Background Paper on Whole-Cell, Killed, Oral Cholera Vaccines

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1. Executive Summary

1.1. Preamble

Cholera, an acute watery diarrheal disease, caused by toxigenic strains of the bacterium *Vibrio cholerae* O1 and O139, causes an estimated over 2.9 million cases and over 95,000 deaths annually in cholera endemic countries alone and frequent epidemics in other settings with poor water and sanitation infrastructure. Global estimates range from 1.4 – 4.8 million cases and 28,000 – 142,000 deaths every year. The disease is characterized by acute onset watery diarrhea leading to rapid dehydration and death, if not promptly treated with fluid replacement and antibiotics for severe cases. Cholera is transmitted through the fecal-oral route most frequently by way of contaminated water and food and, hence, primarily occurs in settings of poor water and sanitation infrastructure in sub-Saharan Africa, Asia, and more recently in Haiti. Additional complex humanitarian emergencies in recent times, with resulting infrastructure disruptions and population displacements, have added a significant cholera burden globally.

Provision of safe water, adequate sanitation, improved hygiene measures (WaSH), cholera treatment, and cholera vaccination form a toolkit of interventions for comprehensive cholera prevention and control. Cholera vaccination is an important short- to medium-term tool for cholera prevention and control while longer-term interventions for water and sanitation infrastructure systems are put into place and in crisis/refugee settings where longer term infrastructure changes are not feasible. Three killed, whole-cell (WC) oral cholera vaccines (OCVs) are currently prequalified by the World Health Organization (WHO) for procurement by United Nations agencies and are available for global use: Dukoral, Shanchol and Euvichol (Shanchol and Euvichol are available through the global OCV stockpile). In 2010, the WHO issued a revised position statement based on data available at the time with the recommendations that OCVs should be considered in preemptive situations (prevention before an outbreak starts) as part of comprehensive cholera control plans, and could be considered in reactive situations (once an outbreak starts) depending on the local epidemiology and feasibility of conducting campaigns. The recommendations emphasized the need to sustain critical cholera control interventions in outbreak situations and additional documentation of these experiences given very limited OCV use in outbreak settings. Since 2010, there has been tremendous progress on global availability of vaccines and numerous OCV use experiences in both clinical trial and programmatic settings. In June 2013, a global OCV stockpile with an initial stock of 2 million doses was established by WHO with funding support from multiple donors, and in November 2013, Gavi (the Vaccine Alliance) endorsed funding support for the OCV stockpile. The Global Taskforce for Cholera Control (GTFCC) was revitalized by WHO, serving as the secretariat with representation of key global, regional and country partners.

During 2010 – 2016, cholera has continued to be a significant problem globally with large scale epidemics, such as the one experienced in Haiti, and surges in endemic settings of sub-Saharan Africa and Asia leading to increasing efforts by partners to utilize all available tools, including vaccines as part of comprehensive cholera prevention and control programs. This global problem combined with multiple OCV use experiences provide additional data and lessons learned to review and update recommendations for oral cholera vaccine use by the WHO Strategic Advisory Group of Experts on Immunization (SAGE). In November 2015, the WHO SAGE working group on oral cholera vaccines (**Appendix 1**) was established to review the progress made since the last OCV position paper update of 2010.

This background document presents updated information on whole-cell, killed, oral cholera vaccines since the previous oral cholera vaccine position paper (2010), describes the relevant data reviewed by the working group and the resulting proposed recommendations for whole-cell, killed oral cholera vaccines for SAGE deliberation and consideration.

1.2. Key Data and Conclusions

- Several large-scale epidemics, surges in endemic cholera, and multiple humanitarian emergencies have occurred within the last few decades, including since 2010. Cholera continues to cause significant morbidity and mortality globally.

- Oral cholera vaccines (OCVs) prequalified by WHO are available for global use in endemic, epidemic/outbreak and humanitarian emergency situations.

- An OCV stockpile, supported by Gavi and managed by the International Coordinating Group (ICG) is available for rapid access to OCVs in outbreak and humanitarian emergency situations. An additional 'non-emergency reserve' of stockpile vaccine, also supported by Gavi and managed by the OCV working group of the GTFCC, is available for endemic situations. Since the establishment of the stockpile, over 7 million doses from the stockpile have been deployed in over 14 countries in multiple endemic, epidemic, and emergency situations.

- Key conclusions of the evidence review by the SAGE OCV working group, including the Grading for Recommendations, Assessment, Development and Evaluation (GRADE) review for vaccine safety, efficacy (and effectiveness) and safety among pregnant women, are:

    - Vaccine Safety: there is high level of scientific evidence that the currently available WC, killed OCVs are safe among non-pregnant individuals ≥ 1 year old.
    - Vaccine Efficacy and Effectiveness: there is moderate level of scientific evidence that the currently available WC killed OCVs are efficacious and effective with a duration of at least 6 months for a single dose. There is moderate level of scientific evidence that the currently available whole-cell killed oral cholera vaccines with a 2-dose schedule are efficacious and effective for at least 3 years among adults, but not among young children 1 – 5 years old. There is low level of scientific evidence that the currently available WC killed OCVs are effective for at least 5 years (only 2 studies).
    - Vaccine Safety among Pregnant Women: there is moderate level of scientific evidence that the currently available WC killed OCVs are safe for use among pregnant women.
    - Feasibility and Acceptability: OCVs campaigns have been demonstrated to be feasible and acceptable in multiple endemic, epidemic and humanitarian emergency settings.
    - Cost-effectiveness: data on cost-effectiveness is limited and most studies and evaluations have reported costing data only. Modeling studies suggest that cholera vaccination has the potential to be a cost-effective intervention for cholera control in countries at high risk for cholera.

1.3. Proposed Key Recommendations for SAGE Consideration

General Recommendations

1. Given the current availability of prequalified WC killed oral cholera vaccines (OCVs) and data on their safety, efficacy, field effectiveness, feasibility, impact and acceptability in cholera-affected populations, these vaccines should be used in areas with endemic cholera, in humanitarian crisis with high risk of cholera and during cholera outbreaks, in conjunction with other cholera prevention and control strategies.

2. Appropriate case management, WaSH interventions, surveillance and community mobilization remain cornerstones of cholera control. Vaccination is synergistic with those activities.

3. The main objective of vaccination is to reduce disease burden in vaccinated areas, through individual and herd protection, and to prevent the spatial expansion of outbreaks.

4. Mass vaccination campaigns are usually the most practical option for delivering oral cholera vaccines. Schools, religious institutions and other community settings can be appropriate venues for vaccination campaigns using fixed sites. Outreach activities can also be organized. Incorporating cholera vaccination with other vaccination activities can be an alternative or complementary strategy to mass campaigns.

5. Cholera vaccination mass campaigns should be accompanied by WaSH interventions and combined with other health-related interventions.

6. Epidemiological and laboratory surveillance is essential to estimate the burden of disease and understand the impact of vaccination and other interventions.

7. Equitable access to OCV should be ensured for underserved populations exposed to the risk of cholera. OCV stockpiles, supported by GAVI and managed by the ICG (for emergency type of use) and by the GTFCC OCV working group (for use in endemic settings), have been formally established in 2013 for that purpose. Requests to access OCV in any setting should follow the established mechanisms of stockpile management.

8. In all settings, a series of criteria should be considered to guide the decision to vaccinate,
    - The risk of cholera among targeted populations
    - The susceptibility and vulnerability of the population and the risk of spatial extension.
    - The capacity to cover as many persons as possible, eligible to receive the vaccine and living in the targeted area (e.g., ages ≥ 1 or 2 years, depending on the vaccine).
    - Programmatic factors such as the local capacity to organize and conduct a campaign, ability to provide other priority health interventions and population acceptability.

- Cholera vaccination should not be conducted if a campaign has been conducted in the previous 3 years in the same population (with consideration for the quality of the campaign, the vaccine coverage, and any population movements)

9. Countries and agencies accessing the OCV stockpiles should systematically implement M&E activities and provide accompanying data to WHO GTFCC. In particular, M&E activities should provide better estimates of,
    - The impact of OCV to control and prevent cholera outbreaks, including in humanitarian emergency situations
    - The impact of OCV on cholera transmission in endemic settings
    - The vaccine effectiveness using different vaccination strategies and in different age groups
    - The cost-effectiveness of different vaccination strategies and in various settings and age groups

    Guidelines have been developed for this purpose and are accessible on the WHO website.

10. Based on available evidence, there are considerable benefits and very few risks for including pregnant women in OCV vaccination campaigns.

11. OCV should be considered for emergency/relief workers who are likely to be directly exposed to cholera patients or to contaminated food or water, particularly those staying in areas with poor access to healthcare facilities.

12. Vaccination is generally not recommended for long- or short-term travelers to cholera-affected countries.

Control of Endemic Cholera

1. Cholera vaccination should be targeted in priority to high-risk areas or groups, regularly affected by cholera; with culture-confirmed cases detected in at least three out of the last five years and evidence of local transmission. Campaign planning should be carried out to ensure that vaccination takes place prior to any known cholera season.

2. Cholera vaccination in endemic areas should be contingent on multisectoral interventions as part of a long-term plan for cholera prevention and control endorsed at the local and national levels by the relevant ministries and should be budgeted for.

3. Universal vaccination (throughout a country without regard to risk) is not recommended in most countries.

4. Follow up campaigns in the same areas may be considered after 3 years in case of persistent transmission.

5. Strategies targeting specific age groups at higher risk may be considered.

Cholera Control in Humanitarian Emergencies

1. During humanitarian emergencies with a risk of cholera, but without a current cholera outbreak, vaccination with OCV should systematically be considered to help prevent potential outbreaks, as an additional preparedness measure, depending on the local infrastructure (i.e., capacity to organize a vaccination campaign).

2. The decision to vaccinate should be guided by a thorough investigation of the current and historical epidemiological situation, an assessment of the actual risk of cholera, and a clear identification of geographical areas and populations to be targeted.

3. Campaign planning should be carried out to ensure that vaccination takes place prior to any known cholera season. Campaign preparation should be conducted early to ensure that vaccination starts immediately once the vaccines become available in country.

4. In areas of protracted emergencies, follow-up campaigns may be considered after 3 years (or less in case of persistent risk, particularly in case of population movement).

Control of Cholera Outbreaks

1. Cholera vaccination should systematically be considered to help prevent the spread of current outbreaks to new areas, following a thorough investigation of the current and historical epidemiological situation and a clear identification of geographical areas and populations to be targeted.

2. Campaign preparation should be conducted early to ensure that vaccination starts immediately once the vaccines become available in country.

3. Based on available evidence on short-term protection, a single dose strategy could be considered in areas experiencing cholera outbreaks. Considering the limited evidence about the duration of protection, additional vaccination might be needed to ensure longer-term protection.

Additional research and evaluation recommendations are available in Section 5.

2. Introduction and Background

2.1. Key points

1. In 2010, the World Health Organization (WHO) recommended the preemptive use of the available WC killed OCVs in endemic areas among high-risk populations and in areas at risk areas of outbreaks in conjunction with traditional cholera prevention and control interventions. The WHO also recommended that reactive use of OCVs should be considered in active outbreak situations depending on a thorough assessment of the local epidemiological factors, infrastructure and capacity.

2. In May 2011, the World Health Assembly adopted a resolution calling for the implementation of an integrated and comprehensive approach to cholera control, including the use of oral cholera vaccines, where appropriate, in conjunction with other recommended prevention and control methods.

3. Large, protracted cholera outbreaks continue to occur in many parts of the world, including sub-Saharan Africa, and Asia, and in Haiti, which has experienced the largest, most protracted cholera epidemic of modern times.

4. Two newer WC killed OCVs have been prequalified by WHO (Shanchol in 2011 and Euvichol in 2015). Several million doses of Shanchol have been used for cholera prevention and response thus far. New data have become available regarding the safety, acceptability, effectiveness, impact and cost-effectiveness of the vaccines, and their role in a comprehensive, integrated cholera prevention and control strategy.

5. Uncertainties regarding OCV supply and demand predictions prompted the creation of a global OCV stockpile. In 2013, the global OCV stockpile was created with an initial commitment of 2 million doses primarily for outbreak and humanitarian emergency response. In November 2013, Gavi, the Vaccine Alliance approved investment support of US$115 million for the global OCV stockpile during 2014 – 2018, and in June 2016, the Gavi board endorsed support for operational costs of OCV campaigns. Since 2013, over 7 million OCV doses have been deployed from the global stockpile in over 14 countries and vaccine availability is expected to increase with a second prequalified vaccine.

6. In 2014, the Global Taskforce for Cholera Control (GTFCC), was revitalized and an OCV working group was established to provide guidance and recommendations for OCV use in different settings and inform further guidance.

7. These new developments and availability of additional data make this an opportune time for WHO SAGE to revisit and update its recommendations for the use of WC killed OCVs.

2.2. Introduction

Cholera is an acute diarrheal infection caused by ingestion of toxigenic serogroups O1 and O139 of the bacterium *Vibrio cholerae* through direct fecal-oral contamination or ingestion of contaminated water or food. Rapid dehydration and death can occur in a matter of hours, if not promptly and adequately treated with fluid replacement. Cholera primarily occurs in areas with poor access to safe drinking water and inadequate sanitation infrastructure. It remains an important, preventable but neglected public health problem, affecting the most impoverished populations, including those displaced as a result of humanitarian emergencies. It imposes substantial costs on families and public health systems.

Cholera causes an estimated 1.4 to 4.3 million cases, and 28,000 to 142,000 deaths per year worldwide[1]. Over 1.4 billion persons are at risk globally[1] and large scale, protracted epidemics are increasing in frequency compounded by growing occurrence of complex emergencies that result in the breakdown of infrastructure or population displacements. While epidemic cholera attracts attention and accounts for most of the cases reported to WHO each year, endemic cholera continues to exact an unacceptable toll primarily in large parts of Africa, South and Southeast Asia, and more recently in the Americas (Haiti). In 2015, a total of 172,454 cases and 1,304 deaths were reported to the World Health Organization (WHO) by 42 countries with an overall case-fatality rate (CFR) of 0.8%[2]. This, however, only represents a fraction of cases due to lack of diagnostic facilities and massive underreporting. The disease is largely underreported due to several factors and many countries and regions report cases as "acute watery diarrhea" and not cholera. Underreporting may be due to factors such as inadequate disease surveillance and reporting, fear of the macro-economic impact of cholera reports on trade and tourism, and poor access to health services among the very poor and marginalized populations, who are at the highest risk of morbidity and mortality.

The provision of safe drinking water, adequate sanitation, hygiene promotion and robust disease surveillance remain the mainstays of preventing both endemic and epidemic cholera. Fluid replacement, with oral rehydration solution (ORS) if the patient can tolerate intake by mouth, or IV fluids followed by ORS for severe dehydration, serves as the primary treatment for cholera (http://www.who.int/cholera/en/). Additionally, antimicrobial therapy, as an adjunct to fluid resuscitation, has been shown to decrease the duration and volume of diarrhea in cholera patients with severe dehydration[3,4]. Providing populations with widespread access to safe drinking water and effective sanitation are the most durable means of preventing cholera and other enteric diseases, and have additional public health benefits. However, large infrastructure improvements require long term financing, sustained maintenance, and require financial resources that have been demonstrated in practice to be beyond the reach of most of the populations at high risk in the near future, and are sometimes impossible (for example in acute emergencies and displaced populations). Short- to medium term interventions to prevent and control cholera are needed to bridge the gap while long term water, sanitation and hygiene infrastructure is created and maintained. Cholera vaccination is a key option for cholera prevention and control, and appropriate and targeted use of cholera vaccines is increasingly being recognized as a useful complement to improving water, sanitation, and hygiene measures within a comprehensive cholera control strategy[5]. In 2011, the 64th World Health Assembly passed a resolution to consider integrated cholera control strategies, including vaccination, in endemic and epidemic situations (https://www.stopcholera.org/sites/cholera/files/resolution_cholera_a64_r15-en.pdf).

Oral cholera vaccines (OCVs) have been available since the 1990s[5]. A two-dose vaccine consisting of killed whole cells of *V. cholerae* O1 (including classical and El Tor biotypes and Inaba and Ogawa serotypes) and the B subunit of the cholera toxin (WC-rBS), was produced by SBL Vaccin (now by Crucell) and sold as

Dukoral, was prequalified in 1991. Although several field studies with Dukoral were conducted and yielded encouraging results, its use has largely been limited to individual use for travelers from non-endemic to endemic countries. Following a series of technology transfers, a modified whole-cell killed bivalent (O1 and O139) vaccine without the B subunit, was manufactured in Vietnam (ORCVAX/mORCVAX – for local use in Vietnam) and later, India (marketed as Shanchol) and Republic of Korea (Euvichol). Both Shanchol and Euvichol have been prequalified by WHO since September 2011 and December 2015 respectively. Other vaccine candidates are also in different early and late stages of development and are included in the section on 'other oral cholera vaccines'.

In March 2010, WHO issued a position statement regarding OCV use[5]. WHO recommended targeted use of OCVs in endemic settings, in conjunction with other prevention and control strategies. In outbreak situations and during complex emergencies, WHO stated that preemptive vaccination 'should' be considered in areas determined to be at imminent risk for infection, after taking into account the local epidemiologic context and capacity to mount a vaccination campaign, and that reactive vaccination once an outbreak had started 'could' be considered based on the local epidemiological features and response capacity. Given limited reactive vaccine use at the time, WHO encouraged countries and regions to document such experiences.

Several new developments have occurred since the last WHO position paper in 2010, 1) large-scale, protracted outbreaks have continued to occur worldwide. Cholera appeared in Haiti in 2010, and has resulted in the largest protracted epidemic in recent times; endemic areas of sub-Saharan Africa, and Asia have experienced large scale increases in cases and deaths, 2) in addition to Dukoral, which was prequalified in 1991, two easier-to-use OCVs (Shanchol and Euvichol) were prequalified by WHO. Several million doses of Shanchol (and mORCVAX in Vietnam) have been used in public health settings resulting in more available data on safety, efficacy, duration of protection, field effectiveness, impact and cost-effectiveness, 3) the global OCV stockpile was established to ensure that supply would be available for prompt response in outbreak and emergency settings[6], and Gavi endorsed funding support for the stockpile by committing US$115 million over 5 years from 2014–2018 (http://www.gavi.org/support/nvs/cholera-vaccine/), 4) the Global Taskforce for Cholera Control (GTFCC) was revitalized in 2014, and an OCV working group established under the GTFCC has been instrumental in reviewing evidence for OCV use in different settings, including an expansion of stockpile OCV use in endemic settings.

In November 2015, a SAGE OCV working group was established to review evidence regarding safety, effectiveness, acceptability, cost-effectiveness and impact on cholera transmission of OCVs since the 2010 WHO recommendations.

This document is intended to provide a detailed update on new developments and data regarding cholera and the currently available, whole-cell, killed oral cholera vaccines after 2010 to inform discussions and recommendations by the WHO SAGE during its meeting in April 2017.

2.3. Previous Recommendations from the 2010 WHO Position Paper on Oral Cholera Vaccines

- Cholera control should be a priority in areas where the disease is endemic. Given the availability of 2 oral cholera vaccines and data on their efficacy, field effectiveness, feasibility and acceptance in cholera-affected populations, immunization with these vaccines should be used in conjunction with other prevention and control strategies in areas where the disease is endemic and should be considered in areas at risk for outbreaks.
- 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 to bring about an immediate response while the longer term interventions of improving water and sanitation, which involve large investments, are put into place.
- In cholera-endemic countries, vaccinating the entire population is not warranted. Rather, vaccination should be targeted at high-risk areas and population groups. The primary targets for cholera vaccination in many endemic areas are preschool-aged and school-aged children. Other groups that are especially vulnerable to severe disease and for which the vaccines are not contraindicated may also be targeted, such as pregnant women and HIV-infected individuals. Periodic mass vaccination campaigns are probably the most practical option for delivering cholera vaccines. Incorporating cholera vaccination into routine vaccination schedules may be an alternative or complementary strategy to mass vaccination campaigns.
- Since the documented duration of significant protection for the oral cholera vaccine is 2 years, it is recommended that initial vaccination with 2 doses be followed by a booster dose every second year. Once data on the longer-term efficacy of any oral cholera vaccine become available, the recommended interval between initial and booster vaccination may be extended.
- The mainstay of control measures to be implemented during ongoing epidemics should remain (i) providing appropriate treatment to people with cholera, (ii) implementing interventions to improve water and sanitation and (iii) mobilizing communities. Pre-emptive vaccination should be considered by local health authorities to help prevent potential outbreaks or the spread of current outbreaks to new areas. Finalizing of predictive risk-assessment tools to help countries determine when pre-emptive cholera vaccination might be used is needed urgently; these tools should be made available and field-tested as soon as possible.
- Given the recent large and prolonged outbreaks of cholera (for example, in Angola and Zimbabwe), reactive vaccination could be considered by local health authorities as an additional control measure, depending on the local infrastructure and following a thorough investigation of the current and historical epidemiological situation, and clear identification of geographical areas to be targeted. Considering the lack of experience with implementing reactive vaccination against cholera, the feasibility and impact of vaccination in halting ongoing outbreaks should be documented and widely disseminated. Pre-emptive or reactive vaccination should cover as many people as possible who are eligible to receive the vaccine (for example, children aged ≥1 years or ≥2 years, depending on the vaccine), and should be conducted as quickly as possible.
- It is strongly recommended that surveillance for microbiologically confirmed cases of cholera be instituted and integrated into already existing surveillance systems or networks to measure the burden of disease and monitor the seasonality and the impact of vaccination and other interventions in high-risk populations.

2.4. The Global Taskforce on Cholera Control (GTFCC)

The Global Task Force on Cholera Control (GTFCC) is a network of partner institutions which was revitalized in response to the 2011 World Health Assembly (WHA) resolution for "Cholera mechanisms for control and prevention". The goal of the GTFCC was to strengthen WHO's work on cholera prevention and control, including improved collaboration and coordination among relevant WHO departments and other relevant stakeholders. A revitalization process was initiated in December 2012 and completed in early 2014.

The objectives of the GTFCC are to, 1) support the design and implementation of global strategies to contribute to capacity development for cholera prevention and control globally, 2) provide a forum for technical exchange, coordination, and cooperation on cholera-related activities to strengthen countries' capacity to prevent and control cholera, especially those related to implementation of proven effective strategies and monitoring of progress, dissemination and implementation of technical guidelines, operational manuals, etc., 3) support the development of a research agenda with special emphasis on evaluating innovative approaches to cholera prevention and control in affected countries, 4) increase the visibility of cholera as an important global public health problem through integration and dissemination of information about cholera prevention and control, and conducting advocacy and resource mobilization activities to support cholera prevention and control at national, regional, and global levels.

The first meeting of the GTFCC was conducted in June 2014, following which 7 working groups were established over the next 1 – 2 years, and included working groups on, a) epidemiology and surveillance, b) laboratory and surveillance, c) oral cholera vaccines, d) case management, e) water, sanitation and hygiene (WaSH), f) communications, advocacy and social mobilization, g) training. Of the 7 working groups envisaged, 5 are fully functional. The goal of the working groups has been to review evidence and provide guidance to the GTFCC in key domains of cholera prevention and control. Below are some key areas of work accomplished by the five working groups within their respective domains.

a) Epidemiology and Surveillance Working Group
   - Development of standardized surveillance terms and updated case definitions, including coordination with the laboratory and surveillance working group on use of RDTs and molecular diagnostics for surveillance.
   - Ongoing work on updating existing guidance ("Yellow Book") on cholera outbreaks and response.

b) Laboratory and Surveillance Working Group
   - Development of a guidance note on potential use of available rapid diagnostic tests (RDTs), including when and where to use RDTs, interpretation of results and test characteristics with limits and performance. Ongoing work to define target product profile for ideal RDTs and facilitation of RDT prequalification process.
   - Development of a WHO briefing document with updated information on the use of DNA-based molecular techniques for field usage.
   - Ongoing work to harmonize antimicrobial susceptibility testing for resistance detection and verification to avoid conflicting results.

c) Oral cholera vaccines Working Group
- Development and review of a guidance note on OCV use in pregnancy, including a comprehensive review of existing literature.
- Development and review of a guidance note on OCV use among international travelers, including a comprehensive review of existing literature.
- Review and voting on OCV use requests in endemic hotspot situations (e.g., Haiti OCV use request)
- Ongoing work on prioritization of the OCV research agenda and integration with other cholera control measures.

d) Case Management/Patient Care Working Group
- Agreement on standardized approaches to organization of case management in outbreak situations, infection control practices at different levels of care and use of antibiotics for cholera treatment.
- Validation of current recommendations on use of oral rehydration solution (ORS), intravenous fluids and zinc.
- Validation of current recommendations on treatment of children with severe acute malnutrition and cholera.
- Ongoing work with a review of the current knowledge on treatment of pregnant women with cholera.

e) Water, Sanitation and Hygiene (WaSH) Working Group

Given the multitude of interventions and strategies that fall within WaSH, the WaSH working group is subdivided into multiple subgroups.
- WaSH strategies sub-group: Ongoing work to identify specific WaSH interventions in various contexts including emergency response, ongoing preparedness, long-term interventions and integration with OCV campaigns.
- Efficiency of WaSH interventions subgroup: Ongoing work to identify and develop an investment case methodology for WaSH interventions.
- WaSH practices subgroup: Ongoing work to formulate recommendations for key WaSH practices to be implemented at the local level for cholera control.
- Advocacy and funding subgroup: Ongoing work to identify evidence-based approaches, including essential personnel, materials and budget, to advocate for WaSH interventions in high cholera-risk areas.

2.5. Magnitude of the Problem of Cholera

Cholera is an acute watery diarrheal disease caused by the highly infectious facultative anaerobic Gram-negative, pathogenic, toxigenic bacterium *Vibrio cholerae* serogroups O1 and O139 belonging to the family *Vibrionaceae*. Humans are the only natural host for the pathogen. While there are more than 200 serogroups of *V. cholerae*, only two toxigenic ones, O1 and O139, are known to cause disease[7]. There is no known cross-protection between the O1 and O139 serogroups. The O139 serogroup first emerged as a cause of epidemics in 1992 in India and Bangladesh and accounted for ~2-9% of cases in Bangladesh for about a decade. China and Philippines recently reported cases of O139 [8], but overall cases seem confined to South and South-East Asia. The serogroup O1 has two biotypes – El Tor and classical. El Tor, the cause of the world's seventh cholera pandemic, which began in 1961 and is still ongoing, has replaced classical strains, which are thought to have been responsible for the six previous pandemics in modern history. El Tor infections have a greater rate of asymptomatic or mild cases than the classical O1 – 75% of El Tor infections can be asymptomatic (vs. 59% for classical) and only 2% become severe as compared to an estimated 11% of infections with the classical biotype[9]. A new variant strain of *V. cholerae* O1 was identified in 2001[10]. This new strain identified is of the El Tor biotype, but it produces the cholera toxin formerly produced only by classical strains. These new variant strains appear to be predominant strains globally [10,11], are more virulent and cause more severe illness than the original El Tor strains [12,13]. Both El Tor and classical biotypes of the O1 serogroup can further be classified into two serotypes – Ogawa and Inaba[1], and some degree of cross-protection occurs between the two serotypes, Ogawa and Inaba.

