Vaccination Strategies to Combat an Infectious Globe: Oral Cholera Vaccines

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ABSTRACT

Cholera is a substantial health burden in many countries in Africa and Asia, where it is endemic. It is as well responsible for ongoing epidemics in sub-Saharan Africa which are becoming greater in terms of frequency, extension, and duration. Given the availability of two oral cholera vaccines and the new data on their efficacy, field effectiveness, feasibility, and acceptance in cholera-affected populations and in travelers, these vaccines should be used in endemic areas, in travelers for these areas and should be considered in areas at risk for outbreaks. The two vaccines currently available in worldwide are: (1) The killed oral vaccine (Dukoral, licensed by SBL–Sweden to Crucell–Holland) is recommended since 1999 by WHO and consists of a mixture of four preparations of heat or formalin killed whole cell *Vibrio cholera O1* (Inaba and Ogaba serotypes, and classical and El Tor biotypes) that are then added with purified recombinant cholera toxin (CT) B subunit. Because CT cross-reacts with *Escherichia coli* LT the vaccine also provides short-term protection against ETEC (enterotoxigenic *E. coli*) which is of added benefit for travelers. It is available in more than 60 countries. (2) A bivalent O1 and O139 whole cell oral vaccine without CT B subunit (Shanchol) has been lately developed in Vietnam (licensed by VaBiotech–Viet Nam to Shantha Biotechnics–India. It is available in India and Indonesia. A structured search of papers in PubMed and reports on cholera vaccines by WHO and CDC, as well as critical reading and synthesis of the information was accomplished. Inclusion criteria were defined according to reports quality and relevance.

Key words: Cholera vaccines, Travelers, Vaccine-delivery strategies

INTRODUCTION AND DISEASE BURDEN

Cholera was repeatedly one of the most dreaded pandemic diseases in history, being able to spread rapidly to large numbers of people, of whom a high proportion died. Cholera remains today an important disease in areas where population overcrowding and poor sanitation are common, such as in slums and refugee camps in developing countries.[1]

Cholera is an acute diarrheal illness of variable severity caused by infection of the intestine with the bacterium *Vibrio cholerae* (serogoups O1 and O139). The incubation period is extremely short (2 h to 5 days). It typically causes intense diarrhea (often with no abdominal pain) and occasional vomiting, being able to produce dehydration and shock.[2]

About 75% of the people infected with cholera do not develop any symptoms; 15–20% develop a mild or moderate, self-limited diarrheal disease; in 5–10% of cases, however, patients develop very severe sudden watery diarrhea which can rapidly lead to severe dehydration that may cause death to a previously healthy adult within a few hours. Complications include renal failure, pulmonary oedema, profound hypoglycemia and seizures in young children, and abortion in pregnant women. When properly treated, the disease has a mortality rate of less than 1%; otherwise, the rate of mortality reaches 30–50% of the severe cases.[2,3]

Transmission occurs through direct faecal–oral contamination or through ingestion of water and food contaminated with *V. cholerae* by sewage water. Raw or undercooked shellfish and fish, raw vegetables, and fruits are often related to cholera transmission; any food can get

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contaminated during preparation or storage. Cooked rice is an excellent growth medium, as are lentils, millet, and other cooked grains and legumes with neutral pH. Freezing foods or drinks does not prevent cholera transmission.[4,5]

ETIOLOGY

Vibrio cholerae is a Gram-negative monotrichous *bacillus*. On the basis of somatic O antigen polysaccharids, there are over 200 serogroups. Only the O1 and O139 serogroups cause epidemic disease. Strains other than those are called non-O1 non-O139 *V. cholera* and do not cause cholera symptoms. Serogroups O5, O37 and O141 can cause small outbreaks of diarrheal disease, but no epidemics.[6]

The O1 serogroup is divided into two biotypes: classical and El Tor (currently circulating). Both biotypes cause similar symptoms. Each of the O1 biotypes can be further subdivided into two major serotypes, Ogawa and Inaba. Ogawa strains produce the A and B antigens and a small amount of C, whereas Inaba strains produce only the A and C antigens. A third serotype, Hikojima, produces all the three antigens but is rare and unstable. A toxin is responsible for the diarrhea and only 5 μg of it are able to cause the disease.[7]

GEOGRAPHICAL DISTRIBUTION

The current seventh pandemic wave began in the south of Asia in 1961 and spread to Africa in 1971 and to America in 1991 (the year 1991 was marked by the entry of *V. cholerae* into Peru and other Andean countries, from which it has since spread throughout South and Central America. This was the first time cholera had invaded the Americas in more than 100 years). Unlike the previous pandemics, the seventh is caused by *V. cholerae* biotype El Tor.

Since 2005, the re-emergence of cholera has been noted in parallel with the ever-increasing size of vulnerable populations living in unsanitary conditions. Nowadays most of the cases and epidemics happen in Africa and in a lower proportion in Asia. During 2008, the following countries in Africa reported over 10,000 cases: Zimbabwe, Democratic Republic of Congo, South Africa, Guinea Bissau, and Angola. In Asia, during the same period of time, most of the cases occurred in Afghanistan, India, and Indonesia.[8]

In 1992, a new serogroup emerged in Bangladesh and caused an extensive epidemic. It is a genetic derivative of the EI Tor biotype differing in the antigenic structure and being highly able to spread. It elaborates the same toxin (CT), but its polysaccharide structure is different from those in O1 strains. Designated *V. cholerae* O139 Bengal, the new serogroup has now been detected in 11 countries and could cause a new pandemic. In 2008, it has been reported only in China (32% of the 151 cases) and Thailand (2 of the 435 cases). It has not been found in Africa.[1]

New strains have been recently identified in Bangladesh which express the same toxin produced by classic strains, but being more virulent. They also have been reported in certain countries of East Africa and Asia, causing severe cholera outbreaks.[9]

IMMUNE RESPONSE

After ingesting the *V. cholera* with food or water, steps in the pathogenicity of cholera include colonization of the small intestinal mucosa, production of the pilus structure and elaboration of the enterotoxin cholera toxin (CT), an 84 kD multimeric protein consisting of a central active A subunit bound to five surrounding B subunits. The B subunit is responsible for the binding of the toxin to the GM1 ganglioside receptors on epithelial cell surface, whereas the A subunit, an ADP-rybosilating enzyme, is responsible for the toxicity of the toxin through stimulation of the target cell adenylate cyclase, leading to hypersecretion of fluids and loss of electrolytes. Immunity to *V. cholerae* infection is serogroup-specific, so that immunity to O1 does not protect from infection with serogroup O139.[9,10]

SUSCEPTIBLE POPULATION

Everyone is susceptible to cholera, regardless of age or other factors. Still, certain factors can increase the personal susceptibility to the disease as follows:

1. *Reduced stomach acid or hypochlorhydria*: *V. cholerae* cannot survive in an acid environment (pH equal or inferior to 4.5). Hypochlorhidria increases the proportion of viable bacteria able to cross the gastric barrier and colonize the intestine.
2. Type 0 blood: People with type 0 blood are more likely to develop cholera probably because they have more receptors on their cellular surface which facilitate bacterial colonization and adhesion.
3. Compromised immunity: The risk for complications and death due to cholera is greater in immunocompromised people like malnourished children or HIV patients.
4. Travelers from more developed areas to countries with deficient drinkable water supply and improper handling of food are likely to develop cholera if do not implement preventive measures. Within the last decades, the risk for travelers to contract cholera was one to two cases per million travelers; nevertheless, recent estimates

that it could be as high as 5 per 1000 for travelers visiting countries in which a cholera outbreak is occurring.

Infected people, not necessarily becoming ill, eliminate bacteria during 7 to 14 days, being able to contaminate the environment and/or infect other people. El Tor biotype produces more asymptomatic carriers than the classic biotype. A chronic carrier state (more than 3 weeks) is less frequent.

DIAGNOSIS

Clinical diagnosis should be considered when acute watery diarrhea is present, especially if rapid dehydration occurs and the patient lives or has recently been to an endemic or epidemic area for cholera and there are no pathognomonic signs or symptoms.

Definitive laboratory diagnosis is based on the identification of the cholera *bacillus* in stool samples or culture on specific media complemented with agglutination and biochemistry techniques. Detection of anti-lipopolysaccharide antibodies to *V. cholerae* in plasma takes at least 7 days; therefore, serological tests are useful just for retrospective confirmation of the infection. Antibodies to CT arise between 1 and 4 weeks after the infection and remain indefinitely.

TREATMENT

The main treatment consists of replacing fluids and salt lost with severe vomits and diarrhea. Early rehydration with oral rehydration salt (ORS) solution or IV solutions (preferably with Ringer lactate) in severe cases, greatly reduces mortality. WHO recommends travelers to include ORS into their health kit.[11]

In severe cases, an effective antibiotic (azithromycin, ciprofloxacin, norfloxacin, etc.) reduces the severity of the disease and the duration of the symptoms and the carrier state. Resistance to trimethoprim-sulfamethoxazole, furazolidon, and tetracycline has been reported recently.

Routine treatment with antibiotics, or "mass chemoprophylaxis", has no effect on the spread of cholera and it is not recommended. Anti-diarrheal drugs (i.e. loperamide) are not recommended either.

PREVENTIVE MEASURES

Measures to prevent cholera mainly consist of providing vulnerable population with safe water and efficient sewage systems. Health education and proper food handling, especially frequent hand washing are also measures of a paramount importance.

Two oral cholera vaccines are currently available. Recent data on the effectiveness, feasibility, and cost-effectiveness of oral cholera vaccination were considered and recommendations are that the two oral cholera vaccines should be used in areas with endemic cholera and considered for use in areas at risk for cholera outbreaks, in conjunction with other cholera prevention and control strategies.[12,13]

VACCINES

Since the identification of the causal agent by Robert Koch in 1880, various vaccines have been used, like those produced by Ferrán in Spain in 1884 and Haffkine in Russia in 1894. In 1959, a new parenterally administered, killed whole-cell cholera vaccine has been widely available for many years. The WHO requirements for this vaccine were first adopted in 1959 and revised in 1968; an addendum was incorporated in 1973. However, this vaccine offers at best only limited protection (45%) of short duration (3 months) and produces unpleasant side-effects in many vaccines. In view of the limitations, the vaccine has not been considered satisfactory for general public health use, and in 1973 the Twenty-sixth World Health Assembly abolished the requirement in the International Health Regulations for a certificate of vaccination against cholera.[14]

Two types of cholera vaccine have been developed since then, a killed oral vaccine (WC/rBS, whole cell/recombinant B subunit, Dukoral®) and a live attenuated oral vaccine (CVD 103-HgR, Orochol®), which stopped being manufactured in 2004 and consisting of one innocuous effective (95% against *V. cholerae* Classic and 65% against *V. cholerae* El Tor). Both have been shown to be safe, immunogenic, and efficacious.[15]

Two cholera vaccines are currently available in the world:[16]

1. The first vaccine WC/rBS (whole cell/recombinant B subunit), Dukoral®, licensed by SBL Vaccin, Sweden and available in several countries, consists of four batches of heat- or formalin-killed whole-cell *V. cholerae* O1, representing both serotypes (Inaba and Ogawa) and both biotypes (classical and El Tor), and added with purified recombinant CT subunit B (CTB). The whole cell/recombinant B subunit (WC/rBS) vaccine–given orally with buffer to neutralize stomach acidity–was found, in field trials in Bangladesh and Peru, to confer 85–90% protection during 6 months in all age groups after administration of 2 doses 1–2 weeks apart. The protective antibodies last in 60% of the vaccines

(children older than 6 months and adults) for 2 years. Recent reviews of the study in Bangladesh show efficacy of WC/rBS is boosted by herd protection. Dukoral® is available in over 60 countries and has been pre-qualified by WHO. The vaccine also provides short-term protection against ETEC (enterotoxigenic *E. coli*), which is of added benefit for travelers. In developed countries, it is recommended to travelers to cholera and ETEC risk areas.

2. A variant of the Dukoral® vaccine containing no recombinant CTB-subunit has been produced and tested in Viet Nam. It is administered in two doses, one week apart. A field trial conducted in Nha-Trang, Viet Nam, showed an efficacy of 66% against *V. cholerae* El Tor after 8 months in all age groups tested. A modified WC vaccine developed in India–Shanchol® (Shantha Biotechnics Ltd., India)–was commercialized in this country in 2008. Among its advantages, the facts that it is bivalent (offers protection against both serogroups), it does not require cold chain conservation (it does not need a buffer due to the lack of the B subunit) and it is low-cost. This new vaccine is pending WHO prequalification (application submitted in September 2009) and if successful would join Dukoral® for use in cholera-affected countries.[16] Cholera vaccines are especially suitable for travelers to risk countries.[17-20]

USE OF CHOLERA ORAL VACCINES IN ENDEMIC AREAS AND DURING EPIDEMICS

Public health use of cholera oral vaccines in mass vaccination campaigns is relatively recent. WHP have recently supported some vaccination campaigns (Mozambique 2003–2004, Sudan 2004, Indonesia 2005) and WHO official recommendations for its use in complex emergencies were issued in 2006 and state that due to the difficulties to assure other measures, vaccination should be used as an additional public health tool and should not replace usually recommended control measures such as improved water supplies, adequate sanitation, and health education, despite its high cost and the heavy logistics associated with its use.

A new WHO position paper on the use of cholera vaccine is currently justified due to the following:[16]

1. Changes in trends in the epidemiology of the disease (such as the replacement of the original *V. cholera*e O1 El Tor by new strains that produce the classical CT, in parts of Asia and Africa, causing a more clinically severe disease; and epidemics in sub-Saharan Africa are becoming greater in terms of frequency, extension, and duration).
2. Changes in the evidence of the economic burden of the disease.
3. Changes in the evidence of the effectiveness, feasibility, and cost-effectiveness of oral cholera vaccine both in endemic and crisis situations.
4. The development of a lower-cost vaccine specifically for use in developing countries. This new vaccine consists of a modification (removal of the B subunit) of a killed whole-cell bivalent (O1/O139) produced in Vietnam which does not need a buffer for administration.

Taking into account the evidences above, as well as the fact that cholera outbreaks can disrupt health systems, cholera control should be a priority in endemic areas.

The WHO Strategic Advisory Group of Experts (SAGE), the principal advisory group to WHO for vaccines and immunization, developed the following definition of endemic cholera to guide control strategies: the occurrence of faecal culture-confirmed cholera diarrhea in a population in at least 3 of the past 5 years.

At its latest meeting so far (December, 2009) SAGE made a number of recommendations on endemic cholera control:

Given the availability of two oral cholera vaccines (one prequalified and the other pending prequalification) and new data on their efficacy, field effectiveness, feasibility, and acceptance in cholera-affected populations, immunization with these vaccines should be used in areas where the disease is endemic and should be considered for use in areas at risk for outbreaks in conjunction with other prevention and control strategies. Vaccination should not disrupt the provision of other high priority health interventions to control or prevent cholera outbreaks. Vaccines provide a short-term effect that can be implemented for immediate response while the longer term intervention of water and sanitation improvements, which involve large investments, should always be put into place.

Specific cholera vaccination strategies should not be prescribed to countries since the appropriate strategies will differ by country, depending on the epidemiological pattern of the disease and the capacities of the immunization program and health system, among other factors. Countries should consider the following options for strategies to control endemic cholera through vaccination.

a) Scope of vaccination

In cholera-endemic countries, vaccination should be targeted at high-risk areas and population groups, due to the fact that vaccination of the entire population is not warranted.

b) Where to vaccinate

Vaccination should be targeted at areas where two of the following criteria have been met: (i) detection of culture-confirmed cholera in at least 3 of the past 5 years; (ii) record of an incidence rate of cholera of at least 1/1000 population in any of these years; and (iii) if population-based incidence rates are not available, high-risk areas or groups have been identified using information collected from local public health officials.

c) Who to vaccinate

In situations where funding is limited, priority should be given to high-risk groups: the primary targets for vaccination should be preschool-aged and school-aged children. Other groups that are especially vulnerable to severe disease can also be targeted, such as pregnant women (here is no reason to expect toxicity when killed cholera vaccines are used) and people infected with HIV. Vaccinating older age groups should also be considered if funding is available.

d) Vaccine-delivery strategies

The most practical option for delivering oral cholera vaccines are usually periodic mass vaccination campaigns. Community settings such as schools and religious institutions can be appropriate venues for vaccination campaigns. Incorporating cholera vaccination into routine vaccination schedules can be an alternative or complementary to mass vaccination campaigns (for instance, to reach young children between campaigns).

e) Frequency of vaccination

It is recommended that initial vaccination with two doses is followed by revaccination every second year, due to the documented duration of significant protection for oral cholera vaccines (2 years). This recommended interval between initial and booster vaccinations could be extended when data on the longer term efficacy of oral vaccines become available.

Pre-emptive vaccination should be considered by local health authorities to help prevent potential outbreaks or the spread of current outbreaks to new areas. Therefore, the need for predictive risk-assessment tools is urgent; these tools should be developed and field-tested as soon as possible.

Reactive vaccination could be considered as an additional control measure which could be implemented after a thorough investigation of the current and historical epidemiological situation has been completed and geographical areas to be targeted have been clearly identified. The feasibility and impact of vaccination in stopping ongoing outbreaks should be documented and the findings widely disseminated.

Pre-emptive or reactive vaccination should cover as many people as possible and should be conducted as quickly as possible.

The mainstay control measures during ongoing epidemics should consist of providing appropriate treatment to people with cholera, implementing water and sanitation interventions, and mobilizing communities. It is strongly recommended that surveillance of microbiologically confirmed cases of cholera be instituted to determine the burden of disease and impact of the interventions.

According to SAGE, cholera vaccines need to be placed on the priority list for WHO prequalification so that the newly licensed low-cost Shanchol® vaccine (Shantha Biotechnics Ltd., India), developed specifically for use in cholera-affected countries, could be accepted for review and if successful join Dukoral® (SBL Vaccin, Sweden) on WHO's list of prequalified cholera vaccines. The prequalification of Shanchol® and other cholera vaccines in the future would remove a major roadblock to the increased use of oral vaccines in developing countries.

The Global Alliance for Vaccines and Immunisation (GAVI) has stated that supporting the introduction of cholera vaccine until 2013 will not be reconsidered until 2013. International NGOs that deal with cholera outbreaks, foundations, agencies, and bilateral donors are a potential source of funding for introducing the vaccine. It would be vital, as SAGE felt, to prepare a business case for oral cholera vaccines to provide critical information to donors regarding the potential demand for these vaccines (to be used in endemic settings and for the creation of a vaccine stockpile to prevent or control outbreaks), the costs and cost-effectiveness of vaccination in meeting this demand, possible funding sources and the funding gap.

Use of the oral killed whole cell vaccine in programs to control endemic cholera is a very cost-effective strategy, especially if herd protective effects are considered.[21]

USE OF ORAL CHOLERA VACCINES IN TRAVELERS TO RISK AREAS

Cholera risk for travelers has been documented in several papers.[22] In most of the countries where licensed, WC/

rBS cholera vaccine is indicated in subjects travelling for more than 7 days to cholera-endemic or epidemic countries, or else in shorter stays if the trip or the traveler involves high-risk circumstances.[17,20,23,24] It is usually recommended in travel health practices (pretravel advice), because it offers protection against travelers' diarrhea (TD) caused by ETEC (Enterotoxigenic *E. coli*). TD is the most frequent syndrome among travelers in most of the visited regions and affects 20–60% of travelers, and the most common cause of TD worldwide is enterotoxigenic *E. coli* (ETEC), which induce watery diarrhea associated with cramps and with low grade or absent fever. Certain authors consider that the protection of WC/rBS against TD is very low.[25] The efficacy of vaccination against cholera is high (85%), and its impact on public health is very positive,[26,27] given the associated mortality in endemic zones and epidemic periods. The efficacy of WC/rBS against the ensemble of TDs is logically lower because the vaccine prevents TDs caused by *V. cholerae* and by LT-ETEC, even by ETEC combined with *Salmonella enteric*,[28] but fails to do so with the high number of remaining pathogens.

Vaccine recommendation is clear in subjects travelling to cholera zones, as well as in those travelling to zones at risk of TD who suffer from previous conditions where TD may have serious consequences.[19,29-32]

Several recent studies show that the effectiveness of cholera vaccine WC/rBS in the prevention against TD is 43–60% depending on travelers' risk. Moreover, the mean duration of TD in vaccinated travelers with the disease is shortened. According to the cost–benefit analysis studied, the recommendation for WC/rBS vaccination in subjects travelling to zones at risk of TD is beneficial for the traveler, regardless of trip duration and visited continent.

ONGOING DEVELOPMENT OF OTHER CHOLERA VACCINES

a) A live attenuated, single-dose, oral vaccine (*V. cholerae* 638) developed in Cuba, already tested in Phase II trials in Mozambique;[33] building on the success of strain 638. Cuban investigators have developed an analogous vaccine candidate derived from an O139 strain that should go into clinical trials soon.
b) A live attenuated O1 El Tor strain (Peru-15) developed as an oral vaccine by AVANT Immunotherapeutics (USA) under the name CholeraGarde™, which elicited a 62% protection against *V. cholerae* challenge in North American volunteers[34] and was found to be safe and immunogenic in a Phase II trial in Bangladesh.[35] Efficacy studies (Phase IIb) were reportedly imminent. Meanwhile, Peru-15 was engineered to express and secrete high levels of CTB. The resulting strain, Peru-15pCTB, was shown to be genetically stable, and elicited high anti-CTB, LT-neutralizing antibody titers and high vibriocidal antibody titers when administered by the oral route to rabbits or by the intranasal route to mice. Peru-15pCTB will, therefore, replace Peru-15 as an oral, single-dose, bivalent cholera/ETEC vaccine candidate.[36] The vaccine currently is undergoing phase I/II clinical trials;[37]
c) Two live attenuated strains of *V. cholerae* O139 (Bengal 15, similar to Peru-15, and CVD112), which have been shown to be immunogenic and safe in Phase I trials in human volunteers;[38]
d) An injectable O-antigen-conjugated vaccine, in preclinical development at the Pasteur Institute in Paris;
e) An injectable plasmid DNA vaccine, in development at the Putra University in Malaysia and the Malaysia National Biotechnology Directorate;
f) A rice-based oral vaccine made from transgenic rice seeds that appears to be stable for more than 1.5 year at room temperature. When fed to mice, the transgenic seeds elicited antibodies protecting the animals from oral challenge with CT;[39]
g) A nasal route administered proteoliposome-based formulation that elicits vibriocidal antibodies in mice.[40]

CONCLUSION

Taking into account the new trends in the epidemiology of cholera, as well as the changes in the evidence of both the economic burden of the disease and the effectiveness and feasibility of currently available oral cholera vaccines, new strategies concerning cholera vaccination should be considered and implemented.

The two oral vaccines are, therefore, a basic preventive measure to protect both the population living in endemic and epidemic areas and travelers visiting those areas.

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