When, How, and Where can Oral Cholera Vaccines be Used to Interrupt Cholera Outbreaks?

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Abstract Cholera continues to be a major global health problem, at times causing major and prolonged outbreaks in both endemic and nonendemic settings in developing countries. While improved water quality, sanitation, and hygiene (WASH) will provide the ultimate solution to prevention of this disease burden, this is a far-off goal for most developing countries. Oral cholera vaccines (OCVs) have been demonstrated to be effective in the control of cholera outbreaks, and constitute useful tools to be used in conjunction with efforts to improve WASH. Two killed OCVs are prequalified by WHO for purchase by UN agencies for international use. Recently, WHO has launched a global stockpile of killed OCVs for use to control outbreaks. Rational deployment of OCV from this stockpile will require consideration of costs, feasibility, disease epidemiology, and the protective characteristics of the vaccine deployed, as well as effective and rapid coordination of processes and logistics used to make decisions on deployment and delivery of the vaccine to the population in need. Despite not having data on all the questions of relevance as to how to use OCVs to control cholera outbreaks in different settings, there is clearly more than enough evidence to initiate their use, as answers to remaining questions and refinement of policies will mainly come with experience.

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1 Introduction

Cholera, an acute watery diarrheal disease caused by *Vibrio cholerae* O1, and less commonly by *V. cholerae* O139 remains a major global health problem (Sack et al. 2004). It causes epidemics, often well publicized in the wake of natural disasters and other humanitarian emergencies, as well as less well-publicized endemic disease, though the latter accounts for the major portion of the global disease burden. Cholera vaccines have been developed since the late nineteenth century, not long after the cholera vibrio was discovered. Early generation vaccines were killed whole cells (WCs) delivered parenterally. These vaccines were in widespread use for nearly 100 years without adequate evaluation of their safety and protection. When rigorous trials were finally undertaken in the 1960s, the trials found that those vaccines that were acceptably non-reactogenic failed to confer either high-grade or long-term protection. Based on this evidence, in 1973 the 26th World Health Assembly amended the International Health Regulations by removing the requirement for cholera vaccination on the certificate for international travel. WHO also recommended against the use of these vaccines for control of cholera globally (Clemens et al. 1994).

While parenteral cholera vaccines were experiencing their demise as public health tools, considerable progress was being made in the understanding of natural immunity to cholera. It had been well recognized that in cholera-endemic populations, natural cholera infections confer protection against recurrent cholera. The same was observed in North American volunteers who were challenged and re-challenged experimentally with cholera. The basis for this protection was determined to be mucosal immunity, primarily IgA secretory antibodies directed to the lipopolysaccharide (LPS) O antigen of cholera organisms, and to a lesser

extent to cholera toxin. Antibacterial and antitoxin antibodies were found to protect synergistically. Importantly, it was found that the most efficient way to induce this mucosal immunity is by oral delivery of vaccine antigens (Holmgren et al. 1992; Svennerholm and Holmgren 1976; Svennerholm et al. 1984). Attention thus turned to the development of orally administered cholera vaccines (OCVs). Despite the ensuing development of safe and effective OCVs, these vaccines have until recently failed to be embraced as public health tools for developing countries. The reasons have been several. Some have cited vaccine expense, moderate levels of vaccine protection, and the logistic challenges associated with vaccine storage and administration. Also mentioned have been concerns that delivery of these vaccines might interfere with other control efforts in the context of cholera outbreaks, and the expectation that global efforts to improve water quality, hygiene, and sanitation (WASH) will soon control cholera.

Unfortunately, the past decade has not witnessed a decline in cholera incidence or mortality. To the contrary, we have observed unusually large and protracted outbreaks in Angola, Zimbabwe, Central and West Africa, Somalia, and Haiti. Further, cholera has now become endemic in Haiti, after nearly a century in which cholera was not reported in this country (Harris et al. 2010). Global statistics on cholera published by WHO, with their acknowledged limitations, have shown no decline in global cholera burden (WHO 2012a, b, c). A recent analysis of global cholera disease burden estimated that there are approximately 2.8 million cholera cases and 91,500 cholera deaths in cholera-endemic countries, and 87,000 cases and 2,500 deaths in cholera epidemics (Ali et al. 2011), and these figures may be conservative. In this context, the international public health community has recently expressed interest in using new generation OCVs in concert with non-vaccine interventions as public health tools to control cholera. This interest has been spurred in part by the development, licensure, and international qualification by WHO of the first low-cost OCV, which has been found to be safe and effective in a large trial in India (Sur et al. 2009). As well, WHO has recently committed to the creation of a global stockpile of OCVs that can be deployed for the control of cholera outbreaks (WHO 2012, b, c). It is still be debated how best to use such a vaccine stockpile, or other reserves of OCVs. In this chapter, we review the available vaccines and their characteristics and outline factors that should be considered in the targeting of the vaccines for control of cholera outbreaks, including the use of a vaccine stockpile.

2 Currently Licensed OCVs

Currently licensed OCVs consist either of genetically attenuated live organisms or of killed cholera WCs, with or without the addition of cholera toxin B subunit (CTB). Three vaccines are currently licensed: a vaccine consisting of recombinant CTB together with O1 serogroup killed WCs (Dukoral^{TM}), a vaccine containing both O1 and O139 serogroup killed WCs, but no CTB (produced as Shanchol^{TM} in

India and mORCVAX™ in Vietnam), and a genetically attenuated version of an originally virulent O1 serogroup classical Inaba strain (Orochol™ and Mutachol™) (Shin et al. 2011).

2.1 rCTB-WC Oral Vaccine (Dukoral™)

Developed in Sweden, this killed oral vaccine contains O1 serogroup formalin- or heat-killed WCs representing both the classical and El Tor biotypes and the Ogawa and Inaba serotypes, together with recombinant cholera toxin CTB (rCTB); it is the first oral cholera vaccine to have achieved international licensure and prequalification by WHO for purchase by United Nations agencies (Holmgren et al. 1992). Its composition reflects the appreciation that antibacterial and antitoxic immunity confer synergistic protection against cholera (Svennerholm and Holmgren 1976; Svennerholm et al. 1984). The vaccine is licensed for persons 2 years of age and older; a two-dose regimen is given to persons aged 5 years and older, while a three-dose regimen is recommended for younger persons with doses being given 1–6 weeks apart. The vaccine is coadministered with a bicarbonate buffer to prevent destruction of the rCTB by gastric acid (Clemens et al. 1986). A large randomized, placebo-controlled trial in a rural Bangladeshi population with endemic cholera demonstrated that an earlier version of the vaccine (with chemically extracted rather than recombinant CTB), given in a three-dose regimen, was safe and conferred 85 % protection against cholera for 4–6 months after dosing; protection declined to 62 % at one year and 57 % during the second year, becoming negligible thereafter (Clemens et al. 1990). Additional analyses of the trial found two doses to be as protective as three doses. Short-term cross-protection against LT-ETEC was also demonstrated (Clemens et al. 1988). Reanalysis of the trial found that the vaccine conferred indirect ("herd") protection to both non-vaccinees and vaccinees (Ali et al. 2005). The high level of short-term protection against cholera was later confirmed in a randomized, placebo-controlled trial of a two-dose regimen of rCTB-WC in Peruvian military volunteers, who, in contrast to the Bangladeshi population, were presumed to have lacked previous natural exposure to cholera and thereby also natural immunity to cholera (Sanchez et al. 1994).

2.2 Bivalent Killed WC-only OCV (Shanchol™ and mORCVAX™)

In addition to its evaluation of CTB-WC cholera vaccine, the trial in Bangladesh of killed OCVs demonstrated the safety and long-term protection by a killed WC-only OCV, lacking CTB. Motivated by these findings, in the late 1980s the Vietnamese government, led by Professor DD Trach, initiated cooperation with

Sweden to develop and produce an inexpensive WC-only OCV in Vietnam (Clemens et al. 1990). A two-dose monovalent, O1 serogroup, killed WC-only OCV, containing killed cholera strains similar but not identical to those in Dukoral™, was developed in Vietnam and found to be safe and to confer 66 % protection against cholera at 8–10 months following vaccination in an open field trial in Hue, Vietnam (Trach et al. 1997, 2002). This vaccine, which was licensed in Vietnam as ORCVAX™ in 1997, had the additional advantage of not requiring coadministration of oral buffer. It was subsequently made bivalent (O1 and O139), and over 20 million doses have been administered in Vietnam's public health programs to date (Lopez et al. 2008).

Though used widely in Vietnam, this vaccine was not suitable for international use because of several production and standardization problems, and because the Vietnamese national regulatory authority (NRA) was not approved by WHO (2004). To enable internationalization of an improved version of this inexpensive and easily produced vaccine, in 2004 the International Vaccine Institute (IVI) in Seoul, Korea initiated a program to modify the constituent strains, production technology, quality control procedures, and standardization assays for the vaccine, and to transfer this modified bivalent WC-only OCV to Shantha Biotechnics in India, whose NRA is WHO-approved. The O1 serogroup constituents of this O1–139 bivalent vaccine were the same as those in Dukoral™, albeit in different quantities, so that the total O1 serogroup LPS content of Shanchol™ is approximately twice that of Dukoral™. Because the vaccine does not contain CTB, no concomitant oral buffer is required. A large, randomized, placebo-controlled trial of this vaccine among 66,900 nonpregnant residents aged 1 year and older in Kolkata, India found a two-dose regimen of the vaccine, given approximately 2 weeks apart, to be safe and to confer 66 % protection against O1 serogroup cholera with no decline of protection during 3 years of follow-up (Sur et al. 2009). Further analysis of this trial has revealed sustained protection at 5 years after vaccination as well as evidence of vaccine herd protection (Clemens, unpublished data; Ali et al. 2013).

All episodes of cholera in the Kolkata trial were due to a newly emergent El Tor biotype that elaborates classical biotype cholera toxin. This vaccine was licensed as Shanchol™ in India in 2009 for persons aged 1 year and older, and was subsequently prequalified by WHO for purchase by UN agencies. It is available at $1.85 per dose to the public sector in developing countries. In addition, the improved vaccine production technology has been transferred back to Vietnam, where it is licensed by VaBiotech as mORCVAX™.

2.3 Live Oral CVD-103HgR Vaccine (Orochol^{TM} or Mutachol^{TM})

To date, CVD 103-HgR is the only genetically attenuated, live OCV to have achieved licensure. Developed by Professors James Kaper and Myron Levine at the University of Maryland, this vaccine is derived from the virulent O1 serogroup, Inaba serotype, classical biotype strain 569B. The basis for its attenuation is a deletion in the gene encoding cholera toxin A subunit, while still expressing CTB. The strain was further engineered to be Hg-resistant to serve as a diagnostic marker (Kaper and Levine 1990). Given as single dose with oral buffer, this vaccine was tested in Phase 1–2 studies that enrolled over 4,000 volunteers and was found to be safe at doses of up to 5×10^9 viable organisms. Doses of $2–8 \times 10^8$ viable organisms were found to be reliably immunogenic and protective against an experimental challenge with both Inaba and Ogawa cholera vibrios in North American volunteers; protection was seen against challenges as early as 1 week and as late as 24 weeks after dosing (Tacket et al. 1992, 1999; Suharyonom et al. 1992; Su-Arehawaratana et al. 1992; Levine et al. 1988). However, when tested in developing countries, serum vibriocidal antibody responses to a 10^8 dose were substantially lower in magnitude than those seen in US volunteers. Accordingly, when CVD103-HgR entered Phase 3 testing for efficacy in a cholera-endemic setting, the dose selected for testing was 5×10^9. In this trial, performed in North Jakarta, Indonesia, 67,508 persons aged 2–41 years were randomized to a single dose of CVD103-HgR or placebo. Vaccine efficacy against treated episodes of O1 serogroup cholera was 14 % at 4 years of follow-up, and no significant protection was observed during any year of follow-up (Richie et al. 2000).

CVD103-HgR was licensed as Orochol^{TM} (also as Mutachol^{TM}) by the then Swiss Serum and Vaccine Institute (now Crucell) as a single-dose vaccine at a dose of 2×10^8 viable organisms for travelers aged 2 years and older. A dose of 2×10^9 is offered in a different presentation (Orochol E^{TM}) that is intended for use in developing countries, but to date no developing country has used this product in routine public health programs. It is given as a single dose with a booster dose recommended 6 months later. A post-licensure study of mass immunization with a single dose of 2×10^9 viable organisms, given following the onset of an epidemic in Micronesia, found that vaccination was feasible and was associated with a 79 % reduction in the risk of cholera (Calain et al. 2004). However, because this was not a double-blinded, randomized, controlled trial and because the findings of this study were at variance with those of the trial in North Jakarta, the findings will require confirmation in future studies. Another post-licensure study with a similar dose found the vaccine to be safe, albeit associated with lower immune responses, in HIV-infected adults in Mali (Perry et al. 1998). Although the vaccine is still licensed, production has been suspended by the manufacturer, and the vaccine has not yet been prequalified by WHO.

Table 1 Factors to consider when deciding on deployment of oral cholera vaccines to control a cholera outbreak

Epidemiological setting for vaccination
Burden of cholera morbidity and mortality
Protective characteristics of the vaccine
Clinical effectiveness of the vaccine
Balance between costs and effects

3 Issues to Consider in the Use of OCVs for Outbreaks

The decision to use OCVs, and how to use them, for controlling cholera outbreaks requires consideration of several factors, among which there is a complex interplay (Table 1).

3.1 Epidemiological Setting

While there is no formal definition of a cholera "outbreak", the term loosely refers to temporally defined increases in cholera incidence in specific populations. In developing countries, outbreaks of cholera occur in two distinct settings: endemic and epidemic. Endemic cholera occurs as a result of ingestion of cholera vibrios from their permanent environmental reservoirs and does not require exogenous introduction into a population. As determination of transmission routes is not practical in most settings, a pragmatic definition of endemic cholera has been proposed by WHO as cholera recurring in time and place, with occurrences in a defined population in at least three of the past 5 years (WHO 2010). Endemic cholera is well illustrated by cholera occurring in the Ganges delta of India and Bangladesh. Outbreaks of endemic cholera tend to be influenced by environmental and climatic variables, and usually occur in a recurrent seasonal pattern. In contrast, outbreaks of epidemic cholera, initiated by exogenous introduction of cholera vibrios, usually occur unpredictably, as illustrated by the recent major epidemic in Haiti as well as outbreaks that have been documented in fairs, feasts, pilgrimages, and such complex emergencies as refugee crises and natural disasters (Mintz et al. 1994; Harris et al. 2010).

The difference in predictability between outbreaks in endemic versus epidemic settings frames different approaches to use of OCVs. In predictable, endemic settings, OCVs can be delivered either preemptively, in anticipation of outbreaks, or reactively, in response to the outbreaks. In contrast, while it is known that epidemic cholera can occur following complex emergencies, such as refugee crises, earthquakes, and floods, not all such emergencies are followed by cholera outbreaks, and we lack a validated instrument to accurately differentiate those emergencies that are at very high risk for outbreaks versus those at lower risk. Thus, preemptive delivery of OCVs in such emergencies cannot be justified on the basis of evidence, leaving

Table 2 Features distinguishing epidemic from endemic cholera (from Clemens et al. 1994)

Feature	Epidemic	Endemic
Occurrence	Not predictable	Predictable
Preexisting natural immunity	Uncommon	Common
Clinical severity	Greater	Lesser
Asymptomatic infections	Less common	More common
Higher risk in children	No	Yes
Modes of transmission	Few	Many
Nonhuman reservoirs	Uncommon	Common

reactive vaccination once outbreaks are identified as the only practical option. Because a greater potential preventive impact can be anticipated with appropriately timed preemptive vaccination than with reactive vaccination once the outbreak has started, preemptive use of OCVs in endemic settings has been relatively non-controversial, as reflected in recent WHO recommendations. In contrast, reactive vaccination has been questioned as an effective strategy, although recent WHO recommendations allow for reactive vaccination "as an additional control measure, depending on local infrastructure and following a thorough investigation of the current and historical epidemiological situation, and clear identification of the geographical areas to be targeted" (WHO 2010).

Several additional features distinguish endemic from epidemic cholera (Table 2). Routes of transmission for epidemic cholera tend to be few in number, so that, when sources are identified via epidemiologic studies, simple water-sanitation-hygiene (WASH) interventions can often be designed. Conversely, in endemic cholera, routes and sources of transmission are multiple, making simple WASH interventions less likely to succeed by themselves and strengthening the argument for vaccination. In endemic settings, cholera occurs against the background of age-related acquisition of preexisting natural immunity, owing to past cholera exposures. In contrast, in epidemic settings, cholera tends to occur in populations with little preexisting immunity. These features help to explain the greater level of clinical severity in epidemic than in endemic cholera. They also provide an explanation for young age groups, with less background immunity, having highest rates of cholera in endemic settings, while the incidence of cholera tends to be age-independent in epidemic settings. Thus, in endemic settings, a case can be made to limit targeting of vaccination to younger persons, whereas general populations constitute the appropriate target in epidemic settings.

3.2 Burden of Cholera Morbidity and Mortality

It would seem obvious that use of OCVs should be reserved for settings with high cholera incidence and high cholera mortality. However, operationalization of this concept is complex. Despite the recurrent, apparently predictable pattern of

Table 3 Duration of recent cholera outbreaks in specific areas

Location	Year(s)	Duration
Pohnpei, Federated States of Micronesia (Calain et al. 2004)	2000/2001	9 months
Lusaka, Zambia (Sasaki et al. 2008)	2003/2004	27 weeks
Angola (various areas) (WHO 2007, 2008)	2006/2007	15 months
Harare, Zimbabwe (Mukandavire et al. 2011)	2008/2009	>9 months
Haiti (various areas) (Ministere de la Santa Publique et de la population 2012)	2010	18+ months

endemic cholera, several factors conspire to make targeting of OCVs in such settings challenging. Country level statistics on cholera reported to WHO are known to be underestimates, at times severe, due to limitations in laboratory capabilities in making microbiological diagnoses, weaknesses in health information systems, and economic disincentives for countries to report cholera. Moreover, endemic cholera may exhibit great geographical heterogeneity within a country, so that countrywide and regionwide statistics may not be applicable to all areas. As well, cholera in endemic settings may exhibit major year-to-year variations in disease incidence (Glass et al. 1982). Adding to the complexity is the fact that high cholera incidence does not necessarily equate to high cholera mortality, which depends on how well served a population is with cholera treatment facilities. Indeed, it is in places where treatment is lacking that cholera is often underdiagnosed and underappreciated as a public health problem. All of this means that decisions to vaccinate against endemic cholera will frequently have to be made on the basis of local knowledge about the incidence and case-fatality of cholera, however, incomplete.

As already mentioned, epidemic cholera is usually unpredictable. Most cholera epidemics occur in countries afflicted by natural or political emergencies, such as earthquakes, floods, warfare, and refugee crises. In many such situations already fragile or inadequate water, sanitation, and health care systems collapse, leading not only to a cholera outbreak but also to an overloaded or collapsed health care system, with resulting high case-fatality rates. In situations where a cholera outbreak additionally occurs in a setting that has previously been cholera-free for a long time, as was the case for the major cholera outbreak in Haiti in 2010, the situation is further worsened by the lack of the natural immunity that develops with age in cholera-endemic settings, leading to increased morbidity and mortality, which tends to occur with equal rares in young and old alike (Table 3).

3.3 Protective Characteristics of the OCVs

Several protective characteristics of the OCV to be used should be considered when deliberating on whether to deploy an OCV to control an outbreak. Table 4 summarizes several of these features for the two currently available, WHO-prequalified OCVs, Dukoral™ and Shanchol™.

Table 4 Features of the two licensed and available oral cholera vaccines (after Shin 2011)

Feature/characteristic	rCTB-WC (Dukoral™ Crucell)	WC-only (Shanchol™ Shantha Biotech; mORCVAX™ VaBiotech)
Cellular constituents	O1 serogroup El and classical biotypes	O1 serogroup El and Classical biotypes; O139 serogroup
Number of doses in primary regimen	2 doses given 1–6 weeks apart (3 doses for children 2–5 years of age)	2 doses given 14 days apart
Need for booster dose and frequency	After 2 years (every 6 months for children 2–5 years of age)	After 3 years
Minimal age of use according to license	2 years old	1 year old
Safety/tolerability	High, including in HIV+ individuals	High, presumably including HIV+ individuals (given similarity of the vaccine to Dukoral™)
Administration during pregnancy contraindicated	No	No
Time of onset of protection after full dosing	No data (presumed 1 week)	No data (presumed 1 week)
Protective efficacy	57 % at 2 years after vaccination	80 % at 5 years after vaccination
Protection against clinically severe cholera	Greater than against clinically mild cholera	No demonstrated difference in protection against clinical cholera by severity
Protection greater in 5+ year olds than in younger persons?	Yes	Yes
Protection by biotype	Greater against classical than against El Tor cholera; protection also against newly emergent hybrid El Tor cholera	Data available only for El Tor cholera; protection also against newly emergent hybrid El Tor cholera
Confers herd protection?	Yes	Yes
Confers cross-protection against LT-ETEC	Yes	No
Requires coadministration with liquid buffer?	Yes	No
Storage temperature and shelf life	2–8 °C; 3 years	2–8 °C; 2 years
WHO prequalified?	Yes	Shanchhol™: yes mORCVAX™: no
Price per dose to the public sector	$5.25 (negotiated price for WHO)	Shanchol: $1.85 mORCVAX: $0.75 (projected)

The magnitude of vaccine protection is of clear importance. Vaccine protection is typically expressed by the term "protective efficacy" (PE), calculated as the relative reduction of disease incidence in individual vaccinees attributable to their receipt of the vaccine. This value is generally quoted as 60–70 % for both vaccines at 1 year after immunization. However, this cited PE is itself insufficient for making decisions for several reasons. One reason is that PE, by expressing the relative reduction of disease owing to vaccination, does not provide an index of absolute index of vaccine protection, such as the number of persons who need to be vaccinated to prevent one case of cholera. For example, in an outbreak whose incidence is three cases per 1,000 persons, a 100 % protective vaccine will require vaccination of 333 persons to prevent a single case. In contrast, in an outbreak whose incidence is 50/1,000, as may occur in a refugee camp or urban slum (WHO 2012a, b, c), use of a 50 % protective vaccine will require vaccination of only 40 persons to prevent each case.

A second reason is that enhanced levels of short-term protection may be of importance to the decision to use OCVs to control cholera outbreaks. While protection by Shanchol™ exhibits no enhancement in the short-term, protection by Dukoral™ is markedly higher (ca. 85 %) in the 4–6 months after dosing when antitoxic immunity induced by its CTB component is at hand in addition to the antibacterial immunity induced by the whole-cell vaccine components. Such enhanced short-term protection could be a major asset for a vaccine deployed in a short-lasting outbreak. Conversely, longer term protection may also be of relevance when vaccinating against an outbreak in an endemic setting, or in epidemics whose duration is long, an increasingly frequent phenomenon (Table 4) (Reyburn et al. 2011).

Third, the onset of protection should also be considered. Reactive use of an OCV in an outbreak will be more effective the sooner after initiation of vaccination that protection begins. Both Dukoral™ and Shanchol™ have two-dose regimens (three doses for young children given Dukoral™, with doses separated by 1–6 weeks for Dukoral™ and 2 weeks for Shanchol™). Although there are no efficacy data on how early protection begins for either vaccine, protection is thought to begin 4–7 days after the second dose for each vaccine (e.g., a minimum of ca. 2 weeks after initiating vaccination with Dukoral™ and ca. 3 weeks after the first dose of Shanchol™). For a short-lasting outbreak of only a few weeks' duration, the overall impact of reactive vaccination would be predicted to be minimal with either vaccine, especially considering the time required to recognize the outbreak and to acquire and deliver the OCV (Naficy et al. 1998). Recently, however, it has been appreciated for Shanchol™ that serum vibriocidal antibody responses after the first of the two dose regimen are robust, even higher than after the second dose (Kanungo et al. 2009), hinting that protection may begin even before the second dose. This prediction will be tested in a large-scale, randomized, and placebo-controlled trial to be conducted in Bangladesh.

Fourthly, because PE only reflects direct protection of vaccinees, and does not consider the indirect protective effects of a vaccine via herd protection, it may fail to capture the overall preventive impact of using OCVs at the population level.

Herd protection occurs when a vaccine not only protects vaccinated persons by eliciting immunity to cholera in *individual vaccinees*, but also protects nonvaccinated persons and enhances protection of vaccinated persons by interrupting transmission in *populations* of people, some of whom have been vaccinated. Vaccine herd protection by Dukoral™ and by an early generation killed WC-only OCV were demonstrated in the large Phase III trial of these vaccines done in rural Bangladesh, as well as in a recent demonstration project of Dukoral™ done in Zanzibar (Ali et al. 2005, 2008; Khatib et al. 2012). Data from the former were then used to parameterize a dynamic cholera transmission model for rural Bangladesh. The model showed that use of vaccine with the characteristics of Dukoral™ in rural Bangladesh could nearly extinguish the occurrence of cholera at vaccine coverage level of only 60 %, due to the combined direct and indirect effects of the vaccine (Longini et al. 2007). More recently, further analysis of the Phase III trial of Shanchol™ undertaken in urban Kolkata has also demonstrated both direct and herd protective effects of this vaccine (Ali et al. 2013).

A fifth issue is that OCVs may cross-protect against noncholera pathogens. Because it contains CTB, which is structurally similar to the B subunit of heat-labile enterotoxin (LT) of toxigenic *Escherichia coli* (ETEC), Dukoral™ protects against not only cholera but also against diarrhea due to LT-expressing ETEC. In the Phase III trial of Dukoral™ in Bangladesh, for example, recipients of the vaccine experienced a 67 % reduction of all treated episodes of LT-ETEC and an 86 % reduction of severe LT-ETEC during the initial 3 months after vaccination (Clemens et al. 1988), an observation that has been confirmed in Europeans traveling to ETEC-endemic areas (Peltola et al. 1991). Because ETEC diarrhea is common in most populations experiencing cholera, this added benefit should be taken into account. Conversely, because Shanchol™ does not contain B subunit, it is not predicted to cross-protect against ETEC.

A sixth issue is the clinical spectrum of cholera that is prevented by vaccination. Although it was argued in the past that a deficiency of parenteral cholera vaccines was that they failed to prevent asymptomatic cholera infections, the relevance of this observation to public health impact is unclear (Benenson 1976). On the other hand, it is unarguable that for an OCV to have a major public health impact, it should prevent clinically severe cholera. Both Dukoral™ and Shanchol™ prevent cholera severe enough to require treatment, and thus both are predicted to prevent cholera mortality. In the Phase III trial of Dukoral™, for example, vaccination conferred 26 % protection against all-cause mortality (Clemens et al. 1988). Moreover, there is clear evidence for Dukoral™ that vaccination has an enhanced preventive impact on treated episodes with severe dehydration. For example, in a demonstration project in Beira, Mozambique, Dukoral conferred 84 % protection against all treated cholera episodes and 95 % protection against treated episodes with severe dehydration during 6 months of follow-up (Lucas et al. 2005). In contrast, Shanchol™ exhibited no enhanced protection against those treated cholera episodes presenting with severe dehydration, as opposed to treated episodes of lesser severity, in the Phase III efficacy trial of this vaccine in Kolkata (Clemens, unpublished data).

A seventh consideration relevant to use of OCVs in outbreaks is that protection may vary substantially by host and pathogen characteristics. Protection by both Dukoral™ and Shanchol™ varies by age, being less for young children than for persons vaccinated at older ages. Although in the Phase III trial in Bangladesh Dukoral™ provided almost 100 % protection for children vaccinated at 2–5 years for the first 4–6 months after vaccination, at 2 years of follow-up PE for Dukoral™ was 40 % for this age group as compared to 70 % for older persons (Clemens et al. 1990). At 2 years of follow-up of the Phase III trial of Shanchol™ in Kolkata, India, PE was 50 % for children vaccinated at 1–4 years of age and 80 % for persons vaccinated at older ages (Sur et al. 2009). While these figures appear similar, and recognizing that there are limitations to comparing the results for PE for different vaccines tested in different trials, it is of relevance that the results for Dukoral™ reflect protection against both classical and El Tor cholera, whereas those for Shanchol™ represent protection against only El Tor cholera, the only biotype circulating in Kolkata during the trial. When parsed out by biotype, Dukoral™ protected less well against El Tor cholera at 2 years of follow-up (30 % in 2–5 year olds and 60 % in older persons) (Clemens, unpublished data). As noted earlier, however, absolute rather than relative protection is of great relevance to public health deliberations about using a vaccine, so that in circumstances in which cholera rates are much higher in under-five year olds, as is the case in endemic situations, even these lower values for PE may correspond to a major public health impact.

Another host characteristic that modifies OCV protection is ABO blood group. In the Phase III trial of killed OCVs in Bangladesh, persons who received either Dukoral™ or a killed WC-only OCV exhibited lower levels of protection against cholera if they had O blood group than if they had other ABO groups (Clemens et al. 1989). Populations with a higher prevalence of O blood type, such as those residing in the Ganges delta, would thus be expected to benefit less from vaccination than those with low blood group O prevalence rates.

Yet another host characteristic of importance is preexisting natural immunity to cholera. As noted earlier, outbreaks of epidemic cholera typically affect populations that have experienced little cholera in the past, as was the case in the 2010 outbreak of cholera in Haiti (Harris et al. 2010). It cannot be assumed that vaccine protection will be equivalent in these populations and in populations that have substantial levels of preexisting immunity due to previous natural exposure to cholera. Most evaluations of the protection of both Shanchol™ and Dukoral™ against naturally occurring cholera have been undertaken in populations with endemic cholera and presumably high levels of preexisting immunity. An exception was a trial of Dukoral™ that confirmed a high level of short-term protection against El Tor cholera in Peruvian military volunteers, who were all of blood group O and were presumed to have not at the time of the trial had previous natural exposure to cholera (Sanchez et al. 1994). Field evaluations of these vaccines in populations lacking such immunity constitute an important priority for the future.

Phenotypic characteristics of cholera also may modify vaccine protection. As mentioned earlier, Dukoral™ has been observed to protect less well against classical El Tor biotype than against El Tor classical biotype serogroup O1 cholera. Both Dukoral™ and Shanchol™, however, have shown protection against the newly emergent hybrid El Tor cholera vibrios that expresses classical biotype cholera toxin (Lucas et al. 2005; Sur et al. 2009), which now accounts for all cholera cases in many areas of Asia and Africa, as well as in Haiti.

3.4 Effectiveness of the OCVs

The effectiveness of OCVs when used to control cholera outbreaks has several dimensions (Table 4). One is clinical acceptability. Neither Dukoral™ nor Shanchol™ has been associated with side-effects when given to healthy, non-pregnant individuals. A small, controlled observational study suggested that Dukoral™ inadvertently administered to pregnant women was not associated with adverse pregnancy outcomes (Hashim et al. 2012). Since its licensure, over 15 million doses of Dukoral™ been sold. Post-licensure studies have revealed no safety concerns about use of the vaccine during pregnancy. Small studies have also demonstrated the safety of Dukoral™ when given to persons who are infected by HIV, a feature of great importance in view of the logistical impossibility of testing for HIV in order to target HIV-negative individuals during mass OCV campaigns conducted to control cholera outbreaks (Lewis et al. 1994; Ortigao-de-Sampaio et al. 1998). Although there are no data on the safety of Shanchol™ when administered to HIV-infected or pregnant individuals, the similarities of the WC constituents of Dukoral™ and Shanchol™, and the fact that they are both killed oral vaccines, make it likely that Shanchol™ will be deemed safe when administered to these two patient populations, although studies directly addressing these issues are needed.

Another aspect of clinical effectiveness is the logistic and programmatic feasibility of administering OCVs in outbreak situations. Preemptive delivery of killed OCVs has been demonstrated to be feasible in endemic settings in Beira, Mozamibique (Dukoral™), Orissa, India (Shanchol™), and Dhaka, Bangladesh (Shanchol™); in stable refugee camps in Uganda and Sudan deemed at high risk for cholera (Dukoral™); and in a complex emergency created by the 2007 tsunami in Aceh, Indonesia (Dukoral™) (Cavailler et al. 2006; Dorlencourt et al. 1999; Chaignat et al. 2008; Qadri, personal communication). As well, reactive delivery of Shanchol™ was successfully accomplished in major outbreaks in mass immunization campaigns in Guinea (Medecins sans Frontieres 2013), and Haiti (Ivers et al. 2012). Similarly, ORCVAX™, an earlier generation WC-only OCV similar to Shanchol™, has successfully been delivered reactively in multiple cholera outbreaks in Vietnam, including a large-scale recent outbreak in northern Vietnam (Anh et al. 2011). While these experiences illustrate that both Dukoral™ and Shanchol™ can be delivered to control cholera outbreaks under realistic

public health conditions, it is recognized that the need to coadminister Dukoral™ with relatively large volumes of buffer solution, which is not required for Shanchol™, creates greater supply demands for Dukoral™ and also makes delivery of this vaccine slower and more cumbersome.

Regardless of the safety and feasibility of delivery of these vaccines, it is important that the protection conferred under the demanding and often chaotic circumstances of a cholera outbreak be established. The degree of protection of a vaccine in public health practice (effectiveness) cannot necessarily be predicted from results of prelicensure randomized trials (efficacy), which are usually conducted under idealized circumstances (Clemens et al. 1996). Several vagaries of public health practice, such as broadened criteria for targeting persons for vaccination, and problems encountered with vaccine storage and administration, can lead to a reduction of vaccine impact in relation to that predicted on the basis of prelicensure trials. Conversely, the indirect, or herd protective effects of vaccines, which are typically not measured in prelicensure trials, may substantially enhance vaccine impact beyond that expected on the basis of trials. Thus, it is important to base recommendations on use of OCVs on impacts actually observed in practice.

The protective effectiveness of Dukoral™, delivered preemptively, has been evaluated in practical public health settings in two sites with endemic cholera, one, in a population with a high prevalence of HIV in Mozambique (Lucas et al. 2005) and the other in Zanzibar (Ali et al. 2005, 2008). Each study confirmed levels of PE observed in earlier clinical trials (Clemens et al. 1990). In addition, the Zanzibar evaluation confirmed results of an earlier reanalysis of a Phase III trial that Dukoral™ was capable of conferring herd protection. In aggregate, these studies suggest that the protective impact of using this vaccine in practice will be greater than that expected on the basis of estimates of PE from individually randomized, Phase III trials. To date, no study has evaluated the impact of Dukoral™ when delivered reactively in outbreaks in either endemic or epidemic settings.

No studies of the protective effectiveness of Shanchol™ have been completed to date. As mentioned earlier, Vietnam has used an earlier generation, locally produced, killed WC-only OCV since the early 1990s. A prolonged epidemic of cholera in Hanoi in 2007–2008 provided an opportunity to assess protection conferred by reactive vaccination, which was given as a two-dose regimen to persons aged 10 years and older in January, 2008. A case-control study of cholera occurring between April and June, 2008 revealed 76 % PE by the vaccine in this public health setting (Anh et al. 2011). As well, an effectiveness trial of a locally produced earlier generation killed WC-only OCV delivered preemptively to persons aged 1 year and older in central Vietnam revealed 50 % protection during an epidemic occurring 3–5 years after vaccine campaigns (Thiem et al. 2006).

An important aspect of the effectiveness of OCVs in control of cholera outbreaks is their potential to synergize with concomitant WASH interventions to prevent cholera. Traditionally, provision of clean water, adequate sanitation, and promotion of personal and household hygiene have been the cornerstones of WHO's approach to prevent cholera in outbreak response efforts. In addition to making intuitive sense, use of such interventions to prevent cholera has been

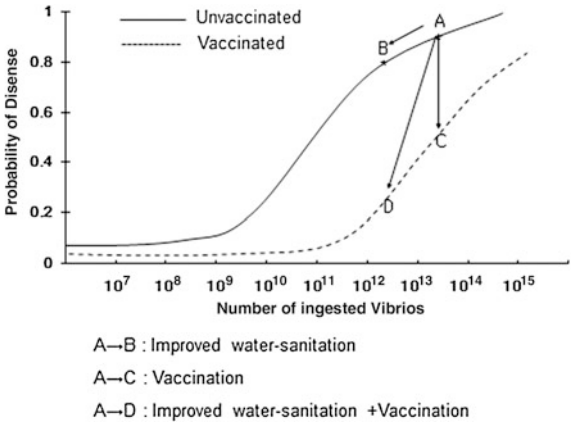

Fig. 1 Hypothetical relationship between the impact of oral cholera vaccines and improvements in water quality-hygiene-sanitation on the risk of cholera, by the size of ingested cholera inoculum. The figure presents two hypothetical curves relating the ingested inoculum of cholera organisms to the probability of diarrhea after ingestion. The *top curve* corresponds to a unvaccinated individual and the *bottom curve* to a vaccinated individual. The *top curve* roughly describes the lower risk of symptomatic cholera after WASH interventions, which act to decrease the frequency and/or dose of ingestion of cholera vibrios (movement from state *A* to state *B*). The bottom curve reflects the same for vaccinated individuals (movement from state *C* to state *D*). The effect of OCVs should be to decrease the probability of becoming ill, at any (or at least most) ingested doses (movement from state *A* to state *C*). Because of these relationships the combined effects of WASH interventions and OCVs should combine to produce a greater preventive effect than either intervention alone (movement from state *A* to state *D*)

documented in a limited number of intervention studies in the Philippines (Azurin and Alverin 1974) and India (Deb et al. 1986). While deployment of OCVs and implementation of WASH interventions have in the past been caste as competitive with one another, there is a good theoretical basis to consider them as complementary, if not synergistic (Fig. 1). A large-scale, cluster-randomized community introduction project of Shanchol™ given with or without a concomitant WASH intervention is now being conducted in urban Dhaka, Bangladesh and will test this prediction (Qadri, personal communication).

While we do not have a great deal of empiric evidence on the protective effectiveness of OCVs as reactive interventions when used in cholera outbreaks, several attempts have been made to predict the effects of hypothetical deployment of OCVs reactively, using mathematical models. One analysis considered hypothetical reactive vaccination with Dukoral™ for persons aged 2 years and above in cholera outbreaks in three settings: Zimbabwe, which was an epidemic setting in 2008/2009; Kolkata, India a setting with endemic cholera considered in respect to its outbreaks in 2003–2005; and Zanzibar, another endemic setting in which outbreaks between 1997 and 1998 were evaluated. The analysis found that prompt initiation of a two-dose regimen of this vaccine would have had a significant impact on outbreaks occurring in all three settings. Moreover, the predicted impact

in the two endemic settings were likely conservative as the 2-year expected duration of vaccine protection would also act to prevent cases in subsequent outbreaks (Reyburn et al. 2011). Five modeling analyses were conducted for the recent outbreak of cholera in Haiti (Chao et al. 2011; Andrews and Basu 2011; Bertuzzo et al. 2011; Tuite et al. 2011; Date et al. 2011). All five found a protective impact, albeit at different levels. The most complete analysis incorporated direct as well as herd vaccine protection, targeted (to high-risk populations) versus nontargeted reactive vaccination, and the interaction of vaccination with varying levels of improvement of hygiene, and estimated the impact on the total epidemic, including cases occurring before vaccination was could be initiated (Chao et al. 2011; Andrews and Basu 2011). This model predicted that if the 30 % of the population deemed at high risk for cholera had been vaccinated reactively shortly after recognition of the epidemic with a vaccine having the characteristics of Shanchol™, and if this high-risk population's level of hygiene had been improved by a modest 10 %, a 55 % reduction in all cholera cases in the outbreak would have occurred.

3.5 Balance Between Costs and Effects of Using OCVs

Increasingly, decisions about deploying health interventions are being greatly influenced by analyses of the balance between costs and the impacts of the intervention, expressed monetarily or as a health metric. As pointed out elsewhere (WHO 2010), a number of cost-effectiveness analyses of the use of cholera vaccines have been published over the years, but most have been flawed by such features as unrealistic assumptions about vaccine targeting strategies, failure to account for all costs, or failure to account for vaccine herd protective effects, the last feature having been appreciated only since 2006 (Ali et al. 2005). As well, it has been persuasively argued that cost-effectiveness may not be terribly relevant to decisions about deploying OCVs in the wake of major emergencies, such as earthquakes, refugee crises, hurricanes, and tsunamis, as other relief efforts in these situations are typically very costly and are instituted without regard to cost-effectiveness (Sack 2003).

The most comprehensive, modern cost-effectiveness analyses of OCVs have been done for preemptive vaccination with OCVs against endemic cholera. One was done for specific sites in Kolkata, India; Beira, Mozambique; Matlab, Bangladesh; and Jakarta, Indonesia; the other was done from the perspective of major WHO regions affected by endemic cholera. The site-specific analyses for a vaccine with the characteristics of Shanchol™ found that, when herd effects are taken into account, mass vaccination of 1–14 year olds and of all individuals aged 1 year and over were both cost-effective, as measured by a cost per DALY gained under three times the GDP per capita of the country. Moreover, programs of childhood vaccination in Beira and Kolkata were very cost effective (cost per DALY gained less than the GDP per capita) (Jeuland et al. 2009). However, this analysis may have

been a bit optimistic as it assumed a price per dose of $1, rather than the $1.85 price for Shanchol™ that has now been established by the manufacturer. A Global Investment Case for a vaccine with the characteristics of Shanchol™ estimated vaccine cost-effectiveness for 33 countries projected to be early adopters of the vaccine over the next several years. The analysis, which assumed a price per dose of $1.85 (albeit with a gradually declining price over time as more producers enter the market) and also took vaccine herd effects into account, found the vaccine to be very cost-effective for programs targeting 1–14 year olds as well as for all persons aged 1 year and over for the African, Southeast Asian, and Eastern Mediterranean regions (International Vaccine Institute 2012). Vaccinating 1–14 year olds was more cost-effective than vaccinating older persons.

4 A Cholera Vaccine Stockpile for Use in Cholera Outbreaks

In 1999, WHO recommended the pre-emptive use of OCV in emergency situations at high risk for a cholera outbreak, associated with a recommendation that an initial 2 million dose OCV stockpile should be established for use in endemic and emergency settings (WHO 1999). For various reasons, reflecting different opinions both within and outside WHO, these recommendations were not implemented. Concerns leading to inaction were raised about high vaccine costs, limitations in vaccine availability, logistic challenges associated with vaccine storage and administration, and logistic problems in administering a two-dose vaccine. Concerns were also expressed that vaccination might interfere with other WHO-recommended control efforts in cholera outbreaks. There was also an underlying optimism in some quarters that through intensified global efforts to improve WASH, the control of cholera together with many other enteric infections could soon be achieved.

Still, the past decade has not witnessed any decline in cholera incidence or mortality. To the contrary, there have been many unusually large and protracted outbreaks in Angola, Zimbabwe, Central and West Africa, Somalia, and Haiti. Indeed, cholera has now become endemic not only in many parts of Africa but also in Haiti, after nearly a century in which cholera was not reported in this country (Harris et al. 2010).

In view of this situation, the 64th World Health Assembly in 2011 called for an integrated, comprehensive strategy of cholera prevention and control, recommending the use of OCV "where appropriate, in conjunction with other recommended prevention and control methods". A follow-up consultation meeting concluded that an OCV stockpile for outbreak control should be established as soon as possible, and a Technical Working Group (TWG) was convened to develop a framework for the implementation of such a stockpile. Its report was recently published (WHO 2012a, b, c), providing criteria and guidelines on many

important aspects relating to the establishment and use of such a stockpile: criteria for choice of stockpiled vaccines and their deployment; the appropriate size, storage and financing of an initial OCV stockpile and the management, partnership and evaluation processes required; and the decision-making procedure and operational issues.

The TWG established several minimum criteria for releasing OCV from a stockpile for reactive vaccination to control epidemics. These include laboratory-confirmed evidence of an outbreak, the availability of a country action plan, and availability of adequate vaccine storage capacity and administration materials to undertake vaccination campaigns (Costa 2009; WHO 2012a, b, c). Some additional recommendations regarding the OCV stockpile and its use include:

(1) *Complementation, not replacement of other control measures.* Establishment of an OCV stockpile should not detract attention from the key established responses to cholera outbreaks. These include (i) detection, diagnosis, and treatment of cases with oral rehydration and antibiotic treatment; (ii) establishment of a safe water supply; (iii) implementation of adequate waste disposal, sanitation, and hygiene; and (iv) communication and social mobilization. It is also emphasized that the creation of an initial, necessarily small, OCV stockpile and its use will not in itself constitute sufficient preparedness for a large and/or sustained cholera epidemic.

(2) *Vaccine properties criteria.* The TWG has identified a number of criteria to guide the choice of vaccine(s) to be stockpiled (see Table 5). These criteria are divided into those for vaccines that should be considered for the initial stockpile, and the partly sharpened criteria that may be requested of the next-generation stockpiled OCVs. The criteria for the first-generation stockpile essentially describe the established properties of both of the two WHO-prequalified OCVs, Dukoral™ and Shanchol™. The criteria for the 2nd-generation stockpile identifies some modified characteristics that are proposed to guide the development of the next-generation OCVs: one-dose rather than two-dose vaccine, heat-stable vaccine, <2-week onset of protection after vaccination, and no age limitations for vaccine administration.

(3) *Criteria for release of stockpiled vaccine.* A set of epidemiological criteria that should inform a decision to release stockpile vaccine in response to an outbreak are identified in the TWG report. Importantly, the report states that stockpiled vaccine will be deployed only *after* the reporting of a culture-confirmed cholera outbreak in any given area, and then *only* if the impact of the vaccination campaign is estimated to be potentially high. The OCV stockpile should be targeted at epidemics in low-income countries.

(4) *Governance, storage, and procurement of OCV stockpile.* It is recommended that the International Coordinating Group (ICG) *decision-making body* that oversees the meningococcal and yellow fever vaccine stockpile should extend its mandate to include OCV. For OCV decisions this group—which comprises MSF, IFRC, UNICEF, and WHO—should be nested within a wider group of organizations (e.g., technical, commercial, civil society, funding) that can

Table 5 Proposed criteria for candidate stockpile OCVs for immediate use, and modification requirements for subsequent medium-term stockpiled vaccine by WHO's Technical Working Group on creation of an oral cholera vaccine stockpile (WHO 2012a, b, c)

	Candidate oral cholera vaccine requirements	
	For immediate stockpile	For medium-term stockpile
Confers protection against	O1 El Tor (Inaba and Ogawa)	O1 El Tor (Inaba and Ogawa)
Number of doses required for protection	2 doses	1 dose
Indication ages	≥2 years	All age groups
Safety/tolerability profile	Only mild, short-term side-effects acceptable	Only mild, short-term side- effects acceptable
Immunocompromised persons (including HIV infection) and pregnancy contraindicated?	No known risk of whole-cell killed vaccines in pregnant women and immune-compromised individuals	Safe and immunogenic for administration
Time of onset of protection after full vaccination	2–4 weeks	<2 weeks
Efficacy 6 months after vaccination	≥50 %	≥50 %
Minimum duration of sustained protection	1 year	1 year
Ability to confer herd protection?	Desirable but not necessary	Desirable but not necessary
Formulation	Single formulation for all ages, including very young children	Single formulation for all ages, including very young children
Buffer acceptable?	Yes	Yes
Can be administered with local water (with or without chlorination)?	Yes	Yes
Presentation and packaging	Multi-vial packaging or single-dose vials	Multi-vial packaging or single-dose vials or multi-dose vials
Cold chain requirements	2–8 °C	Heat stable
Minimum shelf life	2 years	3 years
Country registration	Preferable but not necessary (authorization to use still needed)	Preferable but not necessary (authorization to use still needed)
WHO prequalification	Necessary	Necessary

inform the partnership on their specific areas of expertise. A *vaccine request* may be made by any national or international organization, and the ICG should then make a decision within 48 h. As with existing stockpiles of meningococcal and yellow fever vaccines, country receipt of OCV should then be within 7 days of approval of a request. *Storage* of stockpile vaccine should be the

responsibility of the manufacturer. The OCV stockpile should initially comprise a 3-year supply of 2 million doses per year, which could later increase in size. The stockpile should be maintained on a rotating stock basis. Initial donor contributions should be sought to *finance* vaccine procurement, country preparedness, and planned operational costs for the first 2–3 years. A revolving fund should be established to assure longer term financial stability. A reserved rather than prepaid stockpile is preferred. *A Procurement Reference Group* should be established by the UNICEF Supply Division (UNICEF/SD) to advise on technical issues regarding vaccine and stockpile specifications.

(5) *Monitoring and evaluation.* The TWG report prescribes that a rigorous system of short- and long-term monitoring and evaluation should be embedded within the OCV stockpile mechanism. WHO should establish a stockpile evaluation group to define and implement the detailed monitoring required. As experience and data accrue, the results of this evaluation should enable continuous improvement in the structure and functioning of the stockpile.

While these recommendations reflect the collective views of WHO expert groups, it has to be kept in mind that they are based on expert opinion and are not formally evidence-based. Reactive cholera vaccination still largely remains "terra incognito" with regard to strategies, logistics and real-life impact. It is also clear that use of these criteria will entail a great deal in the way of subjective judgment. This is especially true for the requirement that stockpile vaccine will be deployed only "*when the impact of the vaccination campaign is estimated to be potentially high*". Factors considered by the WHO expert group as likely indicators of a high potential impact of OCV deployment after an outbreak is identified include: (1) high susceptibility of the population to cholera, as reflected by a paucity of cholera cases in the past 2–3 years (and thus a low level of preexisting population immunity to cholera) or high attack rates when past outbreaks have occurred; (2) high vulnerability of the population, as reflected in high case-fatality rates in past outbreaks, the occurrence of cholera in refugee camps, internally displaced people or slums in the affected areas, or the occurrence of cholera in areas with high levels of population movements, high population density, or poor access to clean water, sanitation, or health care; and (3) high risk of spatial extension of the outbreak, as reflected in a short (weeks, not months) time elapsed and a low attack rate since the beginning of the outbreak, a low proportion of health units in the affected districts reporting cholera since the start of the outbreak, or reporting of cases early in the anticipated epidemic season (WHO 2012a, b, c). This last consideration reflects the recognition that although cholera outbreaks have traditionally been thought to be short-lasting, often only a few weeks in duration, several recently reported cholera outbreaks have been very prolonged and widespread (Table 3) (Ministere de la Santa Publique et de la population 2012; WHO 2007, 2008; Mukandavire et al. 2011; Calain et al. 2004; Sasaki et al. 2008; Shultz et al. 2009). Predicting which outbreaks that will be prolonged would obviously have major implications for reactive vaccination strategies.

Another incompletely defined area that may need to be revisited concerns the proposed practical management and financing of the stockpile. It appears to make

good sense to let the ICG, already fulfilling such a role for the meningococcal and yellow fever vaccines stockpiles, be the decision-making body also for OCV. However, the proposal that for OCV, the ICG should *"be nested within a wider group of organizations (*e.g., *technical, commercial, civil society, funding) that can inform the partnership on their specific areas of expertise"* might easily be a roadblock or at least very difficult to operationalize. If the ICG is expected to have formal consultations with this broader group, this would make it difficult for ICG to fulfill its obligation to communicate a decision within 48 h after a vaccine request. More reasonably, in practice the ICG should try to consult with other organizations and entities on a case-by-case basis to ensure that its decisions are guided by complementary know-how, especially on local conditions of relevance for the requested vaccine deployment.

It also remains uncertain to which extent the stockpile, initially comprising two million doses per year and maintained on a rotating stock basis, can be built up solely on "*a reserved rather than prepaid*" basis. The idea behind this proposal is that were vaccine reserved for the stockpile not requested, it could still be used commercially by the manufacturer and thus not entail any costs for the stockpile fund. The problem today is that there is still a very small global commercial market for OCVs, probably below 2 million doses per year. It remains to be seen whether the manufacturer(s) will accept the risk to increase their OCV production for expected use in a stockpile without any guaranteed orders. The longer term maintenance of an expanded OCV stockpile would certainly be greatly facilitated if the market for OCVs, currently largely restricted to travelers, could be expanded through the introduction of OCVs in the control of endemic cholera in high-exposure countries. If prophylactic cholera vaccination were used routinely in populations with high cholera endemicity it should also, in addition to its impact on the endemic cholera situation, reduce the risk of epidemic cholera outbreaks in these populations, since most such outbreaks do indeed occur in countries and populations where cholera is already highly endemic.

Finally, much remains to be learnt from the use of stockpiled vaccine on how best to target vaccination for outbreak response when vaccine supply is limited. Illustrative dilemmas include whether to target vaccination to the affected area or focus on surrounding areas to prevent epidemic spread and whether to focus on densely populated urban high-risk areas or more remote rural areas with higher mortality risk due to poor access to effective treatment. A mathematical cholera transmission model has been used to assess the expected impact of different vaccination strategies if they had been used in the Haiti cholera outbreak in 2010, comparing reactive overall mass vaccination with reactive high-exposure vaccination and reactive ring vaccination (Chao et al. 2011). Not surprisingly, with limited vaccine quantities, concentrating vaccination in high-risk areas would always be the most efficient strategy, and this approach would be even more effective when combined with a campaign to also improve hygiene and sanitation. It was also found important that vaccination be started in high-risk subpopulations within 5 days after the first two cases had appeared in them; waiting for several more cases or having a longer delay seriously diminished the modeled effectiveness

of vaccination. The importance of a rapid response was also evident in a retrospective analysis of a number of cholera outbreaks in Zimbabwe, Kolkata (India), and Zanzibar (Tanzania): the results indicate that reactive vaccination with a two-dose cholera vaccine can substantially reduce the number of cholera cases, the more the larger and longer the epidemic is, and the impact was found to be more than doubled if vaccination can be completed within ca 10 weeks ("rapid response") as compared to 21 weeks ("delayed response") after the start of the outbreak (Reyburn et al. 2011).

Another important issue, in addition to those relating to the logistics in mobilizing and deploying vaccine from the stockpile, would be to assess whether protection by existing OCVs with two-dose regimens begins after intake of the first dose. In cholera-endemic areas where partial natural immunity is built up progressively by age, a single-dose regimen may be sufficient to elicit a protective intestinal immune response in some individuals. It would also be important, outside the direct use of the stockpile but of great relevance to it, to establish reasonable in vitro serological correlates of protection that can be used to expand or modify indications and regimens for current and future OCVs. For use of the OCV stockpile such correlates would be invaluable for studies that could extend age indications and acceptable limits of thermal storage and shelf life. Both of the WHO-prequalified OCVs, Dukoral™ and Shanchol™, are based on heat-stable vaccine components that withstand storage at temperatures up to 37 °C for months, and although the formally approved shelf life of these vaccines is limited to 3 and 2 years, respectively, studies with Dukoral™ have indicated unimpaired safety and immunogenicity of vaccine in humans after storage for almost 15 years (Holmgren, unpublished). Likewise, immunization with two full doses of Dukoral™ in infants 6 months of age in Bangladesh was well tolerated and fully immunogenic indicating that OCV can be safely administered at least down to this age (Ahmed et al. 2009).

5 Concluding Remarks

OCVs are now components of the public health tool box—alongside provision of adequate WASH and treatment—for the control of cholera outbreaks. Deployment of these vaccines preemptively in populations with high levels of cholera endemicity is relatively non-controversial, though the definition of what is "high" may be debated. As illustrated by analyses of hypothetical reactive vaccination in Zanzibar and Kolkata (Reyburn et al. 2011), reactive vaccination in endemic setting, although not an optimal strategy, can also be justified, in view of the multiyear duration of protection conferred by both Dukoral™ and Shanchol™ and the likelihood that vaccination will not only help contain the current outbreak, but the future occurrence of cholera as well. In endemic settings, a case can be made for targeting children aged 1–14 years for vaccination if resources for vaccination are constrained.

When it comes to vaccinating to control unpredictable outbreaks in epidemic settings, models predict a significant impact if reactive vaccination is initiated relatively soon after recognition of the outbreak and is targeted to high-risk populations, provided that the outbreak is relatively prolonged. At present, however, we lack validated tools for predicting the scale and duration of outbreaks after they have begun, and research to develop such tools is greatly needed. Careful evaluation of the results of using the newly created global cholera vaccine stockpile will be helpful in this respect. Preemptive vaccination in the wake of complex emergencies occurring in populations without documented endemic cholera is a much less certain strategy, as we lack validated tools for predicting in which situations cholera is likely to occur.

We currently have two OCVs that are commercially available and approved by WHO for international use: Shanchol™ and Dukoral™. Both are killed oral vaccines with excellent safety profiles, although additional studies of safety when the vaccines are given to pregnant women or persons infected by HIV are needed. Protection by Dukoral™ has been observed among adults in Peru who lacked natural immunity from past cholera exposure (Sanchez et al. 1994); we lack such data for Shanchol™, which has only been evaluated for protection in populations with preexisting natural immunity. The ability to protect immunologically naïve persons is of importance when considering whether to vaccinate in outbreaks occurring in epidemic as opposed to endemic settings, and should be a priority for evaluations of the newly created OCV stockpile. Other factors influencing the choice of Dukoral™ versus Shanchol™ include Shanchol's™ lower expense, simpler dosing regimens (two doses for all age groups), and longer duration of protection and, conversely, Dukoral's™ greater short-term efficacy against cholera and its cross-protection against LT-ETEC.

Despite not having data on all the questions of relevance to use of OCVs to control outbreaks, there is clearly enough evidence to initiate their use, as answers to the questions will come with experience. In this spirit, non-governmental organizations involved in the control of cholera outbreaks, such as MSF and Partners in Health, have used Shanchol™ recently in Africa and Haiti. Evaluations of these experiences, as well as the additional experiences that will be provided by use of the newly created global cholera vaccine stockpile, offer the opportunity to gather this needed evidence and to refine our approaches to vaccinating in the future.

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