Transmission of pathogenic *V. cholerae* in humans occurs through ingestion of contaminated food and water. While only around 25% of persons infected develop symptoms (with an illness to infection ratio ranging from 1:3 to 1:100), 10-20% of those who do become symptomatic experience severe disease, after an incubation period of less than 24 hours to five days. The risk of severe illness is increased by the size of the dose ingested, the lack of immunity from prior exposure to the disease or through vaccination, reduced ability to produce gastric acid (which neutralizes the pathogen), and having blood group O.

Severe cholera (also referred to as cholera gravis) is characterized by profuse watery diarrhea ("rice water stools") and usually vomiting, leading to rapid dehydration. Fluid loss can occur at a rapid rate of one-half to one liter per hour and if not promptly treated, the severe dehydration and resulting complications such as renal failure, shock, hypokalemia, and pulmonary edema can lead to death within hours. Unlike most other diarrheal diseases, cholera can be severe and even fatal in both adults and children. The symptoms of severe cholera are primarily due to the production of cholera toxin. The binding (B) subunit of the cholera toxin attaches to the mucosal surface of the intestine and releases the active (A) subunit, which enters the host cell. This activation of the cholera toxin results in a massive loss of fluids and electrolytes, especially sodium, potassium, and bicarbonate through the stool and vomitus. The stools and often the vomitus of these patients contain high concentrations of cholera vibrios, which can then contaminate water and food sources when passed back into the environment, with the potential for causing cholera outbreaks. Some studies also suggest that human colonization of *V. cholerae* creates a hyperinfectious state of the bacteria that is maintained soon after shedding, and that may contribute to the epidemic spread of the disease [14].

[1] A third Hikojima strain has antigens of both types but is relatively unstable.

Cholera disease burden globally is characterized by both endemic disease and outbreaks/epidemics (described later in the section on surveillance). In addition, humanitarian emergency settings (both acute and chronic) are high-risk situations for cholera given large scale disruptions in water and sanitation infrastructure, population movements and security issues. The reported incidence of cholera has steadily increased since 2000, but the period from 2010 – 2014 saw a dramatic increase in incidence and case-fatality, mostly due to the large outbreak in Haiti and several outbreaks in sub-Saharan Africa [8,15-18]. A cumulative total of 317,534 cases and 7543 deaths (2.38% case fatality rate), and 589,854 cases and 7816 deaths (1.3% case fatality rate) were reported to WHO in 2010 and 2011 respectively, representing an increase in incidence of 43% and 85% over previous years, and a 52% increase in the case fatality rate in 2010 compared with 2009. Although the reported numbers of cases and deaths decreased during the following years, they remain significantly higher than those in the early 2000s. The occurrence of cholera is also intrinsically related to major fluctuations in weather patterns, especially large scale rains as seen with the El Nino weather patterns[19-22]. Figure 1 shows the global burden of cholera cases and deaths from 2010 – 2015 as reported to WHO. Table 1 shows the case counts in several large-scale outbreaks reported since 2010.

A recent estimate showed that there were about 2.9 million cases of cholera annually in 69 cholera endemic countries and 95 000 deaths during 2008–2012 [23]. The same study also showed that sub-Saharan Africa accounted for 60% and south-east Asia accounted for 29% of the cholera cases. **It is to be noted that this represents the tip of the iceberg. Most mild to moderate cases do not seek care and several deaths occur in communities before reaching a heath care facility which are often not reported. Additionally, many high-burden countries in southern Asia and sub-Saharan Africa do not report cases to WHO while some others report cases as 'acute watery diarrhea' and not cholera.** In particular, over 2 million acute watery diarrhea cases are registered in Bangladesh every year, of which an estimated 22% represent cholera cases [18].

Figure 1: Global Cholera Cases and Deaths Reported to the World Health Organization, 2010 – 2015

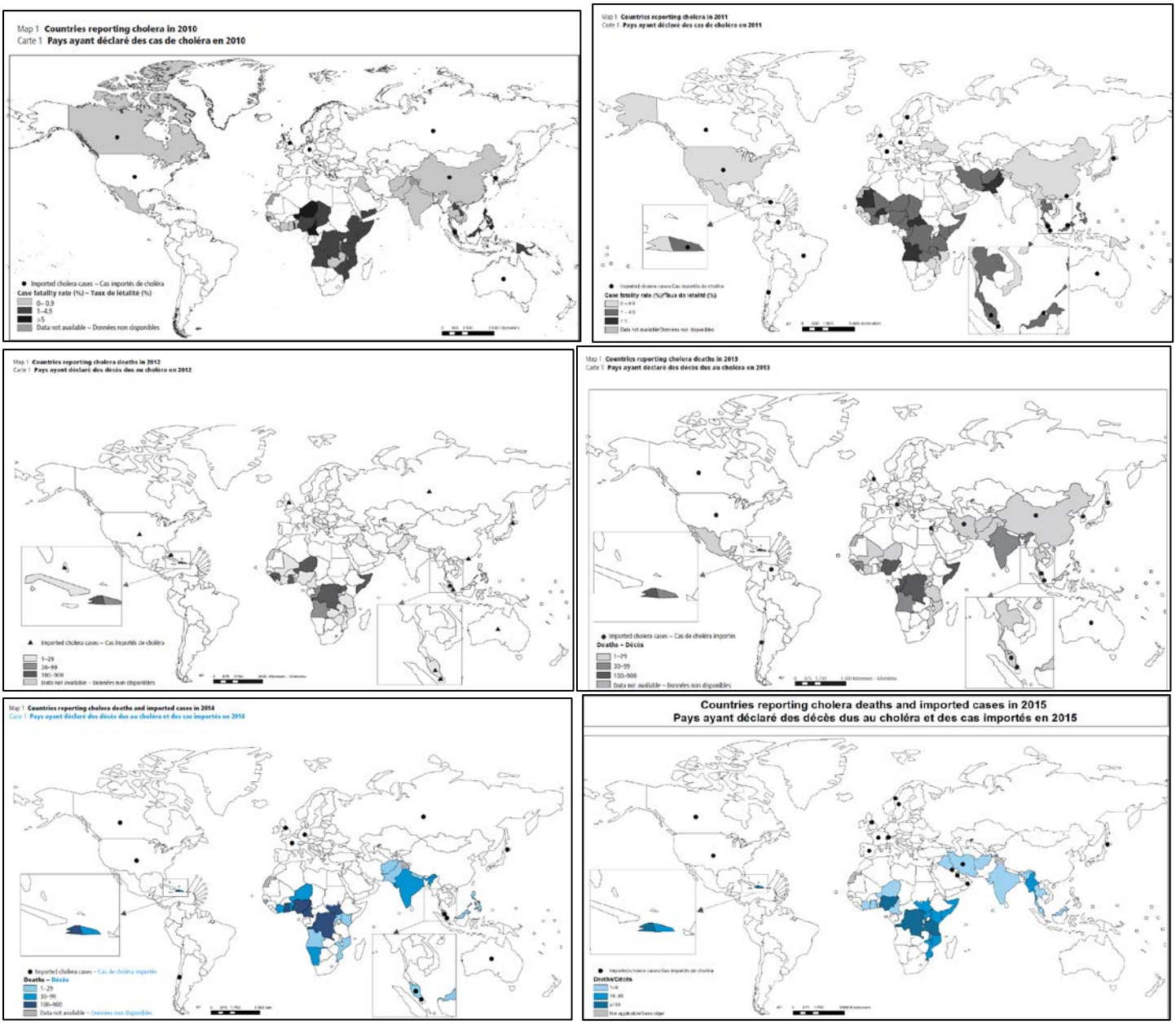


Table 1: Selected* Cholera Outbreaks Reported to the World Health Organization, 2010–2015

Year	Country (WHO Region)	Cumulative number of cases	Cumulative number of deaths	Case-fatality rate
2010–2015	Haiti (AMR)	754,972	8,863	1.2%
2015	Kenya (AFR)	13,291	67	0.5%
2015	Tanzania (AFR)	11,563	144	1.3%
2015	Iraq (EMR)	4,965	2	<0.1%
2014	Ghana (AFR)	28,944	243	0.8%
2014	Cameroon (AFR)	3,355	184	5.5%
2014	Democratic Republic of Congo (AFR)	22,203	372	1.7%
2014	Nigeria (AFR)	35,996	755	2.1%
2013	Angola (AFR)	6,655	86	1.3%
2013	Nigeria (AFR)	6,600	229	3.5%
2013	Somalia (AFR)	6,864	140	2.0%
2012	Democratic Republic of Congo (AFR)	33,661	819	2.5%
2012	Uganda (AFR)	6,326	135	2.0%
2012	Guinea (AFR)	7,350	133	1.8%
2012	Sierra Leone (AFR)	23,124	299	1.3%
2012	Ghana (AFR)	9,548	100	1.1%
2012	Angola (AFR)	1,215	98	8.1%
2012	Iraq (EMR)	4,693	4	0.1%
2012	Philippines (WPR)	1,864	14	0.8%
2011	Somalia (AFR)	77,636	1,130	1.5%
2011	Angola (AFR)	1,810	110	6.1%
2011	Chad (AFR)	17,267	458	2.7%
2011	Niger (AFR)	2,324	60	2.6%
2011	Nigeria (AFR)	23,377	742	3.2%
2011	Afghanistan (EMR)	3,733	44	1.2%
2011	Mali (AFR)	2,220	95	4.3%
2011	Cameroon (AFR)	22,433	783	3.5%
2010	Nigeria (AFR)	44,456	1,712	3.9%
2010	Chad (AFR)	6,395	175	2.7%
2010	Cameroon (AFR)	10,759	657	6.1%
2010	Niger (AFR)	1,154	66	5.7%
2010	Zambia (AFR)	6,794	62	1.0%
2010	Papua New Guinea (PNG) (WPR)	8,997	95	1.1%

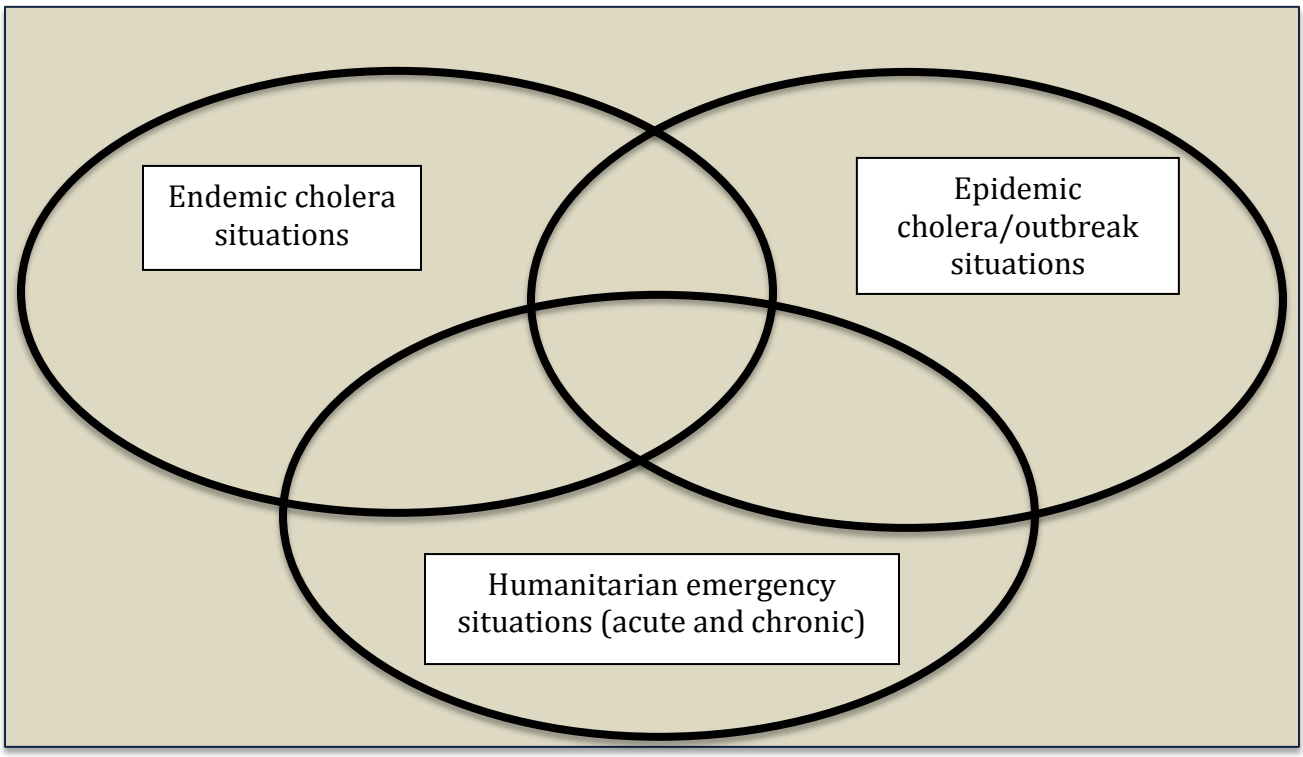
*Not a comprehensive list.

2.6. Cholera Surveillance – Epidemiology and Laboratory Components

Cholera surveillance is a critical component of a comprehensive cholera prevention and control strategy. Effective cholera surveillance entails use of standard case definitions, clear and simple data collections mechanisms, reporting and data analysis procedures, rapid diagnosis of suspected cases and laboratory confirmation, routine feedback of surveillance data, and appropriate coordination at all levels (community, health facility, district, national and international). However, in reality, most countries lack appropriate epidemiological systems and laboratory diagnostic capacity required for surveillance and rapid detection. Since 1962, WHO has been updating global cholera statistics based on cases reported to WHO by national health authorities, but is largely underreported as described earlier. Although notification of cholera cases is no longer mandatory under the current International Health Regulations (IHR) since 2005, WHO recommends assessment of cholera events against the IHR criteria to determine whether there is a need for official notification (http://www.who.int/mediacentre/factsheets/fs107/en/). For the most part, cholera is included within the National Integrated Disease Surveillance and Response (IDSR) or Early Warning and Response Network in humanitarian emergencies (EWARN) platforms. There are, however, numerous variations in case definitions, use of laboratory procedures and reporting mechanisms which impede standardized reporting and comparison of annual trends by region and globally. To address some of these issues, a multi-partner consortium supporting cholera surveillance and research – Africhol (The African Cholera Surveillance Network) was funded by the Bill and Melinda Gates Foundation in 9 African countries in 2009 by building upon and reinforcing existing surveillance systems and laboratory capacities.

Cholera disease burden is characterized by both endemic and epidemic disease, which in reality are two ends of a continuum. In addition, there are a number of situations that increase risk of both epidemic cholera as well as cause a resurgence of cases in already known endemic areas, for example, humanitarian emergency situations which may be acute or protracted crisis situations. Figure 2 illustrates the different cholera scenarios which overlap to a large extent. Biologically, a population is considered to have endemic cholera when there is existence of an environmental reservoir able to maintain infection in the area and does not depend on exogenous introduction [24]. For practical purposes, endemic cholera is defined as the occurrence of fecal culture-confirmed cholera diarrhea in a population in at least 3 of the past 5 years[5], and occurrence of cholera not meeting this definition would be regarded as 'epidemic'. These, however, do not take into account other factors such as water and sanitation conditions required for sustained transmission. Hence, there are vast differences in 'endemic cholera' occurrences in developed versus developing settings. Also, cholera surges in endemic situations usually trigger an epidemic response in terms of public health interventions. An additional term "cholera hotspots" has been used to identify highly endemic areas (frequent spikes in endemic cholera incidence) or areas where populations have a high risk of cholera transmission (e.g. areas with poor WaSH conditions). Exact technical definitions of endemic cholera, epidemic cholera, cholera alert, and cholera hotspots are under development through the 'Epidemiology and Surveillance Workgroup of the GTFCC' (Personal Communication, GTFCC Secretariat, WHO).

Figure 2: Cholera Scenarios



In addition to epidemiological surveillance, laboratory diagnostic capacity forms a critical component of cholera surveillance. Culture of fecal samples from patients remains the standard test for cholera confirmation, and a positive culture test from several patients is required for outbreak confirmation. Although relatively easy to perform, culture requires the availability of skilled personnel, laboratory facilities and sample transport mechanisms, which are not always available. More accurate techniques such as polymerase chain reaction (PCR) methods are becoming available, but require enhanced laboratory capacity. Alternatively, rapid diagnostic tests (RDTs) offer point-of-care diagnostic solutions, can be performed by semi-skilled personnel and can help with rapid detection and reporting in the absence of equipped laboratory facilities, especially in areas with poor health care access. A recent study found that use of a RDT with an enrichment step was equivalent to bacterial culture[25]. Several types of RDTs are available with varying degrees of sensitivity, specificity, commercial readiness and precision in field conditions, and not all are suitable for use. The laboratory working group of the GTFCC is working on streamlining implementation and effective use of RDTs in the field.

Cholera surveillance guidance documents are under development through the epidemiology and surveillance and laboratory working groups of the GTFCC. A working document on cholera surveillance to inform and evaluate OCV use is available as part of the OCV stockpile monitoring and evaluation toolkit (http://www.who.int/cholera/vaccines/surveillance_protocol.pdf?ua=1). Also, a glossary of terms and case definitions has been developed under the Delivering Oral Vaccines Effectively (DOVE) Project at Johns Hopkins University which describes commonly used cholera terms, including surveillance (https://www.stopcholera.org/sites/cholera/files/1.2_glossary_of_cholera_terms.pdf).

2.7. Cholera Treatment

Rapid rehydration constitutes the primary treatment for cholera, either through oral rehydration therapy (ORT) or the administration of intravenous (IV) fluids to replace the loss of fluids and electrolytes, in more severe cases [26]. Patients with no or moderate dehydration are usually treated with oral rehydration salts (ORS); WHO and UNICEF recommend a low osmolarity solution that reduces the incidence of vomiting over the original ORS formulation. The 10-20% of cholera patients who develop severe dehydration must be rehydrated rapidly with IV fluids, preferably Ringer's lactate solution, followed by ORT, once the patient is able to drink. Exact guidelines for management of diarrhea and dehydration and details of rehydration therapy are available through WHO (http://www.who.int/cholera/en/), UNICEF (https://www.unicef.org/cholera/index_71220.html) and other sources[3].

WHO also recommends treatment with antibiotics for severe cases of cholera (http://www.who.int/cholera/prevention_control/Antibiotics_for_cholera_5March2014.pdf), since antibiotic therapy reduces the volume of diarrhea, the duration of illness and time spent in the hospital, as well as the length of time the pathogen is excreted in the stool, thereby potentially reducing transmission of the infection to others[3,4]. WHO recommends doxycycline for treating cholera, with azithromycin as an alternative in areas known to have strains resistant to these first-line drugs (http://www.who.int/cholera/prevention_control/Antibiotics_for_cholera_5March2014.pdf). If patients have access to appropriate care for cholera, the case fatality rate should be minimal. Resistance to first-line antibiotics, as well as multiple-drug resistant (MDR) *V. cholerae*, is a frequent occurrence in cholera-endemic parts of the world and can complicate the treatment of cholera and increase treatment costs.

2.8. Cholera Prevention

Improving access to potable, clean water, adequate sanitation and promoting good hygiene practices (WaSH) remain the mainstays of preventing both endemic cholera and cholera outbreaks [27]. Behavior change interventions to promote hand washing with soap, safe food handling, establishment and enforcement of basic sanitation laws for food industries, including food vendors are important interventions for cholera prevention. In addition, proper case management is vital in reducing mortality from the disease and limiting its spread [27].

Cholera vaccination is a key complementary cholera prevention and control strategy, which can be implemented in the short- to medium-term, while access to other primary prevention measures such as safe water and sanitation improves globally. WHO and the Global Taskforce for Cholera Control (GTFCC) calls for an integrated, comprehensive cholera control strategy which includes the primary WaSH strategies, case management and vaccination [28].

Additional information regarding WaSH is available through WHO (http://www.who.int/cholera/publications/en/), UNICEF (https://www.unicef.org/cholera/index_71218.html), and Centers for Disease Prevention and Control (https://www.cdc.gov/cholera/six-messages.html, https://www.cdc.gov/cholera/training-education.html).

3. Currently Available, Whole-cell (WC), Killed, Oral Cholera Vaccines (OCVs)

3.1. Key Points

- A new generation of whole-cell killed OCVs are available and have been shown to be safe, efficacious and effective in multiple settings.
- Four killed OCVs are available and licensed in different countries – Dukoral, mORCVAX, Shanchol and Euvichol. Of these, three vaccines – Dukoral, Shanchol and Euvichol are prequalified by WHO for procurement by United Nations agencies, such as UNICEF. mORCVAX is currently being produced and locally used in Vietnam. Other vaccine candidates are undergoing manufacturing processes through technology transfers to developing country manufacturers (e.g., Cholvax - Bangladesh), or are under development. An additional single dose, live attenuated OCV has been recently licensed in the United States for adult travelers.
- Herd protection (indirect protection afforded to unvaccinated individuals living in vaccinated areas) has been demonstrated with the current OCVs. This has the potential for increased impact on prevention of cholera transmission and reducing cholera morbidity and mortality.
- Use of OCVs, with established cholera prevention and control measures such as strengthening surveillance, rehydration, antibiotics, provision of safe water and adequate sanitation, and improved hygiene practices, provides a more integrated and comprehensive package of interventions for cholera control globally.
- A global OCV stockpile was established in 2013 and later supported by Gavi, the Vaccine Alliance. The Gavi-supported global OCV stockpile has successfully deployed over 7 million doses to 14 countries in a variety of contexts – humanitarian emergencies, outbreaks, and endemic hotspots.
- Increased demand has stimulated increased global OCV availability through increased production by existing and additional manufacturers at low costs.
- Coordination of governmental and nongovernmental partners by the Global Taskforce for Cholera Control has led to stronger collaborative efforts to support cholera prevention and control in endemic countries and epidemic and humanitarian crisis situations by incorporating disease surveillance, WaSH, case management and vaccines.

3.2. Details of the Available WC, Killed OCVs

Three WHO-prequalified, killed, whole-cell OCVs are currently available for global use[2] - Dukoral (killed whole cell monovalent (O1) vaccine with cholera toxin B subunit), and Shanchol and Euvichol (modified killed bivalent (O1 and O139) whole cell only vaccines).

[2] Other manufacturers in Vietnam and Bangladesh are producing similar OCVs, but are currently planned for national use only.

Vaccine prequalification is an activity led by the World Health Organization intended to ensure that vaccines purchased by UN procurement agencies meet WHO recommendations for quality, safety, and efficacy (http://www.who.int/immunization_standards/vaccine_quality/pq_system/en/).

Killed whole cell monovalent (O1) vaccine with cholera toxin B subunit (WC-BS and WC-rBS)

Dukoral was developed in Sweden (SBL Vaccin, Sweden) and first licensed in 1991. It contains a mixture of the recombinant B subunit (BS) of cholera toxin plus formalin and heat killed whole cells (WC) strains of *V. cholerae* O1 (monovalent) representing serotypes Inaba and Ogawa and biotypes El Tor and Classical. The B subunit of cholera toxin was originally produced chemically (WC-BS), but is now produced by recombinant technology (WC-rBS), but both BS and rBS are identical in terms of immune response [5]. This is to be noted as some of the earlier vaccine studies used the WC-BS formulation of the vaccine. The vaccine does not contain any of the cholera toxin A subunit and is free of its toxic effects. Because the heat labile toxin (LT) *of E. coli* cross reacts with cholera toxin, this vaccine has been shown to provide short term cross protection against diarrhoea caused by enterotoxigenic *E. coli* [29]. The vaccine requires two doses for adults and three doses for children below five years of age. The vaccine requires co-administration of a bicarbonate buffer in safe water to prevent degradation of the toxin B subunit. In Bangladesh, a placebo controlled randomized controlled trial (RCT) in 90,000 individuals aged 2 years and above demonstrated 85% efficacy for 6 months following vaccination and 50% efficacy of 3 years for older children and adults[30]. In Beira, Mozambique, mass vaccination was feasible and effective in preventing cholera in a population with a 20–30% seroprevalence of HIV [31,32]. More than 14,000 people received a least one dose and a case control study demonstrated 78% protection against cholera and 89% protection against cholera with severe dehydration[32]. Of note, all strains isolated in this evaluation were El Tor variants that produced a modified form of the classical cholera toxin, representing a newer, dominant, and more severe variety of cholera. Though WHO prequalified, it has mainly been used as a travellers' vaccine due to limited production, higher price, and relative difficulty for public health use given the need for higher cold chain volume and clean water requirement for reconstitution of the buffer.

Modified killed whole cell only vaccines (WC)

On the basis of the encouraging findings of the use of WC-rBS vaccine, the technology for production of the oral killed whole cell vaccine was transferred from Sweden to Vietnam in the 1980s. The Vietnamese government commenced local development of an inexpensive oral O1 serogroup whole cell only vaccine in the 1980s. This vaccine was similar in composition to WC-rBS except it lacked the B subunit toxin. It was shown to be safe and conferred 66% protection against cholera during an epidemic which occurred 8-10 months following vaccination in an open field trial [33]. The vaccine was made into a bivalent formulation (O1 and O139) and was licensed as mORCVAX (Vabiotech, Hanoi, Vietnam) in 1997. Because the vaccine lacks toxin, it does not require co-administration with an oral buffer. Over 20 million doses were used in Vietnam's public health programs. Unfortunately, this vaccine was not suitable for WHO prequalification as the Vietnamese national regulatory authority (NRA) was not assessed as WHO functional, a condition for pre-qualification, and Good Manufacturing Practice (GMP) considerations. International scientists worked together to improve vaccine constituents and the manufacturing process, and transferred the modified vaccine to India, which had a functional NRA approved by the WHO.

The resulting vaccine, Shanchol (Shantha Biotechnics Ltd, India; now Sanofi Pasteur), was prequalified by WHO in 2011. It was shown to be well tolerated and highly immunogenic in multiple highly endemic and less endemic settings in Vietnam, India, and Ethiopia [34-37]. Shanchol has conferred 67% protection in a double blind randomized placebo controlled trial in more than 67,000 children and adults in Kolkata, India [38,39]. However, levels of protection were not uniform across all age groups. Young children aged one to five years, were significantly less protected with a cumulative efficacy of 42% over 5 years [39]. A large community based feasibility and effectiveness trial with over 267,000 participants in Bangladesh showed that in real life settings in a highly mobile urban community, a population based vaccination program achieving moderate coverage in hyperendemic settings could substantially reduce the burden of disease and greatly contribute to long term cholera control [40]. When comparing responses between one and two vaccine doses, investigators from Kolkata found no increase in seroconversion (4 fold rise in serum vibriocidal antibodies), following a second dose as compared to those after the first dose [41]. Interestingly, this may be directly related to the amount of natural exposure and pre-existing antibodies since higher seroconversion rates were noted following a second dose in comparatively less endemic areas in Haiti and Ethiopia [37]. This suggests that there may be important geographical differences in immunological response in areas of varying cholera exposure. A study in Kolkata compared the immunogenicity of two dosing regimens (14 vs. 28 days apart) and found no difference in the immunogenicity [42]. A phase 3 placebo RCT assessing a single dose of Shanchol in over 200,000 individuals from the hyperendemic setting of Bangladesh found an efficacy of 40% against all cholera cases and 60% protective against cholera cases with severe dehydration over a 6-month period [43]. A recent study in Haiti showed that HIV-infected individuals developed somewhat lower but still appreciable serum vibriocidal antibody responses compared with those in HIV-uninfected individuals, and that among HIV-infected persons, the magnitude of these responses varied inversely with CD4 lymphocyte counts [44].

Similar to Shanchol, Euvichol (Eubiologics, South Korea) is the second affordable OCV which resulted from development of the Vietnamese vaccine. Euvichol was prequalified by WHO in late 2015. It has the same formulation as Shanchol and clinical studies have demonstrated immunological non-inferiority when compared with Shanchol [45]. The entry of Euvichol into the market in 2016 is expected to significantly increase vaccine availability and potential use.

Similar non-inferiority evaluations are underway for another formulation of the whole cell, killed OCV - Cholvax (Incepta, Bangladesh). Once complete, the aim is to increase production capacity, enabling vaccination of large populations at risk in Bangladesh. Similar to the situation with mORCVAX in Vietnam, the Bangladesh NRA is not currently approved by WHO and Cholvax is expected to be available for local use in Bangladesh.

A summary of key characteristics and features of the currently available WC, killed OCVs are presented in Table 2.

Table 2. Key characteristics and features of the currently available killed OCVs (WC-rBS and Modified WC), as of March 2017

Generic Name	WC-rBS	Modified Bivalent WC
Trade Name	Dukoral	mORCVAX (Vietnam), Shanchol (India), Euvichol (Korea), Cholvax (Bangladesh)
Target	O1 (Classical, El Tor – Ogawa and Inaba) Cholera toxin B subunit	O1 (Classical, ElTor – Ogawa and Inaba), O139 No cholera toxin
Regimen	2 doses given 2-6 weeks apart 3 doses for children 2 - 5 years	2 doses given 14 days (or 28 days) apart
Duration of protection	2 years (6 months for children 2-5 years of age)	5 years (Data >5 years is not available)
Age range for vaccination	≥2 years	mORCVAX: ≥2 years others: ≥1 year
Requirement for oral buffer	Yes (bicarbonate buffer in 75 – 150 ml water)	No
Storage temperature	2-8°C	2-8°C[ç]
Shelf life	3 years (36 months) at 2-8°C	30 months at 2-8°C
WHO Prequalification status	WHO prequalified	WHO prequalified - Shanchol and Euvichol
Price to the public sector (per dose)	$5.25	mORCVAX: $0.75 Shanchol/Euvichol: $1.85
Comments	Licensed in more than 50 countries worldwide	Euvichol plans to use squeezable plastic tubes for easier administration
Projected supply[µ]	Figure 6	Figure 6

* Preclinical testing complete and Phase I/II studies being initiated in Bangladesh
Ç Shanchol: growing evidence for stability at elevated temperature (42ºC) and the safety/ immunogenicity profiles are not altered.
£ Enterocoating of rBS is expected to allow for storage at 30-37ºC, but needs to be evaluated
µ Current projections of OCV supply are based on planned replenishment into the stockpile, which is divided into an emergency stock (outbreaks and humanitarian emergencies) and non-emergency reserve (endemic hotspots).

A systematic review of post-licensure deployment of OCVs was published in 2014 and lists experiences with OCV use in multiple endemic, epidemic and humanitarian emergency settings until 2013 [46]. Figure 2 shows the different post licensure OCV campaigns during 1997–2014.

Since the establishment of the OCV stockpile in 2013 until March 2017, a total of 41 OCV campaigns have been conducted in 14 countries through OCV stockpile deployments.

Figure 3: Post-licensure Oral Cholera Vaccine Campaigns, 1997–2014

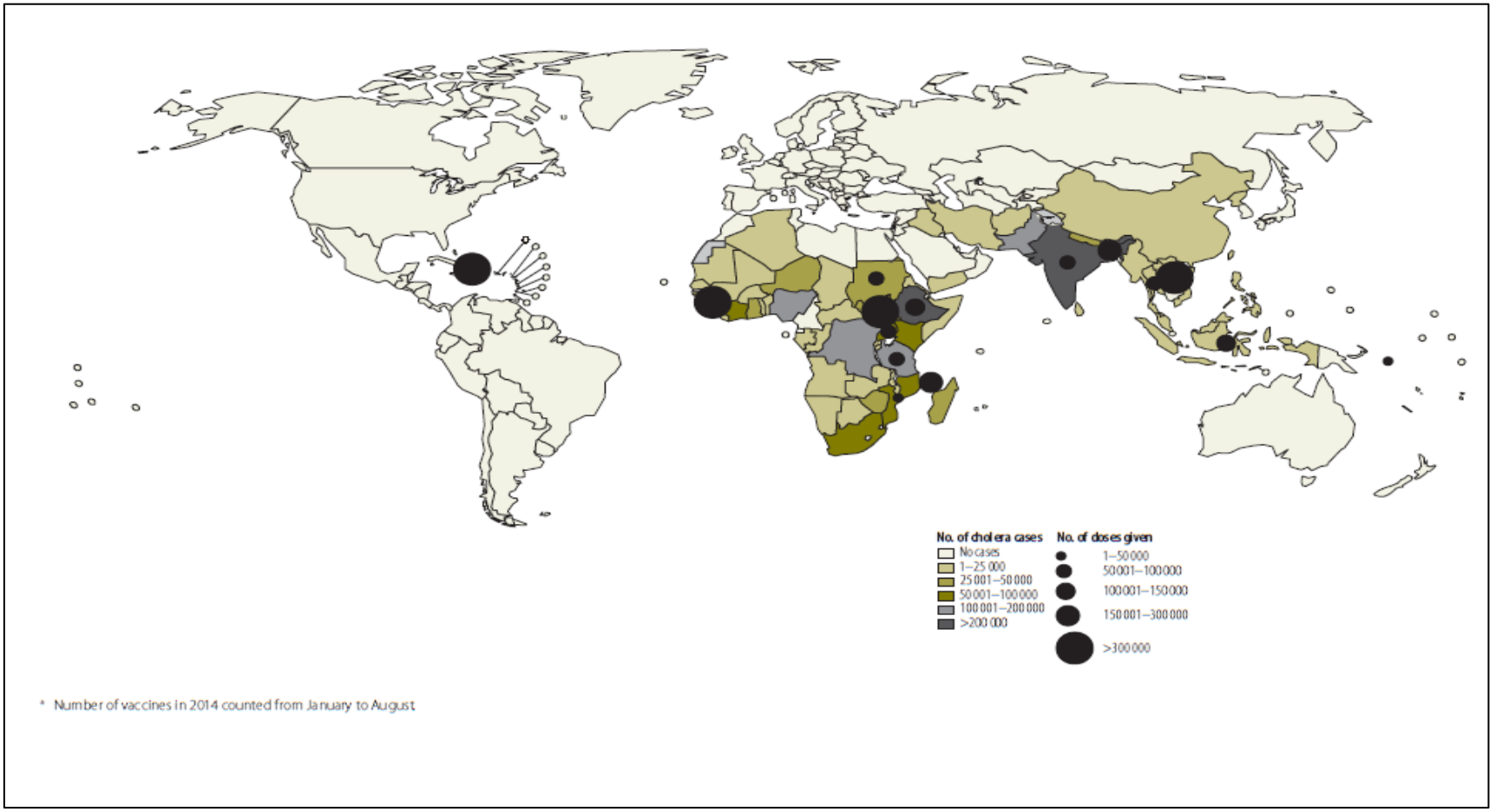


Table 3 lists experiences with OCV use in large-scale phase 3 clinical trials and post-licensure use to date (as of March 2017) including costs and coverage, where available (Preliminary List).

Vaccine & Campaign year	Site	Setting	Target population	No. or doses delivered or Coverage	Costs
Dukoral, 1997	Uganda (Adjumani district)[47,48]	Stable refugee camp, rural Preemptive campaign	44,000	1st dose - 35,613 (81%) 2nd dose – 27,607 (62%)	Vaccine – free (by manufacturer) Local delivery - $0.53 per person
Dukoral, 2000	Comoros (Mayotte Island)[46]	Urban and rural, Preemptive campaign	145,000	2 doses – 93,000 (64%)	Not available
Dukoral, 2003 – 2004	Mozambique (Beira)[31,32,49,50]	Urban	19,550	1st dose – 14,164 (72%) 2nd dose – 11,070 (57%)	Vaccine – free (by manufacturer) Local delivery - $2.01 per person
Dukoral, 2004	Sudan (South Darfur)[51]	Refugee camp (acute crisis), rural Preemptive campaign	45,825	1st dose – 45,502 (93%) 2nd dose – 40,330 (88%)	$7.1 per person Local delivery - $0.7 per person
Dukoral, 2005	Indonesia (Aceh)[51]	Internally displaced persons sites, post-tsunami	78,870	1st dose – 65,505 (79%) 2nd dose - 54,627 (69%)	$17.55 Local delivery – $3.10 per person
Dukoral, 2009	Tanzania (Zanzibar)[52-58]	Urban and rural Preemptive vaccination in an endemic area with seasonal outbreaks	48,178	1st dose – 27,678 (57%) 2nd dose – 23,921 (50%)	$31.46 Local delivery – 3.66 per person
ORCVAX/mORCVAX, 1998 - 2012	Vietnam[59]	Preemptive and reactive vaccination of children (2 – 5 years old) integrated into Vietnam's public health program	~10.9 million	Not available	Not available

Vaccine & Campaign year	Site	Setting	Target population	No. or doses delivered or Coverage	Costs
ORCVAX/mORCVAX, 1998, 2000, 2013	Vietnam (Hue)[50,59-61]	Preemptive vaccination in a cholera endemic area	149,557 (1998) 137,082 (2000)	1998: 1st dose – 125,135 (84%), 2nd dose – 118,703 (79%) 2000: 1st dose - 104,706 (76%), 2nd dose – 103,226 (75%)	1998: $0.89 per person 2013: $1.07 per person
ORCVAX/mORCVAX, 2008	Vietnam (Hanoi)	Reactive vaccination during an outbreak	~370,000	~80% (details not available)	Not available (likely similar to the costs of the other use in Vietnam due to similar procurement and delivery mechanisms
Shanchol, 2006	India (Kolkata)[62]	Urban slum Randomized controlled efficacy trial	52,212 (Vaccine group)	2 doses: 33,127 (63%)	Not available/applicable. Clinical trial setting.
Shanchol, 2011	India (Odisha)[63-66]	Rural Preemptive campaign	51,488	1st dose – 31,552 (61%) 2nd dose – 23,751 (46%)	$6.30 Local delivery costs – $1.13
Shanchol, 2011	Bangladesh (Dhaka)[40,67,68]	Urban slum Cluster randomized trial with 3 arms (vaccine, vaccine+ WaSH, no intervention)	172,754	1st dose – 141,839 (82%) 2nd dose – 123,666 (72%)	$3.93 (vaccine cost was subsidized by manufacturer) Local delivery - $1.63
Shanchol, 2012	Haiti (Port-au-Prince)[69,70]	Urban slum Reactive vaccination in a protracted outbreak situation	70,000	1st dose – 52,357 (75%) 2nd dose – 47,540 (68%)	Not available
Shanchol, 2012	Haiti (Bocozel and Grand Saline)[44,71-74]	Rural Reactive vaccination in a protracted outbreak situation	~50,000	1st dose – 45,417 2nd dose – 41,238 (77 – 79% in Bocozel and 63% in Grand Saline)	Not available

Vaccine & Campaign year	Site	Setting	Target population	No. or doses delivered or Coverage	Costs
Shanchol, 2012	Solomon Islands (Choiseul and Shortland provinces)[46,75]	Rural Preemptive campaign in an area (cholera naïve setting) near a cholera outbreak in Papua New Guinea	~15,000 Children 1 – 15 years old.	1st dose – 11888, 2nd dose - 11318	Not available
Shanchol, 2012	Guinea (Boffa and Forecariah)[76-79]	Rural Reactive vaccination during an ongoing outbreak.	~209,000	1st dose - 172,544 2nd dose – 143,706. Administrative coverage = 68% in Boffa and 51% in Forecariah. Coverage survey – 76%	$6.37 Local delivery costs - $1.97
Shanchol, 2013	Thailand (Tak Province – Thailand Myanmar border)[80]	Rural Stable refugee camp	43,968	1st dose – 36,325 (83%) 2nd dose – 26,753 (61%)	~$8.39 Local delivery costs - $2.45 (personal communication, CDC preliminary results)
Shanchol, 2013	South Sudan (Maban County)[46]	Rural Refugee camps – preemptive vaccination.	146,317	2 doses – 132,000 Coverage survey – 85%	$15.06 Local delivery costs – $3.99
Shanchol, 2013	Haiti (Petite Anse and Cerca Carvajal)[81]	Urban and Rural Preemptive vaccination campaign – first OCV campaign by the Haitian Ministry of Health Some vaccine also used in prisons (documentation in process)	~107,906	Administrative coverage: 92% in Petite Anse and 104% in Cerca Carvajal. Coverage survey: 77% (rural – Cerca Carvajal), 63% (urban – Petite Anse)	$2.9 per dose administered. Local delivery costs - $0.70 per dose administered (note this data is per dose administered and not per person as indicated in earlier reports). (CDC personal communication – Manuscript in Press – Routh et al.)

Vaccine & Campaign year	Site	Setting	Target population	No. or doses delivered or Coverage	Costs
Shanchol, 2014	South Sudan[82-84]	Internally displaced persons' camps. Humanitarian crisis First use of global OCV stockpile	162,577	Coverage estimates (administrative and LQAS) 1) Tonping camp (Juba): 1st dose 94%, 2nd dose 93% 2) UN house camp (Juba): 1st dose 96%, 2nd dose 95% 3) Mingkaman camp (Awerial): 1st dose 82%, 2nd dose 64% 4) Bor camp (Bor): 1st dose 92%, 2nd dose 86% 5) Bentiu camp: not available 6) Malakal camp: 1st dose 97%, 2nd dose 92%	Local delivery costs obtained from the 2 NGOs that delivered vaccine $0.63 and $0.73 per vaccine dose (note: the cost is per vaccine dose and not per person).
Shanchol, 2014	Haiti	Urban and rural – seven communes in three departments (Artibonite, Centre, Ouest)	185,314	2-dose OCV coverage (coverage survey) Artibonite – 70% (LBCL 60%) Centre – 63% (LBCL 55%) Ouest – 44% (LBCL 35%) (Burnett et al – Manuscript in preparation)	Not available
Shanchol, 2015	Malawi (Nsanje district) [85]	Rural Reactive campaign in an area affected by flooding and a cholera outbreak	160,482	Administrative coverage 1st round: 97.6% 2nd round: 85.8% 2 dose coverage – 67.6%	Not available
Shanchol, 2015	Malawi (Chikwawa)	Rural Humanitarian crisis	12,415	Not available	Not available

Vaccine & Campaign year	Site	Setting	Target population	No. or doses delivered or Coverage	Costs
Shanchol, 2015	Iraq (Nationwide in IDP camps)[86]	Reactive campaign following an outbreak. Preemptive campaign in some areas at high risk. IDP and refugee camps, collective centers. Protracted humanitarian crisis	255,000	Coverage survey 2-dose coverage: 87%. Coverage was lower in the South and Central Governorates	Not available
Shanchol, 2015	Zambia (Lusaka)	Reactive campaign using a single dose. Urban - Lusaka	578,000	2-dose coverage = 68.6% (coverage survey)	Not available
Shanchol, 2015	Tanzania (Kigoma)	Rural Humanitarian crisis – camps	246,874	Not available	Not available
Shanchol, 2015	Nepal (Nuwakhot and Dhanding)	Outbreak - urban Post-crisis (post-earthquake)	10,486	2-dose coverage = 98.1% (coverage survey)	Not available
Shanchol, 2015	Cameroon (Mokola, Hina)	Rural Humanitarian crisis	56,044	102% (administrative)	Not available
Shanchol, 2016	Niger (Diffa region)	Rural Humanitarian crisis	98,024	At least one dose = 86.5% (administrative coverage)	Not available
Shanchol, 2016	Haiti (Arcahaie)	Urban – endemic	118,097	96.7% (administrative)	Not available
Shanchol, 2016	Malawi (Lake Chilwa area)	Rural – outbreak	100,000	Coverage survey 1-dose coverage – 83% 2-dose coverage – 69%	Not available
Shanchol, 2016	South Sudan (Wau Shuluk and Melut IDP)	Rural Humanitarian crisis	36,000	Not available	Not available

Vaccine & Campaign year	Site	Setting	Target population	No. or doses delivered or Coverage	Costs
Shanchol, 2016	Democratic Republic of Congo (Kinshasa)	Urban – high risk areas	375,640	Administrative coverage – 1st dose round = 94% Data on 2 dose coverage not available.	Not available
Euvichol, 2016	Haiti (Sud and Grand Anse)	Humanitarian crisis Hurricane affected areas. Single dose campaign.	820,000	Administrative coverage Sud = 90% Grand Anse = 96%	Not available
Euvichol, 2017	South Sudan	Outbreak setting	68,967	Administrative coverage for Round 1 – 44%	Not available

3.3. Scientific Evidence Review

In the following sections, the different key characteristics of the available, killed, whole cell OCVs and related evidence are described. This information has been used to develop the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework for evidence review and recommendations for use of the killed, whole cell OCVs. The GRADE Review is described in subsequent sections.

A) Vaccine Safety

Table 4 below lists the key randomized control trials (RCTs) for OCV that have evaluated 'safety' as one of the outcome measures.

In addition, there are a number of evaluations of the programmatic use of OCVs that have evaluated safety, and the findings have been consistent with the findings of the RCTs listed below.

Table 4: Summary of the key publications related to safety of the currently available, killed OCVs

Reference	Year	Location	Study population	Vaccination or Intervention	Methods	Limitations or Potential Sources of Bias	Relevant Outcomes	Comments
Concha et al. Bull Pan Am Health Organ, 1995	1992	Colombia	1,165 healthy individuals between 12 months and 64 years of age.	2 doses of WC-rBS; heat killed *E. coli* K12 placebo	Randomized, double blind, placebo controlled trial (RCT)	No significant bias	Few symptoms detected during the 3 days following administration of the initial dose and even fewer followed the second dose two weeks later.	
Trach DD et al, Bull WHO, 2002	2002	Vietnam	Trial 1: 144 healthy adults randomized to receive bivalent WC vaccine with or without buffer, WC-rBS vaccine with buffer, or placebo without buffer. Trial 2: 103 healthy children 1 – 12 years randomized to bivalent WC vaccine without buffer, WC-rBS vaccine with buffer or placebo without buffer.	2 doses of bivalent WC vaccine, WC-rBS vaccine, placebo	Randomized controlled trial (RCT)	No significant bias	No significant difference in AEs between any vaccine groups compared with placebo among children and adults. Almost all reported AEs were mild (fever, diarrhoea, abdominal pain, loss of appetite, nausea)	

Reference	Year	Location	Study population	Vaccination or Intervention	Methods	Limitations or Potential Sources of Bias	Relevant Outcomes	Comments
Anh DD et al, Vaccine 2007	2005	Vietnam	144 Healthy male and non-pregnant females aged 18 – 40 years old (74 vaccine, 70 placebo)	2 doses of reformulated bivalent WC vaccine; heat-killed *E. coli* K12 placebo	Randomized, double blind, placebo controlled trial	No significant bias	No significant different in AEs between the vaccine and the placebo groups. No serious AEs were detected. Reported AEs included diarrhoea, abdominal pain, nausea, vomiting, fever, headache and general ill feeling	Subjects with history of diarrhoea, anti-diarrheal treatment or antibiotics during the past week, and history of diarrhoea and abdominal pain lasting 2 weeks during the prior 6 months were excluded.
Mahanabalis et al. PlosOne, 2008.	2006	India	101 healthy individuals (including non-pregnant females) 18 – 40 years old, and 100 children 1 – 17 years old. Non-pregnant female participants.	2 doses of reformulated modified WC-BS vaccine before tech transfer.	Randomized placebo controlled safety and immunogenicity trial (RCT)	No significant bias	No significant difference in AEs between the vaccine and placebo groups.	First study of the reformulated Vietnamese vaccine prior to the technology transfer outside of Vietnam.
Sur et al. Lancet, 2009	2006	India	Individuals ≥1 year old, non-pregnant. 31,932 individuals (1721 clusters) received 2 doses of vaccine and 34968 individuals (1757 clusters) received 2 doses of placebo.	2 doses of Shanchol; heat killed *E. coli* K12 placebo	Cluster-randomised double blind, placebo controlled trial (RCT)	No significant bias	No statistically significant difference in AEs between intervention and control groups. 105 participant reported AEs – 51 were deemed to be serious, 36 (vaccine 18, placebo 18) were admitted to the hospital (most common cause – acute gastroenteritis – 24/36). 15 deaths (vaccine 6, placebo 9).	
Saha et at, Vaccine 2011	2010	Bangladesh	Health adults (18–45 years), toddlers (2–5 years) and younger children (12–23 months) 110 participants in each age group (55 vaccine and 55 placebo)	2 doses of Shanchol	Double blind randomized placebo controlled trial (RCT)	No significant bias	No significant difference in AEs in any age group between vaccine and placebo recipients. No serious AE observed.	
Qadri et al. Lancet 2015	2011	Bangladesh	90 clusters in urban Dhaka slums; ~270,000 persons (95115 – vaccination only; 93091 vaccination + behaviour change + 80690 – no intervention)	2 doses of Shanchol; 2 doses of Shanchol + behaviour change; no intervention	Cluster randomized controlled trial (RCT)	No significant bias	A total of 95 adverse events (AEs) were recorded. (44 vaccination grp, 51 in vaccination and behaviour change group) – all mild AEs No serious adverse event recorded.	
Desai et al, IJIE, 2014	2012 - 2013	Ethiopia	Healthy adults (aged 18 years and above) and children (aged 1–17 years). 216 participants (54 adults+ 54 children in each group)	2 doses of Shanchol 14 days apart; non-biological placebo	Individually randomized, double-blind, placebo-controlled trial (RCT)	No significant bias	No difference in adverse events between vaccine and placebo groups. No adverse event (AE) in the vaccine group. 1 AE in the placebo group – mild. No serious adverse event.	Not a highly endemic setting. Similar baseline characteristics between groups.

Reference	Year	Location	Study population	Vaccination or Intervention	Methods	Limitations or Potential Sources of Bias	Relevant Outcomes	Comments
Baik, et al. Vaccine, 2015	2014	Philippines	Healthy adults (aged 18–40 years) and children (aged 1–17 years) randomized into two groups (Euvichol: 388 Adults, 240 children. Shanchol: 389 Adults, 244 children).	2 doses of Euvichol; 2 doses of Shanchol	Individually randomized controlled, multi-center, non-inferiority trial (RCT)	No significant bias	AEs – 4.4% Euvichol, 6.9% Shanchol. No difference between the two vaccines and between age groups. All mild (headache, fever – most common) No serious adverse events.	Non-inferiority trial comparing Euvichol and Shanchol.
Qadri et al. NEJM, 2016	2014	Bangladesh	Persons ≥1 year old, not severely ill, non-pregnant (Vaccine: 102,552 Placebo: 102,148)	Single dose of Shanchol	Individually randomized, placebo controlled trial (RCT).	No significant bias	No difference in adverse events between the vaccine and placebo group. No difference in serious adverse events.	Follow-up ongoing

B) Vaccine Efficacy (and Immunogenicity studies)

Table 5 below lists the key OCV studies that have evaluated 'vaccine efficacy' as one of the outcome measures. The table also includes immunogenicity studies which corroborate the efficacy findings.

Table 5: Summary of the key publications related to efficacy of the currently available, killed OCVs

Reference	Year	Location	Study population	Vaccination or Intervention	Methods	Limitations or Potential Sources of Bias	Relevant Outcomes	Comments
Clemens et al, Lancet 1990	1985 - 1989	Bangladesh (Matlab)	Children 2 – 15 years old and women 16 years and older (3 doses at 6 weeks interval); 62,285 completed 3 doses (total – 89,596)	WC-BS and WC only vaccines	Randomized double blind, placebo controlled trial	No significant bias	Protective efficacy: 4 – 6 months: all ages – 85% (LBCL 56%); 2 – 5 y/o – 100% (LBCL 80%) 1 year: all ages – 62% (LBCL 50%); 2 – 5 y/o – 38% (LBCL 7%) 2 years: all ages – 58% (LBCL 44%); 2 – 5 y/o – 47% (LBCL 13%) 3 years: all ages – 18% (LBCL -14%); 2 – 5 y/o – nil	Rapidly waning immunity after 2 years. Two doses were found to be as effective as 3 doses except in the 2 – 5 year olds.
Sanchez et al. Lancet, 1994	1994	Peru	Military recruits 16 – 45 years old (1,426 participants)	2 doses of WC-rBS given 7 – 27 days apart	Randomized, double blind placebo controlled trial	No significant bias	Protective efficacy – 86% (LBCL 37%).	
Taylor et al, JID 2000	1994 - 1995	Peru (outskirts of Lima)	2 – 65 years old persons 17,799 received 2 doses (14,997 received a booster dose)	2 doses of WC-rBS given 2 weeks apart, booster dose given 10 months after 2nd dose	Randomized, double blind placebo controlled trial	First year results excluded due to methodological problems	After 2 years the protective efficacy against clinical cholera was 61% (LBCL = 28%). Vaccine efficacy was higher for persons >15 years old: 72% (95% CI 28-89). VE against illness requiring hospitalization was 82% (95% CI 27-96).	
Trach et al. Lancet 1997	1992 - 1993	Vietnam (Hue)	134,453 persons – vaccine and no vaccine groups (no placebo and not randomized); 51,975 completed the 2-dose regimen.	2 doses of ORCVAX (bivalent WC)	Large scale, open field trial	No randomization. No placebo – trial not masked. Study period short compared with cholera trends in Hue. Inclusion vaccine refusers in the control group. Potential differential migration of participants outside the study area.	Protective efficacy over 10 months All ages – 66% (LBCL 46%) Children 1 – 5 years old 68% (LBCL 14%)	

Reference	Year	Location	Study population	Vaccination or Intervention	Methods	Limitations or Potential Sources of Bias	Relevant Outcomes	Comments
Sur et al. Lancet, 2009	2006	India	Individuals ≥1 year old, non-pregnant. 31,932 individuals (1721 clusters) received 2 doses of vaccine and 34968 individuals (1757 clusters) received 2 doses of placebo.	2 doses of Shanchol	Cluster-randomised double blind, placebo controlled trial; heat killed *E. coli* K12 placebo	No significant bias. Study not powered to distinguish levels of protection by year between year 1 and 2.	<u>2-year efficacy data</u> Adjusted protective efficacy = 67% (LBCL=35%) – all ages. <u>By age group</u> 1. 1 – 4 y/o: 49% (LBCL=6%) 2. 5 – 14 y/o: 87% (LBCL=54%) 3. ≥15 y/o: 63% (LBCL=23%) <u>By year</u> Year 1: 45% (LBCL -5%) Year 2: 72% (LBCL 49%)	
Bhattacharya et al, Lancet, 2013	2006	India	Individuals ≥1 year old, non-pregnant. 31,932 individuals (1721 clusters) received 2 doses of vaccine and 34968 individuals (1757 clusters) received 2 doses of placebo.	2 doses of Shanchol	Cluster-randomised double blind, placebo controlled trial; heat killed *E. coli* K12 placebo	No significant bias. Substantial increase in protective efficacy during year 5 (likely due to a large cholera outbreak during year 5, which may have boosted natural immunity in the population). High endemic areas – potential natural immunity boosting.	<u>5-year Efficacy data (per protocol analysis)</u> Adjusted cumulative protective efficacy = 65% (LBCL 52%) <u>By age group</u> 1. 1 – 4 y/o: 42% (LBCL=5%) 2. 5 – 14 y/o: 68% (LBCL=42%) 3. ≥15 y/o: 74% (LBCL=58%) <u>By year of follow-up</u> Year 1: 48% (LBCL -11%) Year 2: 78% (LBCL 52%) Year 3: 67% (LBCL 41%) Year 4: 57% (LBCL 26%) Year 5: 80% (LBCL 40%)	Point estimates by year of follow-up suggested no evidence of decline in protective efficacy. Results did not vary significantly between per protocol analysis and intent to treat analysis.
Saha et al. Vaccine, 2011	2010	Bangladesh	Health adults (18–45 years), toddlers (2–5 years) and younger children (12–23 months) 110 participants in each age group (55 vaccine and 55 placebo)	2 doses of Shanchol	Double blind randomized placebo controlled trial (RCT)	No significant bias	Vibriocidal antibody responses in adults were 60% against Vibrio cholerae O1 Inaba, 72% against V. cholerae O1 Ogawa and 21% against V. cholerae O139. In toddlers, responses were 84%, 75% and 64% and in younger children it was 74%, 78% and 54% against Inaba, Ogawa and O139 serotypes. The responses in all ages were higher in vaccines compared to pre-immune titers or to responses in placebo recipients ($P < 0.001$).	

Reference	Year	Location	Study population	Vaccination or Intervention	Methods	Limitations or Potential Sources of Bias	Relevant Outcomes	Comments
Desai SN et al. AJTMH, 2015	2012 – 2013	Ethiopia	Healthy adults (aged 18 years and above) and children (aged 1–17 years). 216 participants (54 adults+ 54 children in each group)	2 doses of Shanchol 14 days apart; non-biological placebo	Individually randomized, double-blind, placebo-controlled trial (RCT) – immunogenicity bridging trial	No significant limitations or biases. Direct comparison with other trials not possible due to protocol differences and lack of standardization of vibriocidal titres.	Seroconversion against O1 Inaba after 2 doses: 53% (1 – 5 y/o), 89% (6 – 17 y/o), 81% (adults) Seroconversion against O1 Ogawa after 2 doses: 75% (1 – 5 y/o), 90% (6 – 17 y/o), 70% (adults) In general, seroconversion was lower after the 1st dose.	Less endemic setting. Similar baseline characteristics between groups. Vaccine less immunogenic after the 1st dose.
Qadri et al. NEJM, 2016	2014	Bangladesh	Persons ≥1 year old, not severely ill, non-pregnant (Vaccine: 102,552 Placebo: 102,148)	Single dose of Shanchol	Individually randomized, placebo controlled trial (RCT) Passive surveillance for cholera.	6 month duration of protection assessed. Individual randomization – indirect effect not captured.	Protective efficacy=40% (LBCL*=11%) for any cholera, all ages), 63% (LBCL=24%) for severely dehydrating cholera, all ages. <u>By age group</u> 1) 1 – 4 y/o: any cholera 16% (LBCL* = -50%), severe 28% (LBCL = -221%) 2) 5 – 14 y/o: 63% any cholera (LBCL=-39%), severe 84% (-36%) 3) ≥15 y/o: 56% any cholera (LBCL=16%), 64% severe (LBCL=10%)	No protection in younger age groups. Follow-up ongoing.
Baik et al. Vaccine, 2015	2014	Philippines	Healthy adults (aged 18–40 years) and children (aged 1–17 years) randomized into two groups (Euvichol: 388 Adults, 240 children. Shanchol: 389 Adults, 244 children).	2 doses of Euvichol; 2 doses of Shanchol	Individually randomized controlled, multi-center, non-inferiority trial (RCT)	No significant limitations or biases	Euvichol seroconversion against O1 Inaba after 2 doses: 87.4% (1 – 17 y/o), 81.7% (Adults) Euvichol seroconversion against O1 Ogawa after 2 doses: 90.5% (1 – 17 y/o), 80.1% (Adults) Shanchol seroconversion against O1 Inaba after 2 doses: 88.9% (1 – 17 y/o), 76.3% (Adults) Shanchol seroconversion against O1 Ogawa after 2 doses: 88.1% (1 – 17 y/o), 73.9% (Adults)	Non-inferiority trial comparing Euvichol and Shanchol. Data in the youngest age groups not separately described.

*LBCL – Lower bound of the 95% confidence limit

C) Vaccine Field Effectiveness

Table 6 below lists the key studies that have evaluated 'vaccine field effectiveness' as one of the outcome measures. The findings of these studies align with the efficacy findings.

Table 6: Summary of the key publications related to field effectiveness of the currently available, killed OCVs

Reference	Year	Location	Study population	Vaccination or Intervention	Methods	Limitations or Potential Sources of Bias	Relevant Outcomes	Comments
Lucas et al. NEJM, 2005.	2004	Mozambique (Beira)	Study included 43 cases and matched 172 controls (High HIV seroprevalence setting of 20 – 30%)	2 doses of WC-rBS vaccine (3 doses in children)	Observational case control study	No randomization. (however bias indicator study included and shows no bias)	78% protection, 1 – 6 months after vaccination (95% CI: 39 – 92%, p=0.004). Vaccine was equally effective in children <5 years old	High HIV prevalence in the area.
Khatib et al. Lancet Inf Dis, 2012	2009 - 2010	Tanzania (Zanzibar)	Of 48,178 eligible individuals, 23,921 received vaccine in 2009. Outbreak occurred in the area during 2009 – 2010.	2 doses of WC-rBS (Dukoral)	Observational Prospective cohort study. Health facility based diarrhoea surveillance	No randomization. (Bias indicator study suggests absence of any significant bias) Differences between vaccine recipients and non-recipients (gender, access to tap water).	Direct protection 79% (LBCL 47%) Indirect (herd) protection was shown by a decrease in the risk for cholera of non-vaccinated residents within a household's neighborhood as the vaccine coverage in that neighborhood increased.	
Wierzba et al. Vaccine, 2015	2011	India (Odisha)	145 villages, ~50,000 population. Healthy, non-pregnant, ≥1 year old	2 doses of Shanchol	Observational study (case-control test negative design)	Some baseline differences between cases and controls. Test negative design. Potential selection bias Potential difference in risk factors among cases and controls.	Adjusted VE = 69% (LBCL*: 14.5%) Cohort analysis VE=70% (LBCL=48%)	Field implementation or feasibility study. Includes bias indicator analysis. Age specific estimates not available.

Reference	Year	Location	Study population	Vaccination or Intervention	Methods	Limitations or Potential Sources of Bias	Relevant Outcomes	Comments
Qadri et al. Lancet, 2015	2011	Bangladesh	90 clusters in urban Dhaka slums; ~270,000 persons (95115 – vaccination only; 93091 vaccination + behaviour change + 80690 – no intervention)	2 doses of Shanchol; 2 doses of Shanchol + behaviour change; no intervention	Cluster-randomized controlled trial (RCT) Passive cholera surveillance.	No significant bias (bias indicator study included)	<u>Vaccination only group (overall protection)</u> Adjusted VE = 37% (LBCL=13%) <u>By age group:</u> 1) 1 – 4 y/o= 52% (LBCL= -4%) 2) 5 – 14 y/o=33% (LBCL=-88%) 3) ≥15 y/o = 34% (LBCL=6%) <u>Vaccination + behaviour change group</u> Adjusted VE = 45% (LBCL=19%) <u>By age group:</u> 1) 1 – 4 y/o= 23% (LBCL= -65%) 2) 5 – 14 y/o=41% (LBCL=-70%) 3) ≥15 y/o = 49% (LBCL=23%) The adjusted cumulative 2-year total protection was 53% (95% CI lower bound 34%; p=0・0001) in the vaccination only group and 58% (95% CI lower bound 41%; p<0・0001) in the vaccination and behavioral change group	Cluster randomized field effectiveness (phase 4 trial).
Ivers et al. Lancet Global Health, 2015	2012 - 2014	Haiti	Target population: ~45,417 persons vaccinated in Rural Haiti. Reactive vaccination in a protracted outbreak setting.	2 doses of Shanchol	Observational – case control study with bias indicator study	No significant bias (bias indicator study included) Vaccination status assessed mainly through verbal reporting; fewer could be validated by card or registry	In multivariable analyses, vaccine effectiveness was 63% (95% CI 8–85) by self-report and 58% (13–80) for vaccination verified through the card or registry. By age group: VE among children <5 years old = 50% (LBCL=-850). Time since vaccination: VE within 1 year = 87%, ≥ 1 year = 64%.	
Severe et al. AJTMH, 2016	2012 - 2015	Haiti (urban slum)	~70,000 persons in urban slums of Port-au-Prince, Haiti; nearby comparison area which was not vaccinated	2 doses of Shanchol	Observational study Cholera surveillance data from one CTC. VE = (ARU − ARV)/ARU × 100) – attack rates in unvaccinated and vaccinated individuals	Several limitations in data analysis and interpretation	VE estimated to be 97.5% in the vaccinated area compared with unvaccinated area.	Combined WaSH and vaccine related interventions

Reference	Year	Location	Study population	Vaccination or Intervention	Methods	Limitations or Potential Sources of Bias	Relevant Outcomes	Comments
Luquero et al. NEJM. 2014	2012	Guinea	Nonselective mass vaccination campaigns were implemented in the prefectures of Boffa and Forécariah.	2 doses pf Shanchol with an interval of at least 2 weeks	Observational matched case-control study with bias indicator study	No significant bias (bias indicator study included) Small sample size, but power remained high. Potential differences in health seeking behaviour may exist, but this bias is assumed to be small.	2 doses provided at effectiveness measure of 86.6% (56.7-95.8) for all ages. Incomplete dose effectiveness measure: 42.8% (-83.6-82.2)	
Azman et al. Lancet Global Health, 2016	2015	South Sudan	165 000 people were vaccinated with a single dose of oral cholera vaccine in this campaign, which targeted high risk areas of Juba	1 dose of Shanchol	Observational – case-cohort study with bias indicator study	No significant bias (bias indicator study included) Small sample size, which impede to estimate direct vaccine effectiveness through classical matched case-control design. Vaccination status assessed through verbal reporting and vaccination card; 50% could be validated by card or registry	In multivariable analyses, vaccine effectiveness was 87·3% (70·2–100·0).	In press, should be available in the next few weeks

*LBCL= Lower bound of the 95% confidence limit

E) Duration of Protection

Table 7 below lists the key studies that have evaluated 'duration of protection' as one of the outcome measures. Data is available on duration of protection for up to 5 years for a multidose schedule and up to 6 months for a single dose schedule.

Table 7: Summary of the key publications related to duration of protection of the currently available, WC killed OCVs

Reference	Year	Location	Study population	Vaccination or Intervention	Methods	Limitations or Potential Sources of Bias	Relevant Outcomes	Comments
van Loon et al, Vaccine, 1996.	1985 - 1989	Bangladesh (Matlab)	Children 2 – 15 years old and women 16 years and older (3 doses at 6 weeks interval); 62,285 completed 3 doses (total – 89,596)	WC-BS and WC only vaccines; placebo	Randomized double blind, placebo controlled trial	No significant bias	During 5 years of follow-up, there were 144 cases of cholera in the WC-BS group (PE = 49%; P < 0.001), 150 in the WC group (PE = 47%; P < 0.001), and 283 in the placebo group. Protection by each vaccine was evident only during the first three years of follow-up; long-term protection of young children was observed only against classical but not El Tor cholera; 3-year protection against both cholera biotypes occurred among older persons, but at a higher level against classical cholera.	
Thiem et al. Vaccine 2006	1998 - 2000	Vietnam (Hue)	Mass immunization of children and adults with the killed whole-cell oral cholera vaccine was undertaken in half of the communes of Hue, Vietnam, in 1998; the remaining communes were immunized in 2000. In all, 48 confirmed and 21 suspected cases matched to 192 and 84 controls were included.	ORCVAX and mORCVAX	Observational case-control study	No significant bias (bias indicator study included). Inclusion of suspected cases, self-reported vaccination status, small sample size.	No cholera was observed in Hue until 2003, when an outbreak of El Tor cholera made it possible to conduct a case-control study. The overall vaccine effectiveness 3-5 years after vaccination was 50% (95% CI 9- 63).	

Reference	Year	Location	Study population	Vaccination or Intervention	Methods	Limitations or Potential Sources of Bias	Relevant Outcomes	Comments
Bhattacharya et al, Lancet, 2013	2006	India (Kolkata)	Individuals ≥1 year old, non-pregnant. 31,932 individuals (1721 clusters) received 2 doses of vaccine and 34968 individuals (1757 clusters) received 2 doses of placebo.	2 doses of Shanchol	Cluster-randomised double blind, placebo controlled trial; heat killed *E. coli* K12 placebo	No significant bias. Substantial increase in protective efficacy during year 5 (likely due to a large cholera outbreak during year 5, which may have boosted natural immunity in the population). High endemic areas – potential natural immunity boosting.	<u>5-year Efficacy data (per protocol analysis)</u> Adjusted cumulative protective efficacy = 65% (LBCL 52%) <u>By age group</u> 4. 1 – 4 y/o: 42% (LBCL=5%) 5. 5 – 14 y/o: 68% (LBCL=42%) 6. ≥15 y/o: 74% (LBCL=58%) <u>By year of follow-up</u> Year 1: 48% (LBCL -11%) Year 2: 78% (LBCL 52%) Year 3: 67% (LBCL 41%) Year 4: 57% (LBCL 26%) Year 5: 80% (LBCL 40%)	Point estimates by year of follow-up suggested no evidence of decline in protective efficacy. Results did not vary significantly between per protocol analysis and intent to treat analysis.
Khatib et al. Lancet Inf Dis, 2012	2009 - 2010	Tanzania (Zanzibar)	Of 48,178 eligible individuals, 23,921 received vaccine in 2009. Outbreak occurred in the area during 2009 – 2010.	2 doses of WC-rBS (Dukoral)	Observational Prospective cohort study. Health facility based diarrhoea surveillance	No randomization. (Bias indicator study suggests absence of any significant bias) Differences between vaccine recipients and non-recipients (gender, access to tap water).	For 15 months duration, direct protection 79% (LBCL 47%). Indirect (herd) protection was shown by a decrease in the risk for cholera of non-vaccinated residents within a household's neighborhood as the vaccine coverage in that neighborhood increased.	
Wierzba et al. Vaccine, 2015	2011	India (Odisha)	145 villages, ~50,000 population. Healthy, non-pregnant, ≥1 year old	2 doses of Shanchol	Observational study (case-control test negative design)	Some baseline differences between cases and controls. Test negative design. Potential selection bias Potential difference in risk factors among cases and controls.	Adjusted VE = 69% (LBCL*: 14.5%) for approximately 1 year duration. Cohort analysis VE=70% (LBCL=48%)	Field implementation or feasibility study. Includes bias indicator analysis. Age specific estimates not available.

Reference	Year	Location	Study population	Vaccination or Intervention	Methods	Limitations or Potential Sources of Bias	Relevant Outcomes	Comments
Ivers et al. Lancet Global Health, 2015	2012 - 2014	Haiti	Target population: ~45,417 persons vaccinated in Rural Haiti. Reactive vaccination in a protracted outbreak setting.	2 doses of Shanchol	Observational – case control study with bias indicator study	No significant bias (bias indicator study included) Vaccination status assessed mainly through verbal reporting; fewer could be validated by card or registry	Time since vaccination: VE within 1 year = 87%, ≥ 1 year = 64%. In multivariable analyses, vaccine effectiveness was 63% (95% CI 8–85) by self-report and 58% (13–80) for vaccination verified through the card or registry. By age group: VE among children <5 years old = 50% (LBCL=-850).	
Severe et al. AJTMH, 2016	2012 - 2015	Haiti (urban slum)	~70,000 persons in urban slums of Port-au-Prince, Haiti; nearby comparison area which was not vaccinated	2 doses of Shanchol	Observational study Cholera surveillance data from one CTC. VE = (ARU − ARV)/ARU × 100) – attack rates in unvaccinated and vaccinated individuals	Several limitations in data analysis and interpretation	VE estimated to be 97.5% in the vaccinated area compared with unvaccinated are at 37 months.	Combined WaSH and vaccine related interventions

F) Indirect Protection (Herd Protection)

Vaccine-induced herd effects are described in terms of herd immunity and herd protection, and these two terms are often used interchangeably[87]. Herd immunity is generally used to describe the protection of non-vaccinated people exposed to live vaccine organisms transmitted by shedding of these organisms by vaccinees, leading to a protective immune response such as with oral polio vaccine, whereas herd protection refers to reduction in the intensity of transmission of the organism as a result of the presence of vaccinated individuals in the community. Consideration of herd protection thus forms an important aspect of vaccines under consideration for population-level use due to several factors, 1) cost-effectiveness of vaccines, 2) vaccine coverage as needed for adequate disease control, 3) microorganism strain replacement[87].

Table 8 lists the key studies that have evaluated herd protection effects of the currently available, WC, killed OCVs.

Table 8: Summary of the key publications related to herd protection of the currently available, WC killed OCVs

Reference	Year	Location	Study population	Vaccination or Intervention	Methods	Limitations or Potential Sources of Bias	Relevant Outcomes	Comments
Ali et al, Lancet 2005[88]	1985 - 1989	Bangladesh (Matlab)	Children 2 – 15 years old and women 16 years and older (3 doses at 6 weeks interval); 62,285 completed 3 doses (total – 89,596)	WC-BS and WC only vaccines; placebo	Randomized double blind, placebo controlled trial A reanalysis of the original trial data		Vaccine coverage of the targeted population ranged from 4% to 65%. Incidence rates of cholera among placebo recipients were inversely related to levels of vaccine coverage (7·01 cases per 1000 in the lowest quintile of coverage *vs* 1·47 cases per 1000 in the highest quintile; p<0·0001 for trend). Receipt of vaccine by an individual and the level of vaccine coverage of the individual's cluster were independently related to a reduced risk of cholera. After adjustment for the level of vaccine coverage of the cluster, vaccine protective efficacy remained significant (55% [95% CI 41–66], p<0·0001).	This was a reanalysis of the 1985 – 1989 trial data.
Khatib et al. Lancet Inf Dis, 2012[55]	2009 - 2010	Tanzania (Zanzibar)	Of 48,178 eligible individuals, 23,921 received vaccine in 2009. Outbreak occurred in the area during 2009 – 2010.	2 doses of WC-rBS (Dukoral)	Observational Prospective cohort study. Health facility based diarrhoea surveillance	No randomization. (Bias indicator study suggests absence of any significant bias) Differences between vaccine recipients and non-recipients (gender, access to tap water).	Direct protection 79% (LBCL 47%) Indirect (herd) protection was shown by a decrease in the risk for cholera of non-vaccinated residents within a household's neighborhood as the vaccine coverage in that neighborhood increased.	

Reference	Year	Location	Study population	Vaccination or Intervention	Methods	Limitations or Potential Sources of Bias	Relevant Outcomes	Comments
Ali et al. CID, 2013[89]	2006	India (Kolkata)	Individuals ≥1 year old, non-pregnant. 31,932 individuals (1721 clusters) received 2 doses of vaccine and 34968 individuals (1757 clusters) received 2 doses of placebo.	2 doses of Shanchol	Cluster-randomised double blind, placebo controlled trial; heat killed *E. coli* K12 placebo In the cluster design, herd protection was assessed by comparing the incidence of cholera among participants in vaccine clusters versus those in placebo clusters. In the geographic information system (GIS) analysis, herd protection was assessed by evaluating association between vaccine coverage among the population residing within 250 meters of the household and occurrence of cholera in that population.		In the cluster design, the 3- year data showed significant total protection (66% protection [95% confidence interval: 50-78%]; p<0.01), but no evidence of indirect protection. With the GIS approach, the risk of cholera among placebo recipients was inversely related to neighborhood-level vaccine coverage, and the trend was highly significant (p<0.01). This relationship held in multivariable models that also controlled for potentially confounding demographic variables (hazard ratio: 0.94 [95% confidence interval: 0.90-0.98]; p<0.01). Overall, herd protection was evident in analyses using the GIS approach, but not the cluster design approach, likely due to considerable transmission of cholera between clusters.	

G) Dosing Interval (Alternative Schedule and Booster Regimen)

Table 9 lists the key studies that have evaluated an alternative schedule and booster regimen for the currently available WC, killed OCVs.

Table 9: Summary of the key publications related an alternative schedule and booster regimen of the currently available, killed OCVs

Reference	Year	Location	Study population	Vaccination or Intervention	Methods	Limitations or Potential Sources of Bias	Relevant Outcomes	Comments
Kanungo S. PlosNTDs, 2015[42]	2012	India (Kolkata)	356 healthy, non-pregnant individuals ≥ 1 year old randomized to receive the vaccine 14 and 28 days apart.	2 doses of Shanchol using two different regimens (14 days apart and 28 days apart).	Randomized controlled, double blind non-inferiority trial.	No significant bias.	Among adults, no significant differences were noted when comparing the rates of seroconversion for *V. cholerae* O1 Inaba following two dose regimens administered at a 14 day interval (55%) vs the 28 day interval (58%). Similarly, no differences in seroconversion were demonstrated in children comparing the 14 (80%) and 28 day intervals (77%). Following 14 and 28 day dosing intervals, vibriocidal response rates against *V. cholerae* O1 Ogawa were 45% and 49% in adults and 73% and 72% in children respectively.	Evidence of clinical protection needed
Kanungo S. PlosNTDs, 2015[90]	2012	India (Kolkata)	426 healthy, non-pregnant participants, who were not diagnosed with cholera during the 5 year surveillance period	2 dose booster regimen of Shanchol 5 years after the primary 2-dose series	Nested, open label controlled trial among participants previously enrolled in the 2006 efficacy trial. Endpoints were compared between two intervention groups: a boosted population (individuals who received vaccine five years prior and were redosed) and a primary series population (participants who were placebo recipients in the original RCT and were receiving vaccine for the first time. Both of these groups received vaccine at days 0 and 14 and blood were drawn for measurement of vibriocidal titers. A third blood sample was also drawn on day 28 to compare baseline with titers 14 days following doses one and two.	No significant bias.	Among participants receiving a two dose primary series of OCV (n = 186), 69% (95% CI 62%-76%) seroconverted. In the intervention arm (n = 184), 66% (95% CI 59%-73%) seroconverted following a two dose boosting schedule given five years following the initial series. Following a single boosting dose, 71% (95% CI 64%-77%) seroconverted. Children demonstrated 79% (95% CI 69%-86%) and 82% (95% CI 73%-88%) seroconversion after primary and boosting regimens, respectively.	Evidence of clinical protection needed

H) Knowledge, Attitudes and Practices (KAP) Studies

As discussions occurred for inclusion of OCVs into a comprehensive cholera prevention and control package, concerns were expressed regarding the lack of data on any potential synergies vs. interference between vaccination and traditional cholera prevention and control measures. A few studies were conducted which assessed knowledge, attitudes and practices regarding cholera, WaSH and OCVs before and after OCV campaigns and the role of health education and messaging, and are summarized below in Table 10.

Table 10: Summary of selected studies that assessed knowledge, attitudes and practices regarding cholera, WaSH and OCVs, 2010 – current

Reference	Year	Location	Study population	Vaccination or Intervention	Methods	Limitations or Potential Sources of Bias	Relevant Outcomes	Comments
Aibana et al. PlosNTDs, 2013	2012	Haiti (Rural – Bocozel)	Rural Community where a reactive vaccination was conducted (protracted outbreak).	~50,000 individuals ≥ 1 year old, not pregnant	Baseline surveys on knowledge and practice relevant to cholera and waterborne disease to every 10th household during a census in rural Haiti in February 2012 (N = 811). An OCV campaign occurred from May-June 2012 after identical surveys to 518 households randomly chosen from the same region in September 2012. We compared responses pre- and post-OCV campaign.	Effect of other factors/interventions cannot be excluded. Self-reported water treatment and hygiene behaviours. Survey timings (different times of the year – which may influence WaSH behaviours)	Significant improvement in cholera knowledge and practices related to waterborne disease prevention noted at 3 months post-campaign as compared with before the campaign. Post-vaccination, there was improved knowledge with significant increase in percentage of respondents with ≥ 3 correct responses on cholera transmission mechanisms (odds ratio OR] 1.91; 95% confidence interval [CI] 1.52-2.40), preventive methods (OR 1.83; 95% CI 1.46-2.30), and water treatment modalities (OR 2.75; 95% CI 2.16-3.50). Relative to pre-vaccination, participants were more likely post-OCV to report always treating water (OR 1.62; 95% CI 1.28-2.05). Respondents were also more likely to report hand washing with soap and water >4 times daily post-vaccine (OR 1.30; 95% CI 1.03-1.64). Knowledge of treating water as a cholera prevention measure was associated with practice of always treating water (OR 1.47; 95% CI 1.14-1.89). Post-vaccination, knowledge was associated with frequent hand washing (OR 2.47; 95% CI 1.35-4.51).	The campaign incorporated a strong WaSH messaging component. NGO has a strong presence and community-level activities in the area.
Wahed et al. BMC Public Health, 2013	2010	Bangladesh (Dhaka)	Urban slum Dhaka In the setting of a large phase 4 clinical trial	Cluster randomized trial with 3 arms (vaccine, vaccine+ WaSH, no intervention)	Quantitative knowledge, attitudes and practices (KAP survey) and in-depth interviews before the trial.	No comparison point for after the campaign. Self-reported behaviours.	Of 2,830 families, 23% could recognize cholera as acute watery diarrhea and 16% had ever heard of oral cholera vaccine. About 54% of the respondents had poor knowledge about cholera-related issues while 97% had a positive attitude toward cholera and oral cholera vaccine. 1/3rd showed poor practice relating to the prevention of cholera. The findings showed a significant ($p < 0.05$) association between the respondents' knowledge and sex, education, occupation, monthly overall household expenditure, attitudes and practice. In the adjusted model, male sex, having a lower monthly overall household expenditure, and having a less positive attitude toward cholera were the significant predictors to having poor knowledge.	Evaluated KAPs to inform messaging during the campaign

Reference	Year	Location	Study population	Vaccination or Intervention	Methods	Limitations or Potential Sources of Bias	Relevant Outcomes	Comments
Burnett et al. PlosNTDs, 2013	2012	Solomon Islands	Rural	~15,000 children 1 – 15 years old were vaccinated In areas adjacent to an outbreak	Quantitative KAP survey in areas targeted and not targeted for vaccination after the OCV campaign.	Comparability of the vaccinated and unvaccinated groups. Self-reported behaviours	Respondents in vaccinated areas were more likely to have received cholera education in the previous 6 months (33% v. 9%; p = 0.04), to know signs and symptoms (64% vs. 22%; p = 0.02) and treatment (96% vs. 50%; p = 0.02) of cholera, and to be aware of cholera vaccine (48% vs. 14%; p = 0.02). There were no differences in water, sanitation, and hygiene practices.	Cholera naïve setting
Peprah et al, Vaccine, 2016	2014	South Sudan	IDP camps Humanitarian crisis	162,577 persons targeted for vaccination.	Qualitative study semi-structured interviews 4 months after the campaigns	Potential recall issues (study occurred 4 months after vaccination). Limited generalizability.	Reasons for partial and non-acceptance of the vaccination included lack of time and fear of side effects, similar to reasons found in OCV campaigns in non-crisis settings. In addition, distrust in national institutions in a context of fears of ethnic persecution was an important reason for hesitancy and refusal. Other reasons included fear of taking the vaccine alongside other medication or with alcohol. The findings highlight the importance of considering the target populations' perceptions of institutions in the delivery of OCV interventions in humanitarian contexts. They also suggest a need for better communication about the vaccine, its side effects and interactions with other substances.	
Childs et al, AJTMH, 2016	2013	Haiti	Urban Rural	~107,906 persons were targeted for vaccination.	KAP survey was conducted both pre-campaign and post-campaign. Interviewer observation of the household to assess availability of water/water storage was also conducted.	The timing of the survey may have led to inaccurate results (cholera had become endemic). Most outcomes were self-reported behaviours (social desirability or recall bias). Different groups sampled pre and post the campaign. No control area/group	No significant differences in knowledge about causes, symptoms, and prevention of cholera were noted. However, treatment of drinking water significantly decreased along with safe storage of drinking water. These findings highlight the need for future campaigns to include a strong educational component that emphasizes the importance of maintaining appropriate WASH practices for the prevention of cholera and other diarrheal diseases even after vaccination, and highlights the limited effectiveness and duration of protection of OCV.	

Reference	Year	Location	Study population	Vaccination or Intervention	Methods	Limitations or Potential Sources of Bias	Relevant Outcomes	Comments
Scobie et al, PlosNTDs, 2016	2013 - 2014	Thailand	Refugee camp (long standing)	~43,485 persons were targeted for vaccination.	KAP cross-sectional surveys conducted 1 month before and 3 and 12 months after an OCV campaign.	High proportion of non-responding households (non-response bias). Self-report (social desirability or recall bias) Potential issues with accurate translation of questionnaire into all dialects spoken in camp	Compared with baseline, statistically significant differences were noted at first and second follow-up among the proportions of respondents who correctly identified two or more means of cholera prevention (62% versus 78% and 80%), reported boiling or treating drinking water (19% versus 44% and 69%), and washing hands with soap (66% versus 77% and 85%); a significant difference was also observed in the proportion of households with soap available at handwashing areas (84% versus 90% and 95%). Therefore, OCV campaigns may provide opportunities to reinforce beneficial WASH-related KAPs for prevention and control.	High migration rates

I) Note regarding the costing and cost-effectiveness of OCVs

Costs associated with the different OCV campaigns, including local delivery costs, are included in Table 3 earlier in the document.

A cost-benefit comparison of investments in improved water supply and cholera vaccination community-based programs showed, though, that improved water supply interventions and a targeted cholera vaccination program were much more likely to yield attractive cost-benefit outcomes than a community-based vaccination program alone [91].

Using the example of the 2008-2009 cholera outbreak in Zimbabwe, a retrospective cost-effectiveness analysis calculated the health and economic burden with and without a hypothetical reactive oral cholera vaccination. The primary outcome measure was incremental cost per disability-adjusted life year (DALY) averted. Under the base assumptions (50% vaccine coverage among individuals aged ≥2 years), reactive vaccination could have averted 1,320 deaths and 23,650 DALYs. Considering herd immunity, the corresponding values would have 2,920 deaths and 52,360 DALYs averted. Total vaccination costs were estimated to be about US$74 million and $21 million, respectively, with per-dose vaccine price of US$5 and $1. Assuming herd immunity, the corresponding cost was US$980 with vaccine price of US$5, and the program was cost-saving with a vaccine price of US$1. The study concluded that reactive vaccination has the potential to be a cost-effective measure to contain cholera outbreaks in countries at high risk [92].

A more recent study describing the organization, vaccine coverage, and delivery costs of mass vaccination with a new, less expensive oral cholera vaccine using existing public health infrastructure in Odisha, India, demonstrated the affordability of vaccine and delivery costs for resource-poor countries. Vaccine cost at market price (about US$1.85/dose) was the costliest item. The vaccine delivery cost was $0.49 per dose or $1.13 per fully vaccinated person [65]. Although the study noted that without cholera incidence data, it was not possible to estimate the Odisha-specific cost-effectiveness of vaccination, it did cite results from a cholera vaccination economic model using incidence estimates for other high-risk populations in India [65]. Assuming cholera vaccine coverage to be at 80% and 50% of measles vaccine coverage for populations 1-14 years and 15+ years, respectively, in the Southeast Asia region, a cost effectiveness ratio of $785 per DALY averted for programs targeted to ages 1 year and above was estimated [1].

J) Note regarding vaccine impact on disease transmission and trends

Most OCV studies to date have focused on vaccine safety, immunogenicity, effectiveness, coverage, behavioral aspects (knowledge, attitudes and practices), and economic aspects of OCV use, and there are very limited data on impact of OCV use on disease transmission and trends. Several modeling studies have estimated potential vaccine impact in multiple settings with different assumptions, including vaccination strategy, coverage and allocation [92-96] but data on actual impact remain limited.

A study in South Sudan has recently shown some promising results on vaccine impact [97]. Following mass population displacements in South Sudan, preventive cholera vaccination campaigns were conducted

in six displaced persons camps in 2014, but not in the surrounding host communities. In April 2014, two months after vaccine deployment, South Sudan confirmed the first case of cholera in the country, and over 5 months, 6,269 suspected cholera cases were reported, including 156 deaths. Most cases occurred outside vaccinated camps, mainly in communities or camps surrounding vaccinated populations. The epidemic curves within vaccinated camps in Juba had no distinct peak and suggested a series of cholera introductions with little to no onward transmission, whereas estimates in unvaccinated areas showed that despite conditions that may have been less suitable for transmission, transmission occurred for a sufficient and significantly longer time for an epidemic to progress.

More data on actual impact of OCVs on disease transmission and trends are needed in different epidemic and endemic settings.

K) Note on heat stability of the killed whole cell OCVs

Maintenance of cold chain (2 – 8 °C) is currently required for OCVs. However, new data are emerging on the thermostability of the vaccines, which is likely to greatly simplify delivery logistics – similar to the meningococcal A conjugate vaccine following use the controlled temperature chain (CTC) recommendations (http://www.who.int/biologicals/areas/vaccines/controlledtemperaturechain/en/).

A study conducted in Bangladesh showed that the safety and immunogenicity profile of Shanchol was maintained when stored at elevated temperatures of up to 42 °C for 14 days [98]. In 2012, in an outbreak response vaccination campaign in Guinea, vaccine was maintained in cold chain during storage but transported and use at ambient temperatures during vaccination days [78]. Following this campaign, the 2-dose OCV regimen was shown to be 86% effective [77].

The available killed OCVs are good candidates for CTC use and if approved, will help improve storage and delivery logistics, especially in resource-limited settings where cholera usually occurs.

L) Note on coadministration of OCVs with other vaccines

In general, concomitant administration of multiple vaccines, including live attenuated immunizations, is safe and effective. Some restrictions apply for live vaccines – administering a live-virus vaccine within 4 weeks after administration of another live-virus vaccine can decrease immunogenicity to the second administered vaccine, hence it is recommended that live-virus vaccines should be administered the same day or ≥4 weeks apart. Studies of oral polio vaccine and oral rotavirus vaccines, also both live viral vaccines, have shown decreased seroconversion for rotavirus, with the 1st dose, which was subsequently overcome after completion of the three-dose series[99]. Data on coadministration of the currently available whole-cell killed OCVs with other oral vaccines, specifically, oral polio vaccines is lacking. Although the risk of immunological interference due to co-administration of live with non-live vaccines is considered small, if at all any, it has raised a theoretical concern of interference. The manufacturer of Shanchol has recommended a gap of 15 days between Shanchol and OPV given the lack of such data and the emphasis on global polio eradication (Letter issued by Shantha Biotechnics, 2011).

Specifically the WHO polio vaccine position paper (2016)[100] states that the limited available evidence supports the safety and immunogenicity of co-administration of OPV and oral cholera vaccines[101]. The WHO position paper on oral polio vaccines states that both oral and injectable polio vaccines can be co-administered with other vaccines.

A study is planned to specifically evaluate immunogenicity of OCV and OPV when co-administered and results are expected in 2017/2018 (Personal Communication, CDC).

M) OCV Use in Special Populations

i. OCV use in HIV-Infected Individuals

Data on how human immunodeficiency virus (HIV) infection influences susceptibility to cholera infection and immune response to OCVs are limited. A study of the 2005 cholera outbreak in Mozambique suggested a higher attack rate among HIV-infected individuals than among non-HIV-infected persons[102]. This is important in high HIV-prevalent settings, where cholera remains a persistent occurrence. A case-control study evaluating effectiveness of the WC-rBS vaccine in Mozambique found that the vaccine was 78% protective (95% confidence interval = 39%–92%) in a high HIV prevalence setting (20–30% HIV prevalence) [32]. An immunogenicity study with Shanchol in Haiti among adults with and without HIV infection showed 74% seroconversion against the Inaba serotype and 65% seroconversion against the Ogawa serotype among HIV positive adults compared with 91% seroconversion against both serotypes in the HIV negative group [72]; diminished responses were primarily seen among HIV-infected individuals with the lowest CD4 counts. This suggested lower immunogenicity among HIV-infected individuals needs further evaluation with due consideration for the risk of cholera and potential additional dosing regimens among these populations.

ii. OCV use among prison populations

Cholera outbreaks in prisons have long been reported across the world since the 1800s[103]. The source of these outbreaks, which have recorded alarmingly high case fatality rates in some instances, range from infected prisoners exposed within the community who are still shedding when admitted to the prison to contaminated food and water. Prisoners are particularly vulnerable due to overcrowding (some prisons reaching up to 8 times their capacity), poor sanitation and hygiene measures, social marginalization, and inadequate medical services or quarantine actions that favor rapid and prolonged transmission.

Control and prevention measures in use include isolation and quarantine, WASH interventions (installation of hand washing stations, provision of safe water), use of chlorination as a disinfectant, distribution of prophylactic antibiotics, use of emergency treatment units, suspension of visits, and transferring the sick to hospitals/other prisons. However, the ability to implement these measures depends greatly upon available resources, staff, time, and space. Administration of OCVs has rarely been utilized.

Haiti is the first country to have conducted a pre-emptive OCV campaign among prisoners for the prevention of prison outbreaks (Personal Communication, CDC, 2016). Following a national campaign in 2014, the remaining OCV (Shanchol) doses were used to vaccinate prisoners, and staff when possible, in 16 prisons with two doses between November and December of 2014 (11,826 doses dispensed with a total cost of 22,705 USD, not including the vaccine which was borrowed from the global stockpile). Few refused the vaccine and demand was high. A high coverage rate was achieved, which can likely be attributed to the fact that the target population was small and clearly defined. Catch-up vaccinations for those incarcerated following the first dose, and therefore received their first dose during the second dose administration, were left with prison medical staff to be administered 14 days later. Two post-vaccination outbreaks were reported, resulting in only 3 deaths, despite the nationwide increase in cases. In turn, this model showed significant success in involving coordination of many agencies and demonstrated that the OCV use is feasible and potentially a high impact intervention among prison populations.

iii. OCV use in Pregnant Women

Currently the guidance on OCV use in pregnant women is conflicting and ambiguous. The WHO 2010 Position Paper on cholera vaccines mentions pregnant women as a group that, is "especially vulnerable to severe disease and for which the vaccines are not contraindicated" and thus "may also be targeted [for vaccination]"[5]. However, the vaccine package inserts are contradictory, ambiguous and inconsistent. Given that pregnant women are excluded from clinical trials of these vaccines – as is the normal practice with clinical trials of drugs and vaccines – there is lack of data from well-controlled studies on vaccine safety during pregnancy. Consequently, the manufacturers of these vaccines are more cautious.

The package insert for Shanchol states the following – "No specific clinical studies have been performed to evaluate the safety and immunogenicity of Shanchol in pregnant women and for the fetus. The vaccine is therefore not recommended for use in pregnancy. However, Shanchol is a killed vaccine that does not replicate, is given orally and acts locally in the intestine. Therefore, in theory, Shanchol should not pose any risk to the human fetus. Administration of Shanchol to pregnant women may be considered after careful evaluation of the benefits and risks in case of a medical emergency or an epidemic."

The package insert for Dukoral states the following – "The vaccine may be administered during pregnancy and to lactating women." (https://extranet.who.int/gavi/PQ_Web/PreviewVaccine.aspx?nav=0&ID=116). However, product information for Dukoral is not always consistent. The Package Leaflet for users cautions that women who are pregnant, think they may be pregnant or are planning to have a baby or are breast-feeding, should ask their doctor before taking the vaccine. In addition, the 26-page Product Monograph produced by Crucell uses language similar to that in the Shanchol™ package insert - "The effect of Dukoral® on embryo-fetal development has not been assessed and animal studies on reproductive toxicity have not been conducted. No specific clinical studies have been performed to address this issue. The vaccine is therefore not recommended for use in pregnancy. However, Dukoral® is an inactivated vaccine that does not replicate. Dukoral® is also given orally and acts locally in the intestine. Therefore, in theory, Dukoral® should not pose any risk to the human fetus. Administration of Dukoral® to pregnant women may be considered after careful evaluation of the benefits and risks." (http://www.crucellvaccinescanada.com/pdf/110808_Dukoral_PM.pdf)

Given this ambiguity, immunization program managers have been reluctant to diverge from package insert recommendations most campaigns conducted to date have excluded pregnant women. In 2015, the GTFCC secretariat commissioned a literature review on OCV use in pregnancy, which was reviewed and endorsed by the OCV working group for development of interim guidance while the formal SAGE review process occurred (http://www.who.int/cholera/vaccines/Risk_Benefits_vaccinating_pregnant_women_Technical_Note_13Jan2016.pdf).

Data on OCV use in pregnancy are limited compared with data on other vaccine characteristics. Two retrospective studies have systematically documented the safety of OCV use in pregnancy – in Zanzibar with Dukoral (2010), in Guinea with Shanchol (2012)[56,76], in Malawi[104] and Bangladesh[105]. Other studies during OCV campaigns, though not powered to detect effect pregnancy outcomes, have also documented no adverse pregnancy and fetal outcomes among those women who were inadvertently vaccinated [105]. A prospective pregnancy outcome study has recently been completed during an OCV campaign in Malawi in 2015. Results support the conclusion that OCVs are safe to be used during pregnancy, and given the risk of poor outcomes from cholera infection in pregnancy, pregnant women should be vaccinated during OCV campaigns [104] .

Table 11 lists details of the studies that have evaluated pregnancy related outcomes of OCV use. It is to be noted that randomized trials to evaluate pregnancy outcomes may not be possible given the special need for ethical and moral considerations.

Table 11: List of Studies that have evaluated OCV use in Pregnancy, Until March 2017

Study	Study description	Vaccine used	Birth outcomes	Fetuses exposed to vaccine		Fetuses not exposed to vaccine		Relative risk or odds ratio	P value	Comments
				No.	%	No.	%			
Follow-up surveillance of women who were pregnant during mass reactive vaccination campaign, Guinea, 2012 (Grout L et al. 2014)	Retrospective cohort study involving face-to-face interviews with women in vaccinated area who were pregnant in 2012 during cholera epidemic	Shanchol		n=1,312		n=272				No significant differences in outcomes found between fetuses exposed and not exposed. Determination of vaccination and fetal outcomes based on interviews with women (plus confirmation via vaccination cards for a minority of those reporting having been vaccinated).
			Miscarriages (≤5 mo. gestation)	12	1.4	2	0.7	NA	0.689	
			Stillbirths (> 5 mo.)	36	2.8	5	1.8		0.394	
			Total fetal losses	48	3.6	7	2.6	Unadjusted RR = 1.45 Adjusted RR = 1.13	0.350 0.738	
Study of birth outcomes following mass cholera vaccination demonstration project, Zanzibar, 2010 (Hashim 2012)	Face-to-face survey of women conducted 9 months after vaccination campaign to identify women pregnant during campaign and birth outcomes among those vaccinated and not vaccinated.	Dukoral		N=196		N=955				Fetal losses were greater in vaccinated vs. non-vaccinated pregnant women, but differences were not significant and the vaccine group was older, poorer and received less ANC services. Vaccination status determined by vaccination database developed for demonstration project.
			Miscarriages (≤20 weeks)	1	0.5	7	0.7			
			Stillbirths (>20 weeks)	9	4.6	20	2.1			
			Total fetal losses	10	5.1	27	2.8	1.62	0.21	
			Infant deaths	3 (out of 186)	1.6	13 (out of 928)	1.4	Adjusted RR = 1.46	0.56	
Safety of a killed oral cholera vaccine (Shanchol) in pregnant women in Malawi: A prospective cohort study (Ali et al, 2016)	The study was conducted in two nearby districts (Nsanje and Chikwawa) in Malawi. Persons ≥1 year in Nsanje were offered the vaccine. No vaccinations were administered in Chikwawa. The primary endpoint was pregnancy loss (spontaneous	Shanchol	Total fetal losses	N=835 23	2.75	N=835 18	2.16	Unadjusted RR = 1.28 Adjusted RR= 1.24	0.52	No significant differences in outcomes found between fetuses exposed and not exposed. Relatively paucity of data on possible miscarriage during the first trimester. Miscarriages are more likely to occur in the first trimester
			Neonatal death	N=679 8	1.18	N=673 6	0.89	Unadjusted RR = 1.32	0.60	

Study	Study description	Vaccine used	Birth outcomes	Fetuses exposed to vaccine		Fetuses not exposed to vaccine		Relative risk or odds ratio	P value	Comments
				No.	%	No.	%			
	miscarriage or stillbirth, which was compared between women exposed to OCV and women not-exposed to OCV.		Malformation	N=822 2	0.24	N=823 1	0.12	Unadjusted RR = 2.0	0.57	but the enrollment occurred following the vaccine campaign, and miscarriages may have already occurred prior to enrollment; thus, the study was unable to fully characterize the risk of 1st trimester pregnancy loss following OCV vaccination
Safety of the oral cholera vaccine in pregnancy: Retrospective findings from a subgroup following mass vaccination campaign in Dhaka, Bangladesh (Khan et al.)	Retrospective case control study, following a mass vaccination campaign, of pregnancy women who inadvertently received vaccine. The primary end points included any adverse events, spontaneous abortions, stillbirths, and congenital anomalies.	Shanchol	Any adverse event	N = 69 11	16%	N = 69 8	12%	Unadjusted OR = 1.55	0.38	Percent of adverse event and spontaneous abortions were greater in the vaccinated group, but significant differences in outcomes were found. There was substantial loss to follow-up in the study that resulted in a small sample size. Women in the vaccinated group were also followed at an earlier stage making then inherently more likely of reporting adverse events.
			Spontaneous Abortion	N =69 5	7%	N =69 1	1.4%	Unadjusted OR = 5.3		
			Stillbirth	N =69 6	9%	N =69 6	9%	Unadjusted OR = 1		
			Congenital Anomaly	N =69 0	0%	N =69 1	1.4%	Unadjusted OR = 0		

3.4. Global Oral Cholera Vaccine Stockpile

A global cholera vaccine stockpile has been in existence since 2013. As part of a comprehensive cholera control strategy, in September 2011, WHO convened an ad hoc experts' meeting where stockpiling OCV was endorsed as an additional, but necessary and feasible response mechanism for cholera control in outbreak and emergency settings. The stockpile was created to facilitate access to OCVs for underserved populations especially in outbreak and emergency settings, while increasing demand and production resulting in lower unit costs and greater equity of distribution. Accordingly, in June 2013, a global OCV stockpile was created with an initial investment of 2 million doses by multiple partners. In November 2013, the Gavi board endorsed funding support for the OCV stockpile with an investment of $115 million over 5 years (2014 – 2018). The OCV stockpile is managed as a rotating fund by the International Coordinating Group (ICG) which manages similar stockpiles of meningococcal meningitis and yellow fever vaccines for outbreak response. The ICG is comprised of four decision making partners: the International Federation of Red Cross and Red Crescent Societies (IFRC), Médecins Sans Frontières (MSF), United Nations Children's Fund (UNICEF) and WHO, which also serves as the Secretariat. Information on requesting the stockpile vaccine is available at http://www.who.int/cholera/vaccines/ocv_stockpile_2013/en/.

The stockpile was initially established to increase access and availability of OCVs in outbreak and humanitarian emergencies, which remains the primary objective. In addition, discussions within the GTFCC and the different GTFCC working groups highlighted the need to include OCVs within comprehensive cholera prevention and control strategies in recurrent outbreak situations in endemic settings. Since 2015, the OCV working group of the GTFCC proposed that the stockpile be divided into two components – emergency stock and non-emergency reserve (Figure 4). Decisions regarding OCV release from the emergency stockpile are managed by the ICG, and the OCV working group of the GTFCC is responsible for decisions on vaccine release from the non-emergency stock.

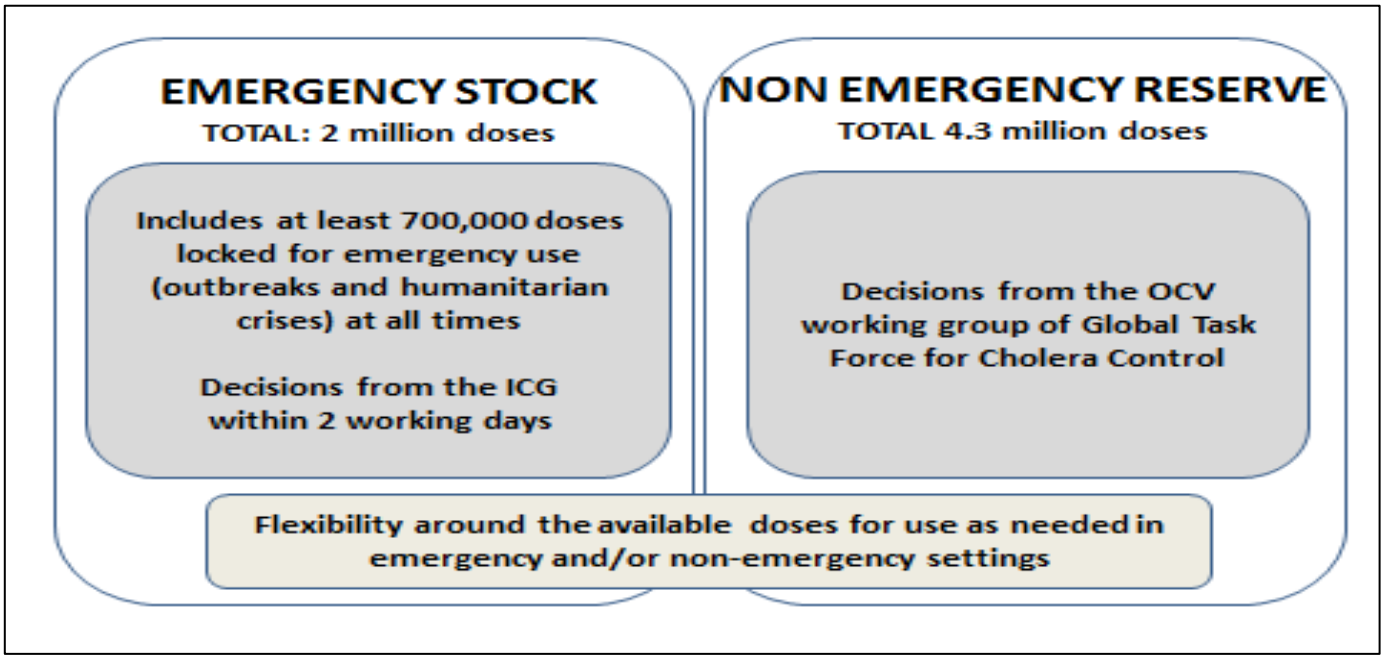
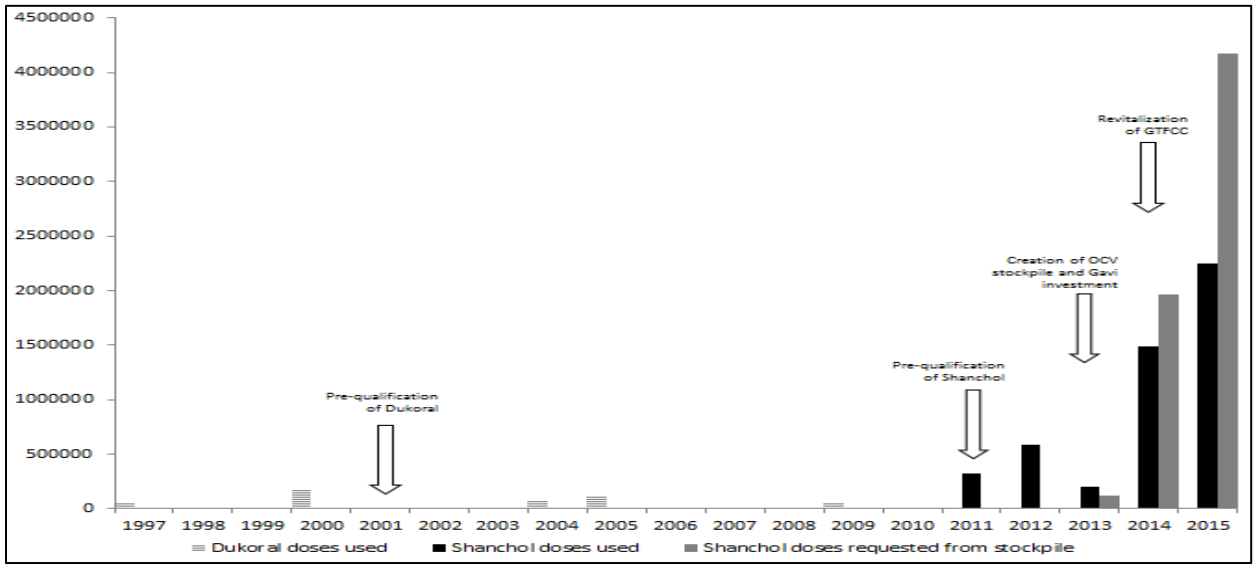


Figure 4: Global OCV Stockpile Components and Number of Available Doses, 2016

Over 7 million doses have been deployed from the global OCV stockpile with successful use in humanitarian crises, outbreaks, and endemic settings (Figure 5 shows data until 2015 with 5 million doses used)**.** Since the inception of the stockpile, OCV availability and supply, as well as OCV requests have steadily increased. In 2015, OCV demand exceeded available supply highlighting the need for increased production.

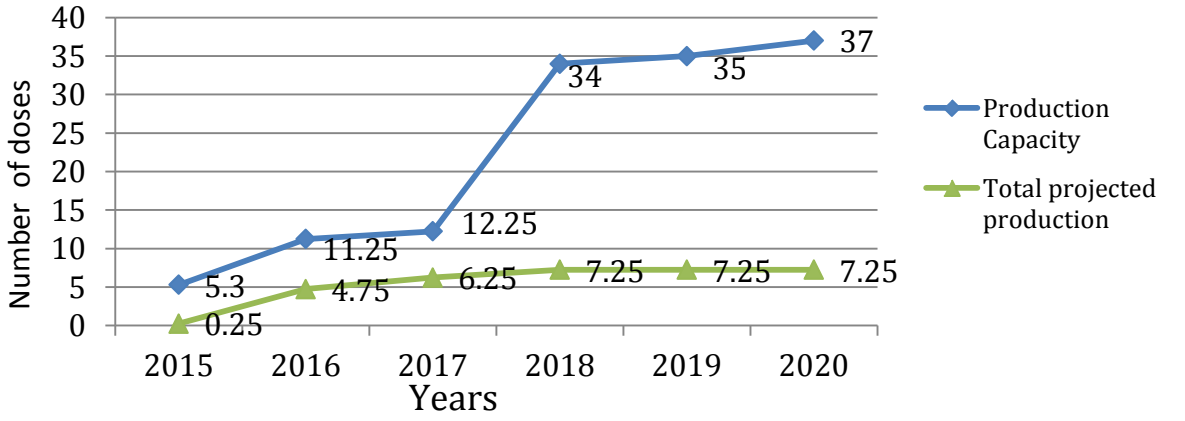
Figure 5: Oral cholera vaccine use and demand 1997-2015



In the current investment period for the OCV stockpile, Shanchol production will remain at approximately 2 million doses per year. Current projections for Euvichol production are for 3-4 million

doses per year, with a maximum production capacity of up to 25 million doses per year (Figure 6). The Bangladesh modified WC only OCV could add another 20 – 40 million doses, initially only for the in-country market, but if eventually prequalified, to the international market. Though forecast demand for oral cholera vaccine has increased, the international global health community should remain cautiously optimistic until vaccine production meets projected demand.

Figure 6: Projected production and production capacity



While an increased body of evidence is available regarding OCV safety, effectiveness, acceptability and cost-effectiveness, more evidence is needed in other areas, notably impact on disease transmission, vaccine dosing and alternative strategies (including incorporation within routine immunization programs and coadministration with other vaccines, alternative delivery strategies, and controlled temperature chain). Unconventional approaches can serve to improve success and even decrease cost, and alternative vaccination strategies, such as the use of a single dose regimen and extended dosing intervals could offer increased benefit to populations with difficulty accessing the traditional two round campaigns. Oral vaccines against enteric infections, including cholera vaccines, have been less immunogenic and efficacious when given to those living in less developed countries, especially in young children. Though the rationale is not completely understood, key factors associated with poor oral vaccine performance in children in developing countries appear to be related to the intestinal environment of these populations. Specific factors that need to be evaluated further include protein energy and micronutrient malnutrition, maternal antibody interference, concomitant parasitic infections, and intestinal mucosal damage due to environmental enteropathy.

Recently, in June 2016, the Gavi board endorsed support for the operational costs of OCV campaigns (http://www.gavi.org/about/governance/gavi-board/minutes/2016/22-june/minutes/02e---consent-agenda---oral-cholera-vaccines-operational-cost-support/). The current Gavi investment for the OCV stockpile covers the period from 2014 – 2018. OCVs will be reconsidered by the Gavi board in 2018 for ongoing long-term support, based on information gathered during the investment period, notably on impact and cost. Hence, monitoring and evaluation, and implementation research is a critical component of OCV use, to help generate the data for appropriately targeting OCV use and maximizing efficient use of OCVs in different contexts and settings.

4. Grading for Recommendations, Assessment, Development and Evaluation (GRADE) Review

4.1. Introduction and Objectives

In accordance to the guidance document for the development of evidence-based vaccine related recommendations (http://www.who.int/immunization/sage/Guidelines_development_recommendations.pdf), the SAGE OCV working group, established in late 2015/early 2016 (Appendix 1) held a series of conference calls and face-to-face meetings to decide on the priority questions to be addressed and for which recommendations need to be developed for SAGE consideration. Accordingly the SAGE OCV WG, prioritized a list of issues for good practice recommendations and for the formal Grading of Recommendations, Assessment, Development and Evaluation (GRADE) review.

The following key questions and outcomes were agreed upon by the working group for a formal GRADE review,

1. What is the evidence that the currently available killed, whole-cell oral cholera vaccines (OCVs) are safe among non-pregnant individuals (Dukoral ≥ 2 years old, Shanchol/Euvichol/mORCVax ≥ 1 year olds?
2. What is the evidence for protective efficacy, effectiveness, and duration of the currently available killed, whole cell OCVs during the first 5 years following immunization among individuals ≥ 1 year old?
3. What is the evidence that the currently available killed, whole-cell oral cholera vaccines (OCVs) are safe among pregnant women?

4.2. Methodology

A thorough literature search was conducted using PubMed to identify all relevant articles using the following search terms - oral cholera vaccine, cholera vaccine effectiveness, cholera vaccine impact, cholera vaccine safety and immunogenicity, cholera vaccine acceptance or acceptability, cholera vaccine use, cholera vaccines in pregnancy. The initial search was conducted in the English language and was later expanded to include Spanish, French, and Russian (Courtesy: Epicentre). An additional search was conducted to identify publications associated with OCV use in pregnancy. An attempt was made to reach out to key cholera vaccine researchers for unpublished data.

Given the large number of studies and evaluations related to safety of OCVs, the SAGE OCV working group made a decision to restrict the GRADE review to randomized controlled trials (RCTs) for the safety question, and to use observational studies as corroborating evidence. A decision was made to focus on data available since 2009 when the newer cholera vaccines became available and are now included in the OCV stockpile. For review of efficacy/effectiveness/duration and safety in pregnancy, all studies including RCTs and observational studies were included. Articles were not considered to be mutually exclusive and an article could provide evidence to answer more than one question of interest.

A total of 28 published studies were included in the GRADE review – 10 for vaccine safety, 20 for vaccine efficacy/effectiveness/duration of protection and 4 for safety among pregnant women.

Outcomes of interest for safety included any adverse event, any serious adverse event, and death. Efficacy, effectiveness, and duration outcomes included efficacy/effectiveness against any cholera (among all ages, <5 year olds, 5–14 year olds, and >14 year olds), efficacy/effectiveness against severe cholera (among all ages, <5 year olds, 5–14 year olds, and >14 year olds). duration for at least 6 months, duration for at least 3 years, and for a few studies duration at for at least 5 years. Safety during pregnancy outcomes of interest consisted of any adverse event, miscarriages, stillbirths, small for gestational age, congenital anomalies, preterm birth, low birth weight, and infant/neonatal death. However, no articles that were reviewed captured information on low birth weight, preterm birth and low birth weight.

A summary of the each publication was prepared using a standard template summarizing the study details, including the study setting, methods, results and limitations, and the details were verified by an additional reviewer. All publications were assessed and graded in terms of their risk of bias, level of indirectness, degree of imprecision, strength of association, and degree of residual confounding.

4.3. Results

Detailed results of the evidence and GRADE review and included in Appendix 2 and Appendix 3. The key results are summarized here.

Question: What is the evidence that the currently available killed, whole-cell oral cholera vaccines (OCVs) are safe among non-pregnant individuals (Dukoral ≥ 2 years old, Shanchol/Euvichol/mORCVax ≥ 1 year olds)?
Conclusion: High level of scientific evidence that the currently licensed OCVs are safe.

Question: What is the evidence for protective efficacy, effectiveness, and duration of the currently available killed, whole cell OCVs during the first 5 years following immunization among individuals ≥ 1 year old?
Conclusion: Moderate level of scientific evidence that the currently licensed oral cholera vaccines are efficacious and effective with duration of at least 6 months for a single dose. Moderate level of evidence that the currently available oral cholera vaccines with a 2-dose schedule are efficacious and effective for at least 3 years among adults, but not among young children 1 – 5 years old. There is low level of evidence that the currently available OCVs are effective for at least 5 years (only 2 studies).

Question: What is the evidence that the currently available killed, whole-cell oral cholera vaccines (OCVs) are safe among pregnant women?
Conclusion: Moderate level of scientific evidence that the currently licensed OCVs are safe for use during pregnancy.

An additional meta-analysis review has been conducted by the OCV working group of the GTFCC and led by Johns Hopkins University. The paper submitted for publication as attached as additional evidence (Appendix 4).

5. Proposed OCV Recommendations for SAGE Consideration

5.1. General Recommendations

1. Given the current availability of prequalified WC, killed, oral cholera vaccines (OCVs) and data on their safety, efficacy, field effectiveness, feasibility, impact and acceptability in cholera-affected populations, these vaccines should be used in areas with endemic cholera, in humanitarian crisis with high risk of cholera and during cholera outbreaks, in conjunction with other cholera prevention and control strategies.

2. Appropriate case management, WaSH interventions, surveillance and community mobilization remain cornerstones of cholera control. Vaccination is synergistic with those activities.

3. The main objective of vaccination is to reduce disease burden in vaccinated areas, through individual and herd protection, and to prevent the spatial expansion of outbreaks.

4. Mass vaccination campaigns are usually the most practical option for delivering oral cholera vaccines. Schools, religious institutions and other community settings can be appropriate venues for vaccination campaigns using fixed sites. Outreach activities can also be organized. Incorporating cholera vaccination with other vaccination activities can be an alternative or complementary strategy to mass campaigns.

5. Cholera vaccination mass campaigns should be accompanied by WaSH interventions and combined with other health-related interventions.

6. Epidemiological and laboratory surveillance is essential to estimate the burden of disease and understand the impact of vaccination and other interventions.

7. Equitable access to OCV should be ensured for underserved populations exposed to the risk of cholera. OCV stockpiles, supported by GAVI and managed by the ICG (for emergency type of use) and by the GTFCC OCV working group (for use in endemic settings), have been formally established in 2013 for that purpose. Requests to access OCV in any setting should follow the established mechanisms of stockpile management.

8. In all settings, a series of criteria should be considered to guide the decision to vaccinate,

    - The risk of cholera among targeted populations
    - The susceptibility and vulnerability of the population and the risk of spatial extension.
    - The capacity to cover as many persons as possible, eligible to receive the vaccine and living in the targeted area (e.g., ages ≥ 1 or 2 years, depending on the vaccine).
    - Programmatic factors such as the local capacity to organize and conduct a campaign, ability to provide other priority health interventions and population acceptability.

- Cholera vaccination should not be conducted if a campaign has been conducted in the previous 3 years in the same population (with consideration for the quality of the campaign, the vaccine coverage, and any population movements)

9. Countries and agencies accessing the OCV stockpiles should systematically implement M&E activities and provide accompanying data to WHO GTFCC. In particular, M&E activities should provide better estimates of,
    - The impact of OCV to control and prevent cholera outbreaks, including in humanitarian emergency situations
    - The impact of OCV on cholera transmission in endemic settings
    - The vaccine effectiveness using different vaccination strategies and in different age groups
    - The cost-effectiveness of different vaccination strategies and in various settings and age groups

    Guidelines have been developed for this purpose and are accessible on the WHO website.

10. Based on available evidence, there are considerable benefits and very few risks for including pregnant women in OCV vaccination campaigns.

11. OCV should be considered for emergency/relief workers who are likely to be directly exposed to cholera patients or to contaminated food or water, particularly those staying in areas with poor access to healthcare facilities.

12. Vaccination is generally not recommended for long- or short-term travelers to cholera-affected countries.

5.2. Control of Endemic Cholera

13. Cholera vaccination should be targeted in priority to high-risk areas or groups, regularly affected by cholera; with culture-confirmed cases detected in at least three out of the last five years and evidence of local transmission. Campaign planning should be carried out to ensure that vaccination takes place prior to any known cholera season.

14. Cholera vaccination in endemic areas should be contingent on multisectoral interventions as part of a long-term plan for cholera prevention and control endorsed at the local and national levels by the relevant ministries and should be budgeted for.

15. Universal vaccination (throughout a country without regard to risk) is not recommended in most countries.

16. Follow up campaigns in the same areas may be considered after 3 years in case of persistent transmission.

17. Strategies targeting specific age groups at higher risk may be considered.

5.3. Cholera Control in Humanitarian Emergencies

18. During humanitarian emergencies with a risk of cholera, but without current cholera outbreak, vaccination with OCV should systematically be considered to help prevent potential outbreaks, as an additional preparedness measure, depending on the local infrastructure (i.e., capacity to organize a vaccination campaign).

19. The decision to vaccinate should be guided by a thorough investigation of the current and historical epidemiological situation, an assessment of the actual risk of cholera, and a clear identification of geographical areas and populations to be targeted.

20. Campaign planning should be carried out to ensure that vaccination takes place prior to any known cholera season. Campaign preparation should be conducted early to ensure that vaccination starts immediately once the vaccines become available in country.

21. In areas of protracted emergencies, follow-up campaigns may be considered after 3 years (or less in case of persistent risk, particularly in case of population movement).

5.4. Control of Cholera Outbreaks

22. Cholera vaccination should systematically be considered to help prevent the spread of current outbreaks to new areas, following a thorough investigation of the current and historical epidemiological situation and a clear identification of geographical areas and populations to be targeted.

23. Campaign preparation should be conducted early to ensure that vaccination starts immediately once the vaccines become available in country.

24. Based on available evidence on short-term protection, a single dose strategy could be considered in areas experiencing cholera outbreaks. Considering the limited evidence about the duration of protection, additional vaccination might be needed to ensure longer-term protection.

5.5. Needs for additional research and evaluation

25. Vaccine coverage
    - Conducting coverage surveys focusing on missed vaccination in high-risk groups may provide essential information to improve overall impact and cost-effectiveness of OCV campaigns.
26. Adverse Events Following Immunization (AEFI)
    - As OCVs have been used extensively in multiple settings globally and have been proven to be safe, AEFI monitoring using routine passive surveillance based on country-level policies may be conducted. Active surveillance should be reserved for new delivery strategies or newer generation cholera vaccines as they become available.

27. Economic analysis
    - It is important to perform systematic economic analyses to measure intervention cost, cost effectiveness and cost benefit in different settings where campaigns have been conducted.
28. Vaccine efficacy and effectiveness
    - Additional research is needed to better inform number of doses, optimal dosing interval (dose spacing) and issues related to duration of protection in different settings. More information is needed on the effectiveness in children 1—5 years old.
    - Further assessment of herd protection is needed.
29. Vaccination impact
    - There is a need to further work on methodologies to measure the impact of vaccination by better defining relevant and meaningful comparison groups and identify standardized indicators across geographies and settings.
30. Alternative strategies of OCV delivery
    - Alternative delivery strategies such as self-administration, outside-the-cold-chain (CTC / ECTC), linking OCV with other health interventions should be further evaluated in a large variety of settings.
    - More information is needed on co-administration of OCV with other vaccines, especially with oral vaccines such as OPV and rotavirus vaccine.

6. Other Oral Cholera Vaccines in Development

a) Vaxchora (PaxVax Inc., USA) —Live Attenuated, Single Dose Oral Cholera Vaccine

The live, attenuated single-dose OCV manufactured in the United States called Vaxchora (manufactured by PaxVax has recently been licensed for adult travelers (18–64 years old) to cholera-affected areas who are between the ages of 18–64 years (http://paxvax.com/about/news/cdc-advisory-committee-immunization-practices-votes-recommend-vaxchora-paxvax%E2%80%99s-single). Vaxchora received marketing approval from the United States (U.S.) Food and Drug Administration (FDA) on June 10, 2016. Vaxchora was redeveloped from a previously available vaccine (Orochol/Mutachol) which was licensed in several countries[106] but manufacturing was discontinued as a result of corporate mergers.

Vaxchora protects against toxigenic strains of Vibrio cholera O1 but not against serogroups O139. It presents as a double-chambered aluminum foil sachet containing the vaccine strain CVD103-HgR. A cold chain (2-8°C) is required. No major safety issues have been detected. The most common adverse reactions were tiredness, headache, abdominal pain, nausea/vomiting, lack of appetite and diarrhea. Efficacy, based on challenge studies for the vaccine has been demonstrated to be approximately 60–90% with a duration of approximately 3 months[107]. Vaxchora is the only live single-dose vaccine for cholera currently licensed.

Additional information on Vaxchora is available at - https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2016-06/cholera-02-wong.pdf and elsewhere[108].

b) Hillchol (Hilleman Laboratories, India) — Modified killed whole cell vaccine with cholera toxin B subunit

A new killed OCV is under development by researchers at University of Goteborg and Hilleman Laboratories, India. The simplified production approach focuses on using one genetically engineered cholera El Tor Hikojima strain that undergoes a single inactivation method. Inclusion of a recombinant low cost cholera toxin with the B subunit in the new formulation would avoid the need for buffer co-administration, strict cold chain requirements, and would offer short term cross protection against enterotoxigenic (ETEC) diarrhea. This modified WC-rBS candidate has been shown to be immunogenic in mice. If shown to be safe and protective in humans, this option could result in lower manufacturing costs and substantially reduce OCV prices. Future work on a new oral mucosal adjuvant for a second generation version may further potentiate intestinal immune responses, leading to improved long term protection among all age groups.

c) Vibrio cholera 638 (Finlay Institute, Cuba) — live attenuated single dose cholera vaccine

A potential live attenuated candidate, Vibrio cholerae 638 is under development by researchers at the Finley Institute in Cuba. Researchers are currently attempting to simplify the production process by decreasing the number of strains and using a single inactivation mechanism in order to ultimately reduce the price. The vaccine candidate uses the vibrio cholera O1 El Tor Ogawa strain to formulate a single oral dose with the attempt to remove the virulence factor (CT) through CTXPhu and hapA deletion. This vaccine is within the Phase 2 and Phase 3 of development. The formulation, buffer, cold chain requirements, safety, efficacy, and duration are yet to be determined.

d) VA 1.3 and VA1.4 (India) — live attenuated single dose cholera vaccine

The Indian government is currently developing a live attenuated OCV, VA1.3 and VA1.4, that is in Phase 2 of the development process. The vaccine candidate uses the vibrio cholera O1 El Tor Ogawa (non-toxigenic) strain to formulate a single, oral dose. VA1.4 cholera vaccine is identical to VA1.3 except for absence of Ampicillin marker. The vaccine attempts to remove the main virulence factor through ctxB gene introduction using a series of genetic manipulations. Formulation, buffer, cold chain requirements, safety, efficacy, and duration are yet to be determined.

e) CholeraGarde (China) — live attenuated single dose cholera vaccine

Designed as a single dose candidate, the live attenuated oral cholera vaccine called CholeraGarde, is under development in China using the vibrio cholera O1 El Tor biotype and Inaba serotype. In attempt to remove the main virulence factor, researchers are working to genetically modify the strain through VCT and recA deletion. Formulation, buffer, cold chain requirements, safety, efficacy, and duration are yet to be determined. Phase 2 studies are ongoing to determine safety and immunogenicity.

f) OraVAX – currently commercialized, supplied through China and the Philippines

The currently commercialized vaccine, OraVax, uses the vibrio cholera O1 strain. The 3 dose enteric-coated capsule regimen does not require a buffer and is recommended for children (>10 years old) and adults. The main differences with Dukoral include no requirement for rBS (no buffer), the inclusion of 5 instead of 4 cholera strains, and potentially pricing.

Similar to Euvichol, non-inferiority evaluations with Shanchol are underway for another formulation of the whole cell, killed OCV - Cholvax (Incepta, Bangladesh). Once complete, the aim is to increase production capacity, enabling vaccination of large populations at risk in Bangladesh.

Table 12 lists the characteristics of the newer cholera vaccines and vaccine candidates.

Table 12: Key characteristics and features of other OCVs

Name	Vaxchora	Hillchol	Vibrio Cholerae 638	VA 1.3, 1.4	CholeraGarde	OraVAX
Target	Travelers ages 18-64 years	TBD	TBD	TBD	TBD	≥11 yo
Regimen	Single dose	Single dose	Single dose	Single dose	Single dose	3 doses (0, 7, and 28 days)
Duration of protection	~3 months	TBD	TBD	TBD	TBD	TBD
Age range for vaccination	18-64 years old	TBD	TBD	TBD	TBD	≥11 years old
Requirement for oral buffer	1 sachet of buffer	TBD	TBD	TBD	TBD	Buffer not required
Storage temperature	2-8°C	TBD	TBD	TBD	TBD	2-8°C
Shelf life	TBD	TBD	TBD	TBD	TBD	TBD
WHO Prequalification status	TBD	TBD	TBD	TBD	TBD	TBD
Price to the public sector (per dose)	TBD	TBD	TBD	TBD	TBD	~10$
Comments	Supplier country: US	Supplier country: India	Supplier country: Cuba	Supplier country: India	Supplier Country: China	Supplier country: China, Philippines

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Appendix 1: SAGE Working Group on Oral Cholera Vaccines

Oral Cholera Vaccine Working Group Members

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Additional Contributions

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Terms of Reference

- To analyze the results of the most recent research and M&E activities implemented during OCV campaigns since the 2010 WHO recommendation with a particular focus on communities' acceptability, safety of OCV, vaccine effectiveness in various settings, cost analysis, impact on cholera transmission in endemic and epidemic settings
- To review evidence and propose recommendations for use of OCV in pregnant and lactating women
- To review evidence and propose recommendations for use of OCV in travelers
- To review evidence and propose updated recommendations for vaccination strategies (Controlled Temperature Chain, single dose, self-administration, administration with other vaccines, ring vaccination)
- To critically discuss the 2010 WHO recommendations on OCV use and propose potential adjustments/revisions for endemic settings ("hotspots"), during humanitarian emergencies and during outbreaks
- To consider the perspectives of development of OCV and discuss the potential impact on the future of cholera control

Declaration of Interests
All members completed a declaration of interests form. One member reported relevant interests summarized below:

Thomas Wierzba

- His institution, the International Vaccine Institute (IV) received until 2014 a grant from the Bill & Melinda Gates Foundation (BMGF). His position as head of the IVI Cholera program, was in part funded through this grant. This interest was assessed as personal, specific and financially significant*.
- His institution received until 2014 a research grant from BMG to support Cholera vaccine development. This interest was assessed as personal, specific and financially significant*.

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* According to WHO's Guidelines for Declaration of Interests (WHO expert), an interest is considered "personal" if it generates financial or non-financial gain to the expert, such as consulting income or a patent. "Specificity" states whether the declared interest is a subject matter of the meeting or work to be undertaken. An interest has "financial significance" if the honoraria, consultancy fee or other received funding, including those received by expert's organization, from any single vaccine manufacturer or other vaccine-related company exceeds 5,000 USD in a calendar year. Likewise, a shareholding in any one vaccine manufacturer or other vaccine-related company in excess of 1,000 USD would also constitute a “significant shareholding”. Funding going to the SAGE member’s research unit needs to be declared. As per WHO assessment of conflicts of interests, “Institution” relates only to the expert’s research/or work unit, as subdivision of the department.

Appendix 2: SAGE Evidence to Recommendations Table

Question: Should the currently available whole cell, killed Oral cholera vaccines (OCVs) be recommended for use among persons ≥1 year old (Shanchol/Euvichol/mORCVax) or ≥ 2 years old (Dukoral), including pregnant women in different cholera endemic, epidemic/outbreak and humanitarian emergency settings?

Population: Individuals in different cholera endemic, epidemic/outbreak and humanitarian emergency settings.

Intervention: Killed, whole-cell oral cholera vaccines

Comparison: Placebo/no vaccination/other prevention and control measures (e.g. WASH)

Outcome: Cases of cholera

Background:

Cholera, an acute watery diarrheal disease, caused by toxigenic strains of the bacterium *Vibrio cholerae* O1 and O139, causes an estimated over 2.9 million cases and over 95,000 deaths annually in cholera endemic countries alone and frequent epidemics in other settings with poor water and sanitation infrastructure. Global estimates range from 1.4 –4.8 million cases and 28,000 – 142,000 deaths every year. The disease is characterized by acute onset watery diarrhea leading to rapid dehydration and death, if not promptly treated with fluid replacement and antibiotics for severe cases. Pregnant women are especially vulnerable from the dehydrating effects of cholera.

OCVs have been available since the 1990s and have been recommended previously by WHO (most recent position statement of 2010). Since 2010, large scale epidemics and surges in endemic cholera have continued to occur and have been compounded by multiple humanitarian emergency situations. In 2013, a global oral cholera vaccine stockpile was established. Several additional studies and evaluations have been conducted of OCV use in different endemic, outbreak and humanitarian emergency settings. Additional data is now available to review evidence for recommendations.

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a priority?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ■ *Varies* ☐	Cholera remains a significant public health problem globally. Global estimates range from 1.4 –4.8 million cases and 28,000 – 142,000	The global burden has significantly increased as a result of humanitarian emergencies (conflict situations, natural disasters and

			deaths every year. An estimated 2.9 million cases of cholera annually in 69 cholera endemic countries and 95,000 deaths during 2008–2012. Pregnant women are especially susceptible to adverse outcomes for themselves and the fetuses as a result of rapid dehydration. Cholera most often occurs among impoverished populations with limited access to health care resources.	environmental factors such as the El Nino phenomenon).
	Are a large number of people affected?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ■ *Varies* ☐	Global estimates range from 1.4 –4.8 million cases and 28,000 – 142,000 deaths every year. An estimated 2.9 million cases of cholera annually in 69 cholera endemic countries and 95,000 deaths during 2008–2012. In 2015, over 172,454 cases and 1,304 deaths were reported to the WHO by 42 countries with an overall case-fatality rate (CFR) of 0.8% (several countries reported high case fatality rates).	The reported numbers are largely underreported due to several factors – inadequate surveillance, fear of impact on trade and tourism etc.
BENEFITS & HARMS OF THE OPTIONS	Are the desirable anticipated effects large?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☐ *Varies* ■	The vaccines have been shown to be efficacious and effective in multiple settings. Additional data showing herd protection effects is also available. However, data on the actual impact on disease transmission is limited.	The impact is dependent on factors such as vaccine coverage. Data on coverage in most settings show that vaccination campaigns have been feasible and acceptable.
	Are the undesirable anticipated effects small?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ■ *Varies* ☐	Safety of the vaccines has been demonstrated in several different settings.	

	What is the overall certainty of this evidence?	No included studies: 28 ☐ Very low ☐ Low ■ Moderate ■ High	Moderate to high level of evidence.	In addition to the 28 studies included in the GRADE review, there are several other evaluations and observational studies that corroborate these findings.
VALUES	How certain is the relative importance of the desirable and undesirable outcomes?	☐ Important uncertainty or variability ☐ Possibly important uncertainty or variability ☐ Probably no important uncertainty or variability ☐ No important uncertainty or variability ■ No known undesirable outcomes	Vaccines have been shown to be safe and effective in multiple settings. No major adverse events have been demonstrated.	
	Are the desirable effects large relative to undesirable effects?	☐ No ☐ Probably No ☐ Uncertain ☐ Probably Yes ■ Yes ☐ Varies		
RESOURCE USE	Are the resources required small?	☐ No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☐ Yes ■ Varies	A global OCV stockpile was established in 2013 and is financially supported by Gavi, the Vaccine Alliance. Gavi also provides funding for operational costs of vaccinations campaigns. Based on the type of settings, the resources required to conduct vaccination activities have varied based on the setting.	Vaccines are available through the Gavi-supported stockpile. Additionally, manufacturers are working to reduce the cost of vaccine to a more affordable pricing.
	Is the incremental cost small relative to the net benefits?	☐ No ☐ Probably No ☐ Uncertain ■ Probably Yes ☐ Yes ☐ Varies	Several costing and cost-effectiveness studies have showed that cholera vaccination is cost-effective at the current vaccine pricing in high burden settings.	There is emphasis also on ensuring the OCVs are integrated into overall country and regional level cholera control plans.

EQUITY	What would be the impact on health inequities?	*Increased* ☐ *Probably increased* ☐ *Uncertain* ☐ *Probably reduced* ☐ *Reduced* ■ <u>Varies</u> ☐	This disease affects mainly populations in poor-resource settings with limited clean water, sanitation and hygiene. The intervention would reduce health-inequities across populations.	
ACCEPTABILITY	Is the option acceptable to key stakeholders?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ■ <u>*Varies*</u> ☐	Since the establishment of the OCV stockpile in 2013, over 7 million doses have been used in over 14 countries in multiple endemic, outbreak, and humanitarian emergency situations, and requests have been made by country-level stakeholders to the ICG. Therefore, it is assumed that the option is acceptable to key stakeholders.	
	Which option is acceptable to target group?	*Intervention* ■ *Comparison* ☐ *Both* ☐ *Neither* ☐ *Unclear* ☐	Multiple evaluations of vaccine coverage and knowledge, attitudes and practices have been conducted which have shown that vaccination has been feasible and acceptable in multiple settings.	
FEASIBILITY	Is the option feasible to implement?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ■ <u>*Varies*</u> ☐	The option will likely be feasible to implement in most settings, though limited access in the context of natural disasters or armed conflict may impede immediate implementation.	

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences *is closely balanced or uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings
	☐	☐	☐	☐	■

Type of recommendation	We recommend against the option ☐	We suggest considering the option ☐ Only in the context of rigorous research ☐ Only with targeted monitoring and evaluation ☐ Only in specific contexts	We recommend the option ■ **The recommendation applies to specific contexts, in specific (sub) populations and in conjunction with other prevention and control measures.**

Recommendation (text)	All recommendations are included in Section 5. Given the current availability of prequalified WC, killed, oral cholera vaccines (OCVs) and data on their safety, efficacy, field effectiveness, feasibility, impact and acceptability in cholera-affected populations, these vaccines should be used in areas with endemic cholera, in humanitarian crisis with high risk of cholera and during cholera outbreaks, in conjunction with other cholera prevention and control strategies such as appropriate case management, WaSH interventions, surveillance and community mobilization. Based on available evidence, there are considerable benefits and very few risks for including pregnant women in OCV vaccination campaigns.
Implementation considerations	Mass vaccination campaigns are usually the most practical option for delivering oral cholera vaccines. Schools, religious institutions and other community settings can be appropriate venues for vaccination campaigns using fixed sites. Outreach activities can also be organized. Incorporating cholera vaccination with other vaccination activities can be an alternative or complementary strategy to mass campaigns. Planning for campaigns should be done in a timely manner so vaccines can be used as soon as they arrive in country. It's beneficial to use vaccines as early as possible in outbreak situations.

Monitoring and evaluation	Monitoring and evaluation activities should be conducted to document experiences and understanding vaccine impact. These are also critical to be done if newer vaccines or newer delivery strategies are implemented.
Research priorities	It is important to perform systematic economic analyses to measure intervention cost, cost effectiveness and cost benefit in different settings where campaigns have been conducted. Additional research is needed to better inform number of doses, optimal dosing interval (dose spacing) and issues related to duration of protection in different settings. More information is needed on the effectiveness in children 1—5 years old. Further assessment of herd protection is needed. There is a need to further work on methodologies to measure the impact of vaccination by better defining relevant and meaningful comparison groups and identify standardized indicators across geographies and settings. Alternative delivery strategies such as self-administration, outside-the-cold-chain (CTC / ECTC), linking OCV with other health interventions should be further evaluated in a large variety of settings. More information is needed on co-administration of OCV with other vaccines, especially with oral vaccines such as OPV and rotavirus vaccine.

Appendix 3: Summary of Evidence GRADE Tables

Safety in general population

Population: Non-pregnant adults and children ≥ 1 year old (Shanchol/Euvichol/mORCVax) or ≥ 2 years old (Dukoral)
Intervention: 2 doses of the currently available killed, whole-cell oral cholera vaccines (OCVs)
Comparison: Placebo or no vaccine/placebo/ other prevention and control measures (e.g. WASH)
Outcome: Serious Adverse Events Following Immunization

What is the evidence that the currently available killed, whole-cell OCVs are safe among non-pregnant individuals (Dukoral ≥ 2 years old, Shanchol/Euvichol/mORCVax ≥ 1 year olds)?				
			Rating	Adjustment to Rating
Quality of Evidence	No. of studies/starting rating		10 RCT[1]	4
	Factors decreasing confidence	Limitation in study design	No serious	0
		Inconsistency	No serious	0
		Indirectness	No serious	0
		Imprecision	No serious	0
		Publication Bias	No serious	0
	Factors Increasing Confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			4
Summary of Findings	Statement on quality of evidence			Evidence supports a high level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome.
	Conclusion			High level of scientific evidence that the risk of serious adverse events following immunization when using the currently licensed OCVs is low.

[1] In addition to the randomized controlled trials, several field studies (field effectiveness and coverage surveys) have evaluated the occurrence of adverse events and the findings of these studies support the high level of evidence from the randomized controlled trials used for grading for safety outcomes.

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Safety in pregnant women

Population: Pregnant women
Intervention: 1-2 doses of the currently available killed, whole-cell oral cholera vaccines (OCVs)
Comparison: Placebo or no vaccine/placebo/ other prevention and control measures (e.g. WASaH)
Outcome: Pregnancy-specific maternal/fetal/neonatal serious adverse events following immunization

What is the evidence that the currently available killed, whole cell OCVs are safe in pregnancy?				
			Rating	Adjustment to Rating
Quality of Evidence	No. of studies/starting rating		1 RCT/ 3 Observational	4
	Factors decreasing confidence	Limitation in study design	Serious[1]	-2
		Inconsistency	No serious	0
		Indirectness	No serious	0
		Imprecision	No serious	0
		Publication Bias	No serious	0
	Factors Increasing Confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			2
Summary of Findings	Statement on quality of evidence			Evidence supports a limited level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome.
	Conclusion			Low level of scientific evidence that the currently licensed OCVs are safe for use during pregnancy.

[1] Kahn et al., the study was nested in a RCT, but not powered to detect a predefined a priory risk (no specific sample size calculation).The control group comprised pregnant women excluded from the trial in the baseline assessment for being pregnant (i.e. non-randomized women) Vaccinated and non-vaccinated pregnant women differed in the baseline risk for adverse pregnancy outcomes. The sample size was small (69 exposed and 69 non-exposed women included in the analysis).The assessment of the pregnancy outcomes was done retrospectively and the primary outcome was any adverse event (no adjusted estimates provided for specific adverse pregnancy outcomes).

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1. Grout L, Martinez-pino I, Ciglenecki I et al. Pregnancy Outcomes after a Mass Vaccination Campaign with an Oral Cholera Vaccine in Guinea: A Retrospective Cohort. *PLoS Negl Trop Dis* 2015. 9(12): e0004274
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3. Ali M, Nelson A, Luquero FJ, et al. Safety of a killed oral cholera vaccine (Shanchol) in pregnant women in Malawi: an observational cohort study. *Lancet Infect Dis* 2017.
4. Khan, Ashraful Islam et al. Safety of the oral cholera vaccine in pregnancy: Retrospective findings from a subgroup following mass vaccination campaign in Dhaka, Bangladesh. Vaccine 2017.

Efficacy and Effectiveness

Population: Non-pregnant adults and children ≥ 1 year old (Shanchol/Euvichol/mORCVax) or ≥ 2 years old (Dukoral)
Intervention: 2 doses of the currently available killed, whole-cell oral cholera vaccines (OCVs)
Comparison: Placebo or no vaccine/placebo/ other prevention and control measures (e.g. WASH)
Outcome: Cases of cholera

What is the evidence for protective efficacy and effectiveness against cholera (any severity) of the currently available killed, whole cell OCVs following immunization among individuals ≥ 1 year old?				
			Rating	Adjustment to Rating
Quality of Evidence	No. of studies/starting rating		11 RCT/ 7 observational	4
	Factors decreasing confidence	Limitation in study design	No serious	0
		Inconsistency	No serious	0
		Indirectness	No serious	0
		Imprecision	No serious	0
		Publication Bias	No serious	0
	Factors Increasing Confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			4
Summary of Findings	Statement on quality of evidence			Evidence supports a high level of confidence that the true effect lies close to that of the health outcome.
	Conclusion			High level of scientific evidence that the currently licensed oral cholera vaccines are efficacious and effective against cholera.

References:

1. Clemens JD, Sack DA, Harris JR et al. Field trial of oral cholera vaccines in Bangladesh: results from three-year follow-up et al. *Lancet* 1990; 335(8684): 270-273.
2. Sanchez JL, Vasquez B, Beque RE et al. Protective efficacy of oral whole-cell/recombinant-B-subunit cholera vaccine in Peruvian military recruits. *Lancet* 1994; 344(8932): 1273-1276.

3. Taylor DN, Cardenas V, Sanchez JL et al. Two-year study of the protective efficacy of the oral whole cell plus recombinant B subunit cholera vaccine in Peru. *JID* 2000; 181(5): 1667-1673.
4. Trach DD, Clemens JD, Ke NT et al. Field trial of a locally produced, killed, oral cholera vaccine in Vietnam. *Lancet* 1997; 349(9047): 231-235.
5. Sur D, Lopez AL, Kanungo S et al. Efficacy and safety of a modified killed-whole-cell oral cholera vaccine in India: an interim analysis of a cluster-randomised, double-blind, placebo-controlled trial. *Lancet* 2009; 374: 1694-1702.
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7. Desai SN, Akalu Z, Teshone S. A Randomized, Placebo-Controlled Trial Evaluating Safety and Immunogenicity of the Killed, Bivalent, Whole-Cell Oral Cholera Vaccine in Ethiopia. *Am J Trop Med Hyg* 2015; 93(3): 527-533.
8. Qadri, F, Wierzba TF, Ali M et al. Efficacy of a Single-Dose, Inactivated Oral Cholera Vaccine in Bangladesh. *NEJM* 2016; 374: 1723-1732.
9. Baik YO, Choi SK, Olveda RM et al. A randomized, non-inferiority trial comparing two bivalent killed, whole cell, oral cholera vaccines (Euvichol vs Shanchol) in the Philippines. *Vaccine* 2015; 33(46): 6360-6365.
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11. van Loon FPL, Clemens JD, Chakraborty MR et al. Field trial of inactivated oral cholera vaccines in Bangladesh: results from 5 years of follow-up. *Vaccine* 1996; 14(2): 162-166.
12. Lucas MES, Deen J, von Seidlein L et al. Effectiveness of Mass Oral Cholera Vaccination in Beira, Mozambique. *NEJM* 2005; 352: 757-767.
13. Khatib AM, Ali M, von Seidlein L et al. Effectiveness of an oral cholera vaccine in Zanzibar: findings from a mass vaccination campaign and observational cohort study. *Lancet* Inf Dis 2012; 12(11): 837-844.
14. Wierzba TF, Kar SK Mogasale VV et al. Effectiveness of an oral cholera vaccine campaign to prevent clinically-significant cholera in Odisha State, India. *Vaccine* 2015; 33(21): 2463-2469.
15. Ivers LC, Hilaire IJ, Almazor et al. Effectiveness of reactive oral cholera vaccination in rural Haiti: a case-control study and bias-indicator analysis. *Lancet Global Health* 2015; 3(3): 162-168.
16. Severe K, Rouzier V, Anglade SB et al. Effectiveness of Oral Cholera Vaccine in Haiti: 37-Month Follow-Up. *Am J Trop Med Hyg* 2016; 94(5): 1136-1942.
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18. Thiem VD, Deen JL, von Seidlein L et al. Long-term effectiveness against cholera of oral killed whole-cell vaccine produced in Vietnam. *Vaccine* 2006; 24(20): 4297-4303.

Efficacy and Effectiveness, severe cholera

Population: Non-pregnant adults and children ≥ 1 year old (Shanchol/Euvichol/mORCVax) or ≥ 2 years old (Dukoral)
Intervention: 2 doses of the currently available killed, whole-cell oral cholera vaccines (OCVs)
Comparison: Placebo or no vaccine/placebo/ other prevention and control measures (e.g. WASH)
Outcome: Cases of severe cholera

What is the evidence for protective efficacy and effectiveness against severe cholera of the currently available killed, whole cell OCVs among individuals ≥ 1 year old?				
			Rating	Adjustment to Rating
Quality of Evidence	No. of studies/starting rating		5 RCT/1 observational	4
	Factors decreasing confidence	Limitation in study design	No serious	0
		Inconsistency	No serious	0
		Indirectness	No serious	0
		Imprecision	No serious	0
		Publication Bias	No serious	0
	Factors Increasing Confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			4
Summary of Findings	Statement on quality of evidence			Evidence supports a high level of confidence that the true effect lies close to the effect on the health outcome.
	Conclusion			High level of scientific evidence that the currently licensed oral cholera vaccines are efficacious and effective in protecting against severe cholera.

References:

1. Clemens JD, Sack DA, Harris JR et al. Field trial of oral cholera vaccines in Bangladesh: results from three-year follow-up et al. *Lancet* 1990; 335(8684): 270-273.
2. Taylor DN, Cardenas V, Sanchez JL et al. Two-year study of the protective efficacy of the oral whole cell plus recombinant B subunit cholera vaccine in Peru. *JID* 2000; 181(5): 1667-1673.

3. Trach DD, Clemens JD, Ke NT et al. Field trial of a locally produced, killed, oral cholera vaccine in Vietnam. *Lancet* 1997; 349(9047): 231-235.
4. Qadri, F, Wierzba TF, Ali M et al. Efficacy of a Single-Dose, Inactivated Oral Cholera Vaccine in Bangladesh. *NEJM* 2016; 374: 1723-1732.
5. Qadri F, Ali M, Chowdhury F et al. Feasibility and effectiveness of oral cholera vaccine in an urban endemic setting in Bangladesh: a cluster randomised open-label trial. *Lancet* 2015; 386:1362-1371.
6. Lucas MES, Deen J, von Seidlein L et al. Effectiveness of Mass Oral Cholera Vaccination in Beira, Mozambique. *NEJM* 2005; 352: 757-767.

Efficacy and Effectiveness, <5 years old, any cholera

Population: Children <5 years of age
Intervention: 2 doses of the currently available killed, whole-cell oral cholera vaccines (OCVs)
Comparison: Placebo or no vaccine/placebo/ other prevention and control measures (e.g. WASH)
Outcome: Cases of cholera (any severity)

What is the evidence for protective efficacy and effectiveness against cholera (any severity) of the currently available killed, whole cell OCVs among individuals <5 years of age?				
			Rating	Adjustment to Rating
Quality of Evidence	No. of studies/starting rating		9 RCT/2 observational	4
	Factors decreasing confidence	Limitation in study design	No serious	0
		Inconsistency	No serious	0
		Indirectness	No serious	0
		Imprecision[1]	Serious	-1
		Publication Bias	No serious	0
	Factors Increasing Confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			3
Summary of Findings	Statement on quality of evidence			Evidence supports a moderate level of confidence that the true effect lies close to the effect of that of the estimate of the effect on the health outcome.
	Conclusion			Moderate level of scientific evidence that the currently licensed oral cholera vaccines are efficacious and effective against cholera (any severity).

[1] Most of the clinical trials were not powered to carryout sub-group analysis resulting in imprecise point estimates in children under-five.

References:

1. Clemens JD, Sack DA, Harris JR et al. Field trial of oral cholera vaccines in Bangladesh: results from three-year follow-up et al. *Lancet* 1990; 335(8684): 270-273.
2. Taylor DN, Cardenas V, Sanchez JL et al. Two-year study of the protective efficacy of the oral whole cell plus recombinant B subunit cholera vaccine in Peru. *JID* 2000; 181(5): 1667-1673.
3. Trach DD, Clemens JD, Ke NT et al. Field trial of a locally produced, killed, oral cholera vaccine in Vietnam. *Lancet* 1997; 349(9047): 231-235.
4. Sur D, Lopez AL, Kanungo S et al. Efficacy and safety of a modified killed-whole-cell oral cholera vaccine in India: an interim analysis of a cluster-randomised, double-blind, placebo-controlled trial. *Lancet* 2009; 374: 1694-1702.
5. Bhattacharya SK, Sur D, Ali M et al. 5 year efficacy of a bivalent killed whole-cell oral cholera vaccine in Kolkata, India: a cluster-randomised, double-blind, placebo-controlled trial. *Lancet* 2013; 13(12); 1050-1056.
6. Saha A, Chowdhury MI, Khanam F et al. Safety and immunogenicity study of a killed bivalent (O1 and O139) whole-cell oral cholera vaccine Shanchol, in Bangladeshi adults and children as young as 1 year of age. *Vaccine* 2011; 29(46): 8285-8295.
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8. Qadri, F, Wierzba TF, Ali M et al. Efficacy of a Single-Dose, Inactivated Oral Cholera Vaccine in Bangladesh. *NEJM* 2016; 374: 1723-1732.
9. Bhattacharya SK, Sur D, Ali M et al. 5 year efficacy of a bivalent killed whole-cell oral cholera vaccine in Kolkata, India: a cluster-randomised, double-blind, placebo-controlled trial. *Lancet* 2013; 13(12); 1050-1056.
10. Lucas MES, Deen J, von Seidlein L et al. Effectiveness of Mass Oral Cholera Vaccination in Beira, Mozambique. *NEJM* 2005; 352: 757-767.
11. Ivers LC, Hilaire IJ, Almazor et al. Effectiveness of reactive oral cholera vaccination in rural Haiti: a case-control study and bias-indicator analysis. *Lancet Global Health* 2015; 3(3): 162-168.

Efficacy and Effectiveness, <5 years old, severe cholera

Population: Children <5 years of age
Intervention: 2 doses of the currently available killed, whole-cell oral cholera vaccines (OCVs)
Comparison: Placebo or no vaccine/placebo/ other prevention and control measures (e.g. WASH)
Outcome: Cases of severe cholera

What is the evidence for protective efficacy and effectiveness against severe cholera of the currently available killed, whole cell OCVs among individuals <5 years of age?				
			Rating	Adjustment to Rating
Quality of Evidence	No. of studies/starting rating		2 RCT	4
	Factors decreasing confidence	Limitation in study design	No serious	0
		Inconsistency	No serious	0
		Indirectness	No serious	0
		Imprecision[1]	No serious	-1
		Publication Bias	No serious	0
	Factors Increasing Confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			4
Summary of Findings	Statement on quality of evidence			Evidence supports a moderate level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome.
	Conclusion			Moderate level of scientific evidence that the currently licensed oral cholera vaccines are efficacious and effective against severe cholera in children under 5.

[1]Most of the clinical trials were not powered to carryout sub-group analysis resulting in imprecise point estimates in children under-five.

References:

1. Qadri, F, Wierzba TF, Ali M et al. Efficacy of a Single-Dose, Inactivated Oral Cholera Vaccine in Bangladesh. *NEJM* 2016; 374: 1723-1732.
2. Qadri F, Ali M, Chowdhury F et al. Feasibility and effectiveness of oral cholera vaccine in an urban endemic setting in Bangladesh: a cluster randomised open-label trial. *Lancet* 2015; 386:1362-1371.

Efficacy and Effectiveness, 5-14 years old, any cholera

Population: Children and adolescents 5-14 years of age
Intervention: 2 doses of the currently available killed, whole-cell oral cholera vaccines (OCVs)
Comparison: Placebo or no vaccine/placebo/ other prevention and control measures (e.g. WASH)
Outcome: Cases of cholera (any severity)

<table>
<tr><td colspan="5">What is the evidence for protective efficacy and effectiveness against cholera (any severity) of the currently available killed, whole cell OCVs among individuals 5-14 years of age old?</td></tr>
<tr><td colspan="3"></td><td>Rating</td><td>Adjustment to Rating</td></tr>
<tr><td rowspan="10">Quality of Evidence</td><td colspan="2">No. of studies/starting rating</td><td>7 RCT</td><td>4</td></tr>
<tr><td rowspan="5">Factors decreasing confidence</td><td>Limitation in study design</td><td>No serious</td><td>0</td></tr>
<tr><td>Inconsistency</td><td>No serious</td><td>0</td></tr>
<tr><td>Indirectness</td><td>No serious</td><td>0</td></tr>
<tr><td>Imprecision</td><td>No serious</td><td>0</td></tr>
<tr><td>Publication Bias</td><td>No serious</td><td>0</td></tr>
<tr><td rowspan="3">Factors Increasing Confidence</td><td>Large effect</td><td>Not applicable</td><td>0</td></tr>
<tr><td>Dose-response</td><td>Not applicable</td><td>0</td></tr>
<tr><td>Antagonistic bias and confounding</td><td>Not applicable</td><td>0</td></tr>
<tr><td colspan="3">Final numerical rating of quality of evidence</td><td>4</td></tr>
<tr><td rowspan="2">Summary of Findings</td><td colspan="3">Statement on quality of evidence</td><td>Evidence supports a high level of confidence that the true effect lies close to that of the estimate on the effect of the health outcome.</td></tr>
<tr><td colspan="3">Conclusion</td><td>High level of scientific evidence that the currently licensed oral cholera vaccines are efficacious and effective against cholera of any severity in individuals 5-14 years of age.</td></tr>
</table>

References:

1. Taylor DN, Cardenas V, Sanchez JL et al. Two-year study of the protective efficacy of the oral whole cell plus recombinant B subunit cholera vaccine in Peru. *JID* 2000; 181(5): 1667-1673.
2. Sur D, Lopez AL, Kanungo S et al. Efficacy and safety of a modified killed-whole-cell oral cholera vaccine in India: an interim analysis of a cluster-randomised, double-blind, placebo-controlled trial. *Lancet* 2009; 374: 1694-1702.
3. Bhattacharya SK, Sur D, Ali M et al. 5 year efficacy of a bivalent killed whole-cell oral cholera vaccine in Kolkata, India: a cluster-randomised, double-blind, placebo-controlled trial. *Lancet* 2013; 13(12); 1050-1056.
4. Saha A, Chowdhury MI, Khanam F et al. Safety and immunogenicity study of a killed bivalent (O1 and O139) whole-cell oral cholera vaccine Shanchol, in Bangladeshi adults and children as young as 1 year of age. *Vaccine* 2011; 29(46): 8285-8295.
5. Desai SN, Akalu Z, Teshone S. A Randomized, Placebo-Controlled Trial Evaluating Safety and Immunogenicity of the Killed, Bivalent, Whole-Cell Oral Cholera Vaccine in Ethiopia. *Am J Trop Med Hyg* 2015; 93(3): 527-533.
6. Qadri, F, Wierzba TF, Ali M et al. Efficacy of a Single-Dose, Inactivated Oral Cholera Vaccine in Bangladesh. *NEJM* 2016; 374: 1723-1732.
7. Bhattacharya SK, Sur D, Ali M et al. 5 year efficacy of a bivalent killed whole-cell oral cholera vaccine in Kolkata, India: a cluster-randomised, double-blind, placebo-controlled trial. *Lancet* 2013; 13(12); 1050-1056.

Efficacy and Effectiveness, 5-14 years old, severe cholera

Population: Children and adolescents 5-14 years of age
Intervention: 2 doses of the currently available killed, whole-cell oral cholera vaccines (OCVs)
Comparison: Placebo or no vaccine/placebo/ other prevention and control measures (e.g. WASH)
Outcome: Cases of severe cholera

What is the evidence for protective efficacy and effectiveness against severe cholera of the currently available killed, whole cell OCVs among individuals 5-14 years of age?				
			Rating	Adjustment to Rating
Quality of Evidence	No. of studies/starting rating		2 RCT	4
	Factors decreasing confidence	Limitation in study design	No serious	0
		Inconsistency	No serious	0
		Indirectness	No serious	0
		Imprecision	No serious	0
		Publication Bias	No serious	0
	Factors Increasing Confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			4
Summary of Findings	Statement on quality of evidence			Evidence supports a high level of confidence that the true effect lies close to the estimate of the effect on the health outcome.
	Conclusion			High level of scientific evidence that the currently licensed oral cholera vaccines are efficacious and effective in children and adolescents 5-14 years against severe cholera.

References:

1. Qadri, F, Wierzba TF, Ali M et al. Efficacy of a Single-Dose, Inactivated Oral Cholera Vaccine in Bangladesh. *NEJM* 2016; 374: 1723-1732.
2. Qadri F, Ali M, Chowdhury F et al. Feasibility and effectiveness of oral cholera vaccine in an urban endemic setting in Bangladesh: a cluster randomised open-label trial. *Lancet* 2015; 386:1362-1371.

Efficacy and Effectiveness, >14 years old, any cholera

Population: Adolescents and adults >14 years of age
Intervention: 2 doses of the currently available killed, whole-cell oral cholera vaccines (OCVs)
Comparison: Placebo or no vaccine/placebo/ other prevention and control measures (e.g. WASH)
Outcome: Cases of cholera

What is the evidence for protective efficacy and effectiveness against cholera (any severity) of the currently available killed, whole cell OCVs among individuals ≥ 14 years of age?				
			Rating	Adjustment to Rating
Quality of Evidence	No. of studies/starting rating		9 RCT/2 Observational	4
	Factors decreasing confidence	Limitation in study design	No serious	0
		Inconsistency	No serious	0
		Indirectness	No serious	0
		Imprecision	No serious	0
		Publication Bias	No serious	0
	Factors Increasing Confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			4
Summary of Findings	Statement on quality of evidence			Evidence supports a high level of confidence that the true effect lies close to the estimate of the effect on the health outcome.
	Conclusion			High level of scientific evidence that the currently licensed oral cholera vaccines are efficacious and effective in individuals >14 years of age against cholera.

References:

1. Clemens JD, Sack DA, Harris JR et al. Field trial of oral cholera vaccines in Bangladesh: results from three-year follow-up et al. *Lancet* 1990; 335(8684): 270-273.
2. Taylor DN, Cardenas V, Sanchez JL et al. Two-year study of the protective efficacy of the oral whole cell plus recombinant B subunit cholera vaccine in Peru. *JID* 2000; 181(5): 1667-1673.
3. Trach DD, Clemens JD, Ke NT et al. Field trial of a locally produced, killed, oral cholera vaccine in Vietnam. *Lancet* 1997; 349(9047): 231-235.
4. Sur D, Lopez AL, Kanungo S et al. Efficacy and safety of a modified killed-whole-cell oral cholera vaccine in India: an interim analysis of a cluster-randomised, double-blind, placebo-controlled trial. *Lancet* 2009; 374: 1694-1702.
5. Bhattacharya SK, Sur D, Ali M et al. 5 year efficacy of a bivalent killed whole-cell oral cholera vaccine in Kolkata, India: a cluster-randomised, double-blind, placebo-controlled trial. *Lancet* 2013; 13(12); 1050-1056.
6. Saha A, Chowdhury MI, Khanam F et al. Safety and immunogenicity study of a killed bivalent (O1 and O139) whole-cell oral cholera vaccine Shanchol, in Bangladeshi adults and children as young as 1 year of age. *Vaccine* 2011; 29(46): 8285-8295.
7. Desai SN, Akalu Z, Teshone S. A Randomized, Placebo-Controlled Trial Evaluating Safety and Immunogenicity of the Killed, Bivalent, Whole-Cell Oral Cholera Vaccine in Ethiopia. *Am J Trop Med Hyg* 2015; 93(3): 527-533.
8. Qadri, F, Wierzba TF, Ali M et al. Efficacy of a Single-Dose, Inactivated Oral Cholera Vaccine in Bangladesh. *NEJM* 2016; 374: 1723-1732.
9. van Loon FPL, Clemens JD, Chakraborty MR et al. Field trial of inactivated oral cholera vaccines in Bangladesh: results from 5 years of follow-up. *Vaccine* 1996; 14(2): 162-166.
10. Lucas MES, Deen J, von Seidlein L et al. Effectiveness of Mass Oral Cholera Vaccination in Beira, Mozambique. *NEJM* 2005; 352: 757-767.
11. Ivers LC, Hilaire IJ, Almazor et al. Effectiveness of reactive oral cholera vaccination in rural Haiti: a case-control study and bias-indicator analysis. *Lancet Global Health* 2015; 3(3): 162-168.

Efficacy and Effectiveness, >14 years old, severe cholera

Population: Adolescents and adults >14 years of age
Intervention: 2 doses of the currently available killed, whole-cell oral cholera vaccines (OCVs)
Comparison: Placebo or no vaccine/placebo/ other prevention and control measures (e.g. WASH)
Outcome: Cases of severe cholera

What is the evidence for protective efficacy and effectiveness against severe cholera of the currently available killed, whole cell OCVs among individuals ≥ 14 years of age?				
			Rating	Adjustment to Rating
Quality of Evidence	No. of studies/starting rating		2 RCT	4
	Factors decreasing confidence	Limitation in study design	No serious	0
		Inconsistency	No serious	0
		Indirectness	No serious	0
		Imprecision	No serious	0
		Publication Bias	No serious	0
	Factors Increasing Confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			4
Summary of Findings	Statement on quality of evidence			Evidence supports a high level of confidence that the true effect lies close to the estimate of the effect on the health outcome.
	Conclusion			High level of scientific evidence that the currently licensed oral cholera vaccines are efficacious and effective against severe cholera in individuals over 14 years of age.

References:

1. Qadri, F, Wierzba TF, Ali M et al. Efficacy of a Single-Dose, Inactivated Oral Cholera Vaccine in Bangladesh. *NEJM* 2016; 374: 1723-1732.
2. Qadri F, Ali M, Chowdhury F et al. Feasibility and effectiveness of oral cholera vaccine in an urban endemic setting in Bangladesh: a cluster randomised open-label trial. *Lancet* 2015; 386:1362-1371.

Efficacy and Effectiveness of a single dose

Population: Non-pregnant adults and children ≥ 1 year old (Shanchol/Euvichol/mORCVax) or ≥ 2 years old (Dukoral)
Intervention: Single dose of the currently available killed, whole-cell oral cholera vaccines (OCVs)
Comparison: Placebo or no vaccine/placebo/ other prevention and control measures (e.g. WASH)
Outcome: Cases of cholera

What is the evidence for protective efficacy and effectiveness of a single dose of the currently available killed, whole cell OCVs among individuals ≥ 1 year old?				
			Rating	Adjustment to Rating
Quality of Evidence	No. of studies/starting rating		1 RCT/ 3 Observational	4
	Factors decreasing confidence	Limitation in study design	No serious	0
		Inconsistency	No serious	0
		Indirectness	No serious	0
		Imprecision	No serious	0
		Publication Bias	No serious	0
	Factors Increasing Confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			4
Summary of Findings	Statement on quality of evidence			Evidence supports a high level of confidence that the true effect lies close to the estimate of the effect on the health outcome.
	Conclusion			High level of scientific evidence that the currently licensed oral cholera vaccines are efficacious for at least 6 months using a single dose.

References:

1. Qadri, F, Wierzba TF, Ali M et al. Efficacy of a Single-Dose, Inactivated Oral Cholera Vaccine in Bangladesh. *NEJM* 2016; 374: 1723-1732.
2. Khatib AM, Ali M, von Seidlein L et al. Effectiveness of an oral cholera vaccine in Zanzibar: findings from a mass vaccination campaign and observational cohort study. *Lancet* Inf Dis 2012; 12(11): 837-844.
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4. Ivers LC, Hilaire IJ, Almazor et al. Effectiveness of reactive oral cholera vaccination in rural Haiti: a case-control study and bias-indicator analysis. *Lancet Global Health* 2015; 3(3): 162-168.
5. Azman AS et al. Effectiveness of one dose of oral cholera vaccine in response to an outbreak: a case-cohort study. Lancet Glob Health. 2016 Nov;4(11):e856-e863.

Duration of protection for at least 3 years

Population: Non-pregnant adults and children ≥ 1 year old (Shanchol/Euvichol/mORCVax) or ≥ 2 years old (Dukoral)
Intervention: 2 doses of the currently available killed, whole-cell oral cholera vaccines (OCVs)
Comparison: Placebo or no vaccine/placebo/ other prevention and control measures (e.g. WASH)
Outcome: Cases of cholera

What is the evidence for protective efficacy, effectiveness, and duration of the currently available killed, whole cell OCVs during the first 3 years following immunization among individuals ≥ 1 year old?				
			Rating	Adjustment to Rating
Quality of Evidence	No. of studies/starting rating		3 RCT/ 2 Observational	4
	Factors decreasing confidence	Limitation in study design	No serious	0
		Inconsistency	No serious	0
		Indirectness	No serious	0
		Imprecision	No serious	0
		Publication Bias	No serious	0
	Factors Increasing Confidence	Large effect[2]	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			4
Summary of Findings	Statement on quality of evidence			Evidence supports a high level of confidence that the true effect lies close to the estimate of the effect on the health outcome
	Conclusion			High level of evidence that the currently available oral cholera vaccines with a 2-dose schedule are efficacious and effective for at least 3 years among adults, but not among young children 1 – 5 years old.

References:

1. Clemens JD, Sack DA, Harris JR et al. Field trial of oral cholera vaccines in Bangladesh: results from three-year follow-up et al. *Lancet* 1990; 335(8684): 270-273.
2. Bhattacharya SK, Sur D, Ali M et al. 5 year efficacy of a bivalent killed whole-cell oral cholera vaccine in Kolkata, India: a cluster-randomised, double-blind, placebo-controlled trial. *Lancet* 2013; 13(12); 1050-1056.
3. van Loon FPL, Clemens JD, Chakraborty MR et al. Field trial of inactivated oral cholera vaccines in Bangladesh: results from 5 years of follow-up. *Vaccine* 1996; 14(2): 162-166.
4. Severe K, Rouzier V, Anglade SB et al. Effectiveness of Oral Cholera Vaccine in Haiti: 37-Month Follow-Up. *Am J Trop Med Hyg* 2016; 94(5): 1136-1942.
5. Thiem VD, Deen JL, von Seidlein L et al. Long-term effectiveness against cholera of oral killed whole-cell vaccine produced in Vietnam. *Vaccine* 2006; 24(20): 4297-4303.

Duration of protection for at least 5 years

Population: Non-pregnant adults and children ≥ 1 year old (Shanchol/Euvichol/mORCVax) or ≥ 2 years old (Dukoral)
Intervention: 2 doses of the currently available killed, whole-cell oral cholera vaccines (OCVs)
Comparison: Placebo or no vaccine/placebo/ other prevention and control measures (e.g. WASH)
Outcome: Cases of cholera

What is the evidence for protective efficacy, effectiveness, and duration of the currently available killed, whole cell OCVs during the first 5 years following immunization among individuals ≥ 1 year old?				
			Rating	Adjustment to Rating
Quality of Evidence	No. of studies/starting rating		1 RCT/ 1 Observational	4
	Factors decreasing confidence	Limitation in study design	Serious[1]	-1
		Inconsistency	No serious	0
		Indirectness	No serious	0
		Imprecision	Serious[2]	-1
		Publication Bias	No serious	0
	Factors Increasing Confidence	Large effect[2]	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of quality of evidence			2
Summary of Findings	Statement on quality of evidence			Evidence supports a limited level of confidence that the true effect lies close to the estimate of the effect on the health outcome
	Conclusion			Low level of evidence that the currently available oral cholera vaccines with a 2-dose schedule are efficacious and effective for at least 5 years.

[1] High rate of loss to follow-up.
[2]Downgraded as there were small sample sizes included in the studies to assess the outcome of duration of protection.

References:

1. Bhattacharya SK, Sur D, Ali M et al. 5 year efficacy of a bivalent killed whole-cell oral cholera vaccine in Kolkata, India: a cluster-randomised, double-blind, placebo-controlled trial. *Lancet* 2013; 13(12); 1050-1056.
2. van Loon FPL, Clemens JD, Chakraborty MR et al. Field trial of inactivated oral cholera vaccines in Bangladesh: results from 5 years of follow-up. *Vaccine* 1996; 14(2): 162-166.

Appendix 4: Submitted Manuscript (protection Against Cholera from Killed Whole Cell Oral Cholera Vaccines: A Systematic Review and Meta-analysis

See PDF Attachment

Protection Against Cholera from Killed Whole Cell Oral Cholera Vaccines: A Systematic Review and Meta-analysis

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Abstract

Background: Killed whole-cell oral cholera vaccines (kOCVs) are becoming a standard cholera control and prevention tool. However, vaccine efficacy and effectiveness estimates have been variable, with differences in study design, location, follow-up duration and vaccines, posing challenges for public health decision making.

Methods: For this systematic review and meta-analysis, we searched PubMed, Embase, Scopus, Cochrane Review Library and ISI Web of Science for trials and observational studies reporting estimates of protection against medically-attended confirmed cholera conferred by kOCVs. We extracted the primary efficacy/effectiveness estimates from each study and estimates by number of vaccine doses, duration and age-group. The main study outcome was average efficacy/effectiveness of two kOCV doses, which were estimated with random effect models.

Findings: Seven trials and six observational studies met the inclusion criteria with an average two-dose efficacy of 58% (95%CI 42–69,I^2=58%) and effectiveness of 76% (95%CI 62–85,I^2=0%). Average two-dose efficacy among children under five years old is less than half of that in those five or older. ($p<0{\cdot}0001$). Two-dose efficacy is similar in the two years following vaccination but diminishes by the fourth year (26%, 95%CI -46–63). One-dose effectiveness within the first year is 69% (95%CI 35-85,I^2=62%) and the only short-term efficacy study reported an estimate of 40% after six months.

Interpretation: Two kOCV doses provide protection against cholera for at least three years. One kOCV dose provides protection at-least in the short-term, which has important implications for outbreak management. kOCVs are effective tools for cholera control programs.

Funding: The Bill and Melinda Gates Foundation

Research in context

Evidence before this study

Killed oral cholera vaccines (kOCVs) are increasingly becoming a standard cholera prevention and control tool, although a clear synthesis of the evidence supporting the degree of vaccine derived protection is lacking. A single systematic review of oral cholera vaccines, both live and killed, covered only early efficacy and safety trials. Their results showed moderate vaccine efficacy of two years after vaccination with two-doses of kOCVs, and no data from subsequent years were available. Children under five years of age were observed to have lower efficacy than those five and older.

Added value of this study

Our study builds upon the previous review of the efficacy of kOCVs by incorporating the relatively large body of additional evidence generated since 2010, including nearly all the evidence generated with the most widely used vaccine, Shanchol. In contrast with the previous review, our study incorporates field-effectiveness studies that are of greater relevance to field use and conducts in-depth sub-analysis to help elucidate the heterogeneity in efficacy/effectiveness estimates. We found that average two-dose efficacy is similar during the first two years after vaccination and begins to decline in the third year with no significant protection in the fourth year. However, in contrast, one large clinical trial estimated high-levels of protection in the fifth-year post vaccination. Short-term effectiveness (the first year after vaccination) is similar between one-dose and two-dose regimens. Even with the inclusion of new evidence, children under 5-year old are only about half as protected as those aged 5 years and older. Finally, we found that the median age of cases enrolled in studies had a strong positive relationship with the estimated level of protection conferred by the vaccine, which helps explain some of the differences between estimates.

Implications of all the available evidence

kOCVs can provide medium to high levels of protection for at least three years, if not longer, when provided as the standard two-dose regimen. One dose can provide similar levels of short-term protection as two doses, making it a practical option in outbreaks where a rapid reduction in short-term risk is needed. More research is needed to understand duration of protection of both one-dose and two-dose regimens and to understand if, and when, booster doses should be provided.

Introduction

For years, cholera vaccines were used infrequently due to evidence gaps, lack of an affordable vaccine, vaccine supply constraints and concerns of diverting resources from other cholera-related interventions. Killed whole-cell oral cholera vaccines (kOCVs) are now becoming part of the standard cholera control and prevention toolkit, joining water, sanitation and hygiene, surveillance and case management interventions.[1] While kOCVs have been used across multiple settings and have been shown to be safe and immunogenic,[2–4] effectiveness and efficacy studies have provided a wide range of effect estimates,[5–9] hindering clear communication to policy makers and clinicians.

The current formulation of kOCVs are like those first developed in the 1970s and 1980s,[10] including killed *Vibrio cholerae* whole cells from both main serotypes, Ogawa and Inaba, with the main antigen being the lipopolysaccharide (LPS) of killed bacteria. The vaccines' LPS concentration has increased since the original vaccines and some kOCVs contain the cholera toxin B-subunit, which was shown to provide no added protection.[10] The currently available vaccines are all licensed as two-dose regimens, although single-dose regimens have recently been tested and suggested as a possibility in outbreak situations or when vaccine supply is limited.

In 2013, a global stockpile of kOCV was created by the World Health Organization (WHO) to ensure vaccine availability for cholera control in outbreaks or humanitarian crises.[12] Gavi, the Vaccine Alliance (Gavi) later committed to fund up to 70-million doses (~$1.85/dose), from 2014 to 2018 to expand the support for vaccination in emergency and non-emergency ('hotspot') settings through the stockpile.[13] Although travellers commonly use kOCVs,[14] most of the world's supply of kOCV is managed and deployed through these stockpiles. Countries wishing to use these vaccines must apply through either the emergency or non-emergency mechanisms, under the responsibility of the International Coordinating Group (ICG) or the Global Task Force on Cholera Control (GTFCC), respectively.[1] Supply of kOCV remains limited compared to the at-risk population size.[15] However, creation of these stockpiles combined with the WHO pre-qualification of a third kOCV, Euvichol (Eubiologics, Seoul, Republic of Korea), in 2015, led to increased availability of these vaccines, opening the possibility for larger campaigns and the broader introduction of the vaccine in high-burden areas.[16]

We present the results of a systematic review and meta-analysis of the published literature on the efficacy and effectiveness of kOCVs. While the public health impact of kOCVs is derived from both the direct protection in vaccinated individuals and the indirect ('herd') protection in both vaccinated and unvaccinated individuals, we focus this review on direct vaccine protection. We summarize the current state of evidence for the kOCV-protection to aid clinicians and public health decision-makers in making rational decisions regarding vaccine use at the individual- and population-levels.

Methods

Search Strategy and Selection Criteria

This systematic review and meta-analysis adhered to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines and is registered in the systematic review registry PROSPERO (2016:CRD42016048232).

We searched PubMed, Embase, Scopus, and the Cochrane Review Library databases on 9-July-2016 and ISI Web of Science on 11-July-2016 for articles containing 'cholera' and 'vaccine' and ('efficacy' or 'effectiveness' or 'protect') in the title or abstract (supplement). We imposed no restrictions on publication date or language. We consulted GTFCC members to identify additional publications.

Definitions and Outcomes

We defined vaccine efficacy as the relative reduction in confirmed cholera risk comparing individuals that received the vaccine to those who did not, as estimated by a randomised clinical trial (RCT). We defined vaccine effectiveness as the relative reduction in risk of confirmed cholera in vaccinated compared to unvaccinated individuals as measured by a case-control, cohort, or case-cohort study. Confirmed cholera was defined as the presence of *Vibrio cholerae* in stool/rectal-swab as determined by PCR, culture, or rapid test.

Data extraction

Two reviewers independently assessed each abstract for inclusion in the full text review, with differences resolved by discussion and consensus. Abstracts in English, Spanish, French, or Chinese were reviewed. Each article was categorized and flagged for full text review if they reported direct or total vaccine efficacy,[17] from a randomized clinical trial, or effectiveness, from an observational study.

During the full text review, both reviewers independently extracted data from manuscripts with primary estimates of direct or total vaccine effectiveness or efficacy into an electronic database, with differences resolved by discussion and consensus. Secondary estimates from trials (e.g., re-analyses in separate manuscripts) using alternative statistical methods or measures of protection were not extracted. We extracted relevant data from text, figures, and tables, and contacted publication authors when data were missing.

We extracted the primary efficacy/effectiveness estimates from each study, and all secondary estimates by number of vaccine doses, duration, and age-group. The main outcomes from these meta-analyses are average efficacy and effectiveness of two kOCV doses. Given the multiple estimates, and often multiple manuscripts, from each study, we focused the primary analyses on estimates of two-dose protection reflecting the duration of the primary study endpoint. For each estimate we extracted the following data: study design, study site, inclusion criteria, vaccine type (Whole-cell [WC] or Whole-cell with B-subunit [WC-BS]), vaccination period, study follow-up period, method of case confirmation, efficacy/effectiveness estimate and 95% confidence intervals, number of vaccinated/unvaccinated cases/controls, number of doses, delay between doses (if more than one), vaccine coverage, age distribution of cases, and serotype and biotype distribution of cases. Extracted data and codebook are available at https://github.com/HopkinsIDD/ocv-VE-review.

Statistical Analyses

We used the reported point estimates of vaccine efficacy/effectiveness and 95% confidence intervals to calculate the standard error of each. For those reporting 1-sided confidence intervals, we re-constructed two-sided 95% confidence intervals using standard (asymptotic) methods.[18] Conditional on these standard errors, we estimated the average vaccine efficacy and effectiveness using random effect models with an empirical Bayes estimator of the between-study variance (τ^2) using the *metafor* package in R.[19,20] We assessed heterogeneity using the I^2 statistic, which is interpreted as the proportion of the total variation in the estimates due to the heterogeneity between studies as opposed to sampling variance.[20] We tested for differences between sub-groups by fitting linear meta-regression models with the subgroup added as a moderator and conducted a Wald Test for the subgroup effect estimate.[21]

Given that individual estimates of vaccine protection represent protection over different time frames from vaccination, we calculated the inverse-variance weighted mean duration of each average estimate to aid in interpreting our results.

Role of the Funding Source

This study was funded by the Bill and Melinda Gates Foundation through a grant to the GTFCC secretariat. The funders had no role in the design and analysis of the research, nor the decision to publish the results.

Results

Search Results

We identified 6,223 records through the database search and one through consultation with experts (Figure 1). Thirty-three publications were eligible for full-text review and 19 met the inclusion criteria for data abstraction. We extracted data from seven clinical trials (13 publications) and six observational studies (six publications), with only two clinical trials conducted outside of Asia and observational studies coming from Africa(4), Asia(1) and the Americas(1).

The seven efficacy studies included in the analyses were randomized placebo-controlled trials,[5,9,24,29,30] except for two with no placebo, [26,28] with randomization at the individual-[5,9,24,29], household- and neighbourhood-levels.[6,26,28] In all efficacy studies, cholera was culture-confirmed . Two trials included a three-dose regimen as their primary end-point,[5,9] four used two doses[6,24,26,28] and one used one dose.[29] The duration between the first two vaccine doses in trials ranged from 14-42 days.[6,9]

The six effectiveness studies eligible for analyses included four case-control studies, one cohort study[22] and one case-cohort study[27]. Most studies enrolled all individuals seeking care for diarrhoea at study health centres as suspected cholera cases with confirmation then performed by stool culture, except two studies that used PCR[27] and RDT[7], respectively, in main analyses. Controls in case-control studies included both those with no diarrhoea matched spatially to cases' homes,[7,8,23] and clinic-based controls with non-cholera diarrhoea.[25] Five studies included efficacy of a 2-dose regimen as their primary end-point,[7,8,22,23,25] and one study used a single-dose regimen.[27] The duration between the two primary vaccine doses in observational studies ranged from 12-25 days.[22,23]

Two-dose Efficacy and Effectiveness

Primary estimates of two-dose regimens were available in five RCTs[5,24,26,28,30] and five observational studies[7,8,22,23,25] (Tables 1 and 2). Observational study estimates pertained to durations of protection ranging from five to 34 months, representing an 18-month weighted mean duration (Figure 2). Trial estimates pertained to durations of protection ranging from four to 36 months, representing a 28-month weighted mean duration (Figure 2). The average two-dose efficacy was 58% (95%CI 42-69, I^2=58%) and the average two-dose effectiveness was 76% (95%CI 62-85, I^2=0%). Average two-dose efficacy did not differ significantly by vaccine type (p=0·53), however they vary by study design (p=0·04, comparing observational to randomized designs).

One-dose Efficacy and Effectiveness

One efficacy and one effectiveness study used protection after one-dose of kOCV as a primary outcome, both only providing estimates of short-term protection (6-months and 2-months).[27,29] Other studies provided estimates of one-dose protection as secondary outcomes, including four additional observational[7,8,22,25] and one additional randomized trial.[29] Given the paucity of evidence of longer-term single-dose protection, and the global discussions around single-dose use in outbreaks, we focused on estimating the average short-term protection (up to one year after vaccination). The average short-term effectiveness of one-dose of kOCV was 69% (95%CI 35-85, I^2=62%), although this conservatively included two estimates of cumulative effectiveness spanning over 1-year.[8,22] The only one-dose clinical trial published estimated 6-month efficacy of 40%. Estimates did not vary significantly by study design (p=0·47). The average short-term one-dose effectiveness is similar to that of two-doses (p=0·31).

Alternative Dose Regimens

We identified two efficacy studies using three kOCV doses. One study provided three doses, each 6-weeks apart (including WC and WC-BS arms).[9] After three years, the efficacy was not significantly different between two and three doses (64% vs. 50%) for the WC-BS arm of the study, but two-dose efficacy was significantly lower than three doses for the WC arm (39% vs. 52%).[34] The second study provided a third dose as a booster ten months after the primary two-dose series and found efficacy (against medically-attended cholera) two years after the first dose was 82% (95%CI 27-95).[5]

Duration of Protection

The average efficacy estimates of kOCV are similar during the first two years post-vaccination (Figure 3, Figure S1), with average efficacy in the first year of 56% (95%CI 42-66, I^2=45%) and 59% (95%CI 49-67, I^2=0) in the second year. The average efficacy starts to drop in the third year (38%; 95%CI 13-57, I^2=48%), and continues to drop to 26% (95%CI -46-63, I^2=74%) during the fourth year, where estimates of efficacy become highly variable between studies. Only one study reported efficacy during the 5th year (81%, 95%CI 41-94).[6]

Protection in Children

Age-group specific estimates of protection were reported by several studies, with most dividing age-groups into under five years old, five to 15 years old and above 15 years old. We estimate the average efficacy of kOCV in under 5-year olds to be 30% (95%CI, 15-42, I^2=0%, weighted mean duration=31 months), significantly less ($p<0{\cdot}0001$) than 64% (95%CI 58-70, I^2=0%, weighted mean duration=34 months) in those five years and older (including estimates of efficacy in those 15 and above, Figure 4). The average effectiveness in under five years old is 78% (95%CI -37-96, I^2=0%, weighted mean duration=9 months) similar ($p=0{\cdot}77$) to 70% (95%CI 44-84, I^2=0%, weighted mean duration=14 months) in individuals aged five years and older, although these are estimated from only two studies.[8,23] Among school-aged children (5-15 years old), the average efficacy, based on results of only two trials,[28,30] is 80% (95%CI 41-93).

Given the differences in protection by age, we explored whether age distribution of cases within each study could explain the heterogeneity in efficacy/effectiveness estimates. Most studies did not report these data, however, authors of seven of the ten studies contacted provided data. While statistical inference with these incomplete and correlated data is limited, we found a striking association between median age of cases and estimated protection. We find that in general, the older the cases, the higher the estimated protection (Figure 5C). The clearest example of this comes from the 5-year trial in Kolkata,[6] where a simple linear model predicts a rise of 2·0 (95%CI 0·55-3·4, adjusted R^2=0·82) percentage points in efficacy for each 10% increase in the median age.

Discussion

Our analyses provide an in-depth summary of the current evidence on the protection conferred by killed oral cholera vaccines and help shed light on observed difference in estimates. We found that kOCVs administered as the standard two-dose regimen provide a moderate to high level of protection for at least three years, with some evidence suggesting longer lasting protection. A one-dose regimen provides significant short-term protection, although no studies with a primary endpoint being one-dose protection after more than six-months have been published. Efficