliminating the need for repeat dosing [100]. A single-dose vaccine, when provided reactively, could therefore be effective in halting explosive cholera outbreaks once they begin. Second, live vaccines, by responding to the intestinal environment and immunological exposure to *in vivo*-expressed bacterial products, could confer greater and longer term protection than the currently available vaccines [100]. In addition, they may be effective in infants and thus could be integrated into infant immunization schedules, greatly facilitating routine cholera vaccination to control endemic disease.

The potential disadvantages of these vaccine candidates at present are that they could theoretically mutate in the environment and become virulent, they require administration with a buffer, and they must be kept frozen.

Even the most advanced candidate cholera vaccines are unlikely to be available on the market for another five to ten years, at the earliest. The most advanced live attenuated cholera vaccine candidates and the most recent studies of these vaccines are summarized in Tables 12 and 13, respectively, and described below.

### A. Peru-15 (Vaccine Technologies, Inc. (VTI), U.S.A. and China)

Peru-15 was developed at Harvard University in the 1990s from a wild strain of *V. cholerae* O1 El Tor Inaba isolated in Peru. The vaccine was engineered to be non-toxinogenic by deleting the ctxA gene that encodes the cholera toxin A subunit, the rtxA gene that encodes the RTX toxin, and the *zot* and *ace* genes. It also lacks flagella, rendering it nonmotile to increase its tolerability and is non-recombinational. The vaccine, transferred to Avant Immunotherapeutics (now Celldex) and then to VTI, is freeze-dried and must be kept frozen. Plans are underway to improve the vaccine’s heat stability to enable its storage at 2-8°C. The vaccine requires a buffer for administration.

In a randomized, placebo-controlled study among U.S. volunteers, the vaccine (provided in a single 2x10⁸ CFU dose) was found to be safe and 98% of vaccinees seroconverted for vibriocidal antibodies (defined as ≥4-fold rise in titers from baseline) [101]. A challenge study three months after...
vaccination among a subset of 36 volunteers resulted in diarrheal rates of 58% among placebo recipients and 4% among vaccinees, for a protective efficacy of 93% [101]. The vaccine was then tested among 70 adults and 240 children 9 months to five years of age in Phase I and II studies in an endemic population in Dhaka, Bangladesh (Table 13) [102, 103]. The vaccine was shown to be safe, with no significant differences in rates of adverse events – all of which were mild – between vaccine and placebo recipients. Seroconversion rates for vibriocidal antibodies ranged from 70% in 9-23 month old, to 75% in adults and 84% in 2-5 year olds. The vaccine also stimulated gut-associated immune responses – with seroconversion rates for LPS-specific IgA antibodies in sera (defined as ≥2-fold rise in titers from baseline) of 88% in adults, 60% in toddlers, and 34% in 9-23 month olds. Seventy-eight percent of adults also responded with LPS-specific IgA antibody-secreting cells (ASC). Responses to cholera toxin were lower, ranging from 46% in toddlers to <20% in adults. Peru-15 was found to invoke immune responses quite rapidly – with the highest increases in antibody titers seen seven days following vaccination in both children and adults.

Table 12. Key characteristics of the most advanced oral live attenuated cholera vaccine candidates

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Peru-15</th>
<th>V. cholerae 638</th>
<th>VA1.4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Developer</td>
<td>Harvard University</td>
<td>Finlay Institute, Cuba</td>
<td>3 Indian government research laboratories</td>
</tr>
<tr>
<td>Producer</td>
<td>VTI, U.S. and China</td>
<td>Finlay Institute, Cuba</td>
<td>Shantha Biotechnics, Hyderabad, India (contract manufacturer)</td>
</tr>
<tr>
<td>Parent strain</td>
<td>O1 El Tor Inaba (C6709)</td>
<td>O1 El Tor Ogawa (C7258)</td>
<td>Non-toxigenic O1 El Tor Inaba strain</td>
</tr>
<tr>
<td>How attenuated</td>
<td>Deletion of entire cholera toxin genetic element and engineered to be non-motile and non-recombinational</td>
<td>Deletion of entire cholera toxin genetic element (CTXΦ) and modification of the hapA gene</td>
<td>Original strain is non-toxigenic (devoid of CTX prophage)</td>
</tr>
<tr>
<td>No. doses</td>
<td>One</td>
<td>One</td>
<td>One</td>
</tr>
<tr>
<td>Formulation</td>
<td>Lyophilized</td>
<td>Lyophilized</td>
<td>Lyophilized</td>
</tr>
<tr>
<td>Need for buffer?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Will be effective in infants?</td>
<td>Potentially (Phase II studies in infants underway)</td>
<td>Data not yet available</td>
<td>Data not yet available</td>
</tr>
<tr>
<td>Cold chain requirements</td>
<td>Must be kept frozen at -20°C</td>
<td>Must be kept frozen at -20°C (can be kept for 3 months at 2-8°C)</td>
<td>Must be kept frozen at -20°C</td>
</tr>
<tr>
<td>Stage of development and human testing</td>
<td>Phase I/II trials in adults, toddlers and infants completed in Bangladesh. Studies underway in 9-12 month-olds when co-administered with measles vaccine in Bangladesh and India and in HIV+ adults in Thailand.</td>
<td>Series of Phase II and challenge studies in adults completed in Cuba. Phase I/II study completed in 2007 in adults in Mozambique. Vaccine will next be tested in children in Phase I/II studies in endemic countries, followed by a Phase III clinical trial.</td>
<td>Phase I/II study in adult men in Kolkata, India completed for VA1.3 vaccine. Phase I/II studies of new version (VA1.4) being planned in Kolkata.</td>
</tr>
<tr>
<td>Will producer apply for WHO pre-qualification?</td>
<td>Yes, if Phase III clinical trial results are positive. Vaccine was developed especially for use in cholera-endemic countries in Africa.</td>
<td>Yes, if clinical trial results are positive. Vaccine was developed especially for use in cholera-endemic countries in Africa.</td>
<td>Likely, if results of clinical trial are positive.</td>
</tr>
</tbody>
</table>
Since Peru-15 is a live vaccine that can potentially mutate in the environment and convert to virulence, its genetic stability after passing through humans was studied, as was the rate of excretion of the vaccine into the environment. The vaccine was found in the adult study to be unchanged after passing through the human gut and was excreted in 1/40 adults (2.5%) and 9/120 children (7.5%).

The vaccine is currently undergoing testing of its safety and immunogenicity in nine month olds, when co-administered with measles vaccine (in Bangladesh and India) and in HIV positive adults (in Thailand). These studies will provide important data on whether the vaccine can be given to infants and is safe and immunogenic in HIV positive individuals. A Phase III efficacy trial to take place in Matlab, Bangladesh is being planned.

B. *V. cholerae* 638 (Finlay Vaccine Institute, Cuba)

Researchers in Cuba developed the live 638 cholera vaccine in the 1990s from an O1 El Tor Ogawa strain (C7258). The entire cholera toxin genetic element (CTXΦ) was removed from the bacterium, and the hapA gene that encodes a hemagglutinin/protease (HAP), possibly responsible for the reactogenicity of earlier live vaccine candidates, was modified [75, 100]. The vaccine, provided in a single dose of $10^9$ CFU, has a freeze-dried formulation and is administered with a buffer. In an early placebo-controlled study among adults in Cuba, the vaccine was found to cause mild adverse events (e.g., loose stools) in 10% of subjects and to be immunogenic, with serum vibriocidal responses in 71-82% of vaccinees and anti-Ogawa LPS IgA ASC responses in 85-100% [100].

A pilot Phase I/II study in 45 men in Havana aged 18-40, conducted in the early 2000s and using a fresh culture of the vaccine prepared *in situ*, found no significant differences in adverse events between vaccine and placebo recipients and no severe adverse events [104]. The seroconversion rate after a single dose of the vaccine was 96% for serum vibriocidal antibodies against Ogawa (defined as $\geq 4$-fold rise in titers from baseline) 14 days after inoculation, and 50% for LPS-specific IgA titers (defined as a $\geq 2$-fold rise in titers). To test the vaccine’s protective efficacy, a subset of 21 subjects (12 vaccinees and nine placebo recipients) was challenged with a virulent dose of cholera one month after dosing. While 78% of placebo recipients (7/9) had diarrhea following the challenge, including two who developed severe cholera, none of the 12 vaccine recipients had diarrhea, resulting in a 100% protective efficacy rate.

Once the vaccine was prepared as a lyophilized product packaged with an antacid buffer, randomized placebo-controlled Phase I/II trials of the vaccine were conducted among 36 adults in Havana, Cuba (in 2005-06) and 120 adults in Maputo, Mozambique (in 2006/07) (R Barbera, personal communication). The vaccine was well tolerated in both trials, though 75% of vaccinees in Havana experienced mild adverse events (stomach rumbling, abdominal pain, nausea) vs. around one-third of placebo recipients. In Mozambique, no significant differences in adverse events were found between vaccine and placebo recipients, including those positive for HIV, hepatitis A, B or C. The seroconversion rates (defined as $\geq 4$-fold rise in titers from baseline) were 100% in the Cuban trial and 97% in the Mozambique study. The results of both trials are expected to be published in 2009 or 2010.

Finlay Institute, the developer and producer of the vaccine, plans on testing the vaccine in Phase I and II trials in children in cholera-endemic areas, before conducting a Phase III clinical trial. Their intention is to have the vaccine WHO pre-qualified for use in cholera-endemic countries in Africa and elsewhere.
C. VA1.4 vaccine (Government of India)

This vaccine was developed by three government-run research laboratories in India from a non-toxigenic strain of *V. cholerae* O1 El Tor, to which the ctxB gene that encodes the cholera toxin B subunit was added. The previous version of the vaccine, VA1.3 also included a gene encoding resistance to ampicillin [105]. The vaccine, provided in a single dose of 5x10⁹ CFU, is, like other live cholera vaccines, lyophilized and administered with a buffer.

### Table 13. Results of recent human studies of the most advanced live attenuated cholera vaccine candidates

<table>
<thead>
<tr>
<th>Study information and data</th>
<th>Peru-15 (U.S.)</th>
<th><em>V. cholerae 638</em> (Cuba)</th>
<th>VA1.3 (India)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of study</td>
<td>Double-blinded randomized, placebo-controlled Phase I/II field trials</td>
<td>Double-blinded randomized, placebo-controlled Phase I/II studies</td>
<td>Double-blinded randomized, placebo-controlled Phase I/II study</td>
</tr>
<tr>
<td>Location</td>
<td>Dhaka, Bangladesh</td>
<td>Havana, Cuba and Maputo, Mozambique</td>
<td>Kolkata, India</td>
</tr>
<tr>
<td>Number and type of subjects</td>
<td>70 adults 18-45 years of age; 240 children 9 months – 5 years of age</td>
<td>36 adults 18-40 years of age in Havana; 120 adults 18-50 in Maputo</td>
<td>304 men aged 16-50</td>
</tr>
<tr>
<td>Safety results</td>
<td>No significant differences in rates of side effects between vaccine and placebo recipients. Mild symptoms in 3% of children and 5% of adults vaccinated.</td>
<td>No significant differences in side effects between vaccine and placebo recipients in Mozambique. In Cuba, 75% of vaccinees vs. 18% of placebo recipients had mild adverse events.</td>
<td>Mild adverse events in 3/186 vaccinees (1.6%)</td>
</tr>
<tr>
<td>Vibriocidal seroconversion rates (≥4-fold rise in titers from baseline)</td>
<td>Adults – 75%; 2-5 year olds – 84%; 9-23 month olds – 70%</td>
<td>100% in Havana; 97% in Maputo</td>
<td>57%</td>
</tr>
<tr>
<td>Seroconversion rates for LPS-specific IgA in sera (≥2-fold rise in titers from baseline)</td>
<td>(for Inaba): Adults – 88%; 2-5 year olds – 60%; 9-23 month olds – 34%</td>
<td>Not available</td>
<td>Not available</td>
</tr>
<tr>
<td>Seroconversion rates for cholera toxin IgA antibody in sera (≥2-fold rise in titers from baseline)</td>
<td>Adults – 7.5-17.5%; 2-5 year olds – 46%; 9-23 month olds – 36%</td>
<td>Not available</td>
<td>77% in vaccinees vs. 32% in placebo recipients</td>
</tr>
<tr>
<td>Rate of fecal shedding</td>
<td>Adults – 0.7%; Children – 7.5%</td>
<td>46% in Mozambique</td>
<td>0%</td>
</tr>
<tr>
<td>Other results</td>
<td>In challenge study in Havana among 21 volunteers 1 month after inoculation, 78% of placebo recipients had diarrhea (2 severe) vs. 0% of vaccinees.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*The vaccine has since been further modified and is now called VA1.4.*

The VA1.3 version of the vaccine was tested in a double-blinded randomized placebo-controlled Phase I/II study among 304 men 16-50 years of age in Kolkata, India, which took place from 1999 to 2004. The vaccine was found to be very safe, with mild adverse events experienced by 3/186 vaccinees.
(1.6%). The rate of seroconversion among vaccinees was 57% for vibriocidal antibodies 15 days after vaccination and 77% for anti-cholera toxin antibodies (≥ 2-fold rise in titers). No fecal shedding of the vaccine occurred in any of the vaccine recipients. Since the trial, the ampicillin resistance was removed from the vaccine, creating the current VA1.4 vaccine. Additional Phase II studies are now required because of this modification and are being planned in Kolkata.

Several other cholera vaccine candidates are at earlier stages of development. This include the Chinese oral live attenuated IEM 108 vaccine, derived from a naturally-attenuated strain of O1 El Tor Ogawa [106]; an injectable conjugate vaccine, consisting of *V. cholerae* O1 Inaba LPS bound to cholera toxin, which was shown in a Phase I study to be safe and to stimulate anti-cholera toxin antibodies [6]; several live vaccines against O139; and other conjugate, subunit and DNA vaccines.
VI. Proposed Recommendations

General:

1. Given the current availability of two oral cholera vaccines (one pre-qualified and the other pending pre-qualification) and new data on their efficacy, field effectiveness, feasibility and acceptance in cholera-affected populations, immunization using these vaccines should be used in areas with endemic cholera and should be considered for use in areas at risk for cholera outbreaks, in conjunction with other cholera prevention and control strategies.

2. Vaccination against cholera should be considered as synergistic and not in competition with water and sanitation improvements and other traditional means of controlling cholera.

3. WHO should prioritize the evaluation for pre-qualification of the modified whole-cell only vaccine and other future cholera vaccines as they become available.

4. While specific cholera surveillance studies are not recommended for every country and setting, it is strongly recommended that surveillance for microbiologically-confirmed cases of cholera be instituted (e.g., via regional or sub-regional networks) to measure the burden of disease and impact of vaccination and other interventions.

Control of endemic cholera:

5. Specific cholera vaccination strategies regarding whether, when, where and how to vaccinate against cholera should not be prescribed to countries, since the appropriate strategies will differ by country, depending on its epidemiological pattern of cholera, capacity of the immunization program and health system, and other local factors. The ad hoc Working Group instead suggests that countries consider the following options for strategies to control endemic cholera through vaccination:

   - **Scope of vaccination:** Universal vaccination (throughout a country) is not warranted in most countries, with some exceptions. Therefore, cholera vaccination can primarily be targeted to high-risk areas and populations.

   - **Where to vaccinate:** Vaccination should be targeted to areas where two of the following criteria are met: a) culture-confirmed cholera has been detected in at least three out of the last five years; b) an incidence rate of cholera of at least 1/1,000 in any of these years has been recorded; or c) if population-based incidence rates are not available, high-risk areas or groups have been identified, based on information collected from local public health officials.

   - **Age groups to target:** Although all age groups are vulnerable to cholera, priority should be given to high-risk groups, if resources are limited. The primary targets for cholera vaccination in many countries will therefore be pre-school and school-aged children. Other groups that are especially vulnerable to severe disease and for which the current vaccines are not contraindicated, can also be targeted, such as pregnant women and HIV-infected individuals. Countries should also consider vaccination of older age groups if funding is available.

   - **Vaccine delivery strategies:** Periodic mass vaccination campaigns are usually the most practical option for delivering oral cholera vaccines. Schools, religious institutions and other community settings can be appropriate venues for vaccination campaigns. Incorporating
cholera vaccination into routine vaccination schedules can be an alternative or complementary strategy to mass vaccination campaigns (for instance, to reach young children between campaigns).

- **Frequency of vaccination:** Since the documented duration of significant protection for the currently-available oral cholera vaccines is two years, it is currently recommended that initial vaccination with two doses be followed by revaccination every second year. Once data on the longer-term efficacy of any oral cholera vaccine becomes available, the recommended interval between initial and booster vaccinations could be extended.

**Control of cholera outbreaks:**

6. Pre-emptive vaccination should be considered by local health authorities to help prevent potential outbreaks or the spread of current outbreaks to new areas.

7. The development of predictive risk assessment tools to help countries determine when pre-emptive cholera vaccination could be used is an urgent need and should be made available and field-tested as soon as possible.

8. Given recent large prolonged outbreaks of cholera (e.g., in Angola and Zimbabwe), reactive vaccination could be considered by local health authorities as an additional control measure, depending on the local infrastructure and following a thorough investigation of the current and historical epidemiological situation and a clear identification of geographical areas to be targeted. Given the lack of experience with reactive vaccination against cholera, the feasibility and impact of vaccination in halting ongoing outbreaks should be documented and widely disseminated.

9. Appropriate treatment of cholera cases, water and sanitation interventions, and community mobilization should remain the mainstays of control measures during ongoing cholera epidemics.

10. Pre-emptive or reactive cholera vaccination should cover as many people eligible to receive the vaccine as possible (e.g., ages ≥ 1 or 2 years, depending on the vaccine), and should be conducted as quickly as possible.

11. Vaccination should not disrupt the provision of other priority health interventions to control or pre-empt cholera outbreaks.

**Research needs:**

12. Further research is recommended in a number of areas to guide policy for the use of oral cholera vaccines, including improved methods of cholera surveillance, operations research to evaluate different vaccination strategies, the testing of reactive vaccination using the currently available oral killed whole-cell-based vaccines to evaluate its impact and feasibility in halting ongoing outbreaks, and research to improve the logistics of using oral cholera vaccines (e.g., new formulations). Suggested research needs are listed in Section VII.
VII. Research Needs for Cholera Vaccines

There is sufficient evidence on which to base the new proposed recommendations on the use of cholera vaccine. However, additional research will improve the effectiveness of the vaccine and will help to focus vaccination on situations where it will provide the most benefit.

A. Surveillance of cholera to guide vaccine use

1. Improved surveillance methods are needed to understand the magnitude of cholera as a public health program in each nation or region, including risk factors for cholera and cholera outbreaks. These methods should be rapid and reliable, but inexpensive.

2. Methods are needed to monitor vaccine usage so that the benefits of the vaccine are understood by national policy makers. This includes providing evidence of herd protection when the vaccine is used widely, monitoring population demand and acceptance of the vaccine, and assessing government responsiveness when cholera outbreaks threaten.

3. Reactive vaccination should be carefully documented and its impact on outbreaks evaluated and widely shared with the scientific community to provide guidance on their use during epidemics and outbreaks. Operational research should be conducted, notably to estimate:
   - The onset of protection after one dose of the vaccine and the proportion of vaccinees protected after one dose six months following vaccination;
   - Vaccination coverage rates for the second dose for different delivery strategies;
   - Optimal timing for vaccination campaigns (through modelling).

4. V. cholerae strains from a sample of cases should be saved and sent to a reference laboratory to detect patterns in antibiotic resistance or other changes in the genetic makeup of the strains that could influence clinical management or use of vaccine. Results from the reference laboratories should guide policy. Follow-up will be needed to determine if reports provided to policy makers result in appropriate practice in the community.

5. There is a need for an updated estimate of the global cholera disease burden, including number of cases and deaths, based on a systematic analysis of available data, including surveillance studies.

B. Vaccine availability, distribution and administration

6. Country-specific operations research is needed to identify optimal methods for the distribution and administration of cholera vaccines in urban and rural settings, including completing the second dose. For example, different countries may find that the vaccine may be provided through mass campaigns or the EPI program by the Government, while others may find the private sector or other alternative strategies to be most appropriate.

7. A strategy that combines vaccination with other cholera control interventions, such as water and sanitation improvements, should be tested in the field and evaluated for its feasibility, effectiveness and impact, including a study of possible synergistic effects.
8. Research should be conducted to test alternative methods of financing cholera vaccination, including local-level financing strategies.

9. Additional studies are needed to determine in what situations cholera vaccination is cost-effective or even cost savings.

10. Research into the possible use of a global cholera vaccine stockpile is needed, in order to determine the optimal use of a stockpile for both outbreak preparedness and use in endemic areas.

11. Studies will be needed on how best to inform populations regarding introduction of cholera vaccines. This includes evaluations on how to use social marketing methods to clarify the vaccines’ appropriate use, benefits, safety, and the need for booster doses.

12. A guide for the use of cholera vaccines in an area which has not had recent public health problems with cholera, but which is experiencing circumstances that put the area at high risk for cholera needs to be developed and evaluated. Examples where such a guide is needed include areas with complex humanitarian or natural disasters.

C. Optimizing public health benefits of the vaccine

13. Heat stability is an important consideration for the distribution and storage of cholera vaccines and the current cholera vaccines are likely to be heat stable even in tropical conditions. Therefore, studies to document the heat stability of cholera vaccines and to determine if a cold chain is not required are urgently needed.

14. The development of a heat stable oral cholera vaccine in new formulations that would be logistically easier to use (e.g. multi-dose vials, dry powder in a sachet, dispersible tablet) should be considered.

15. Evidence for protection from a single dose of the oral killed whole-cell only vaccine is needed to guide the vaccine’s use in areas with continuous high rates of cholera.
VIII. References


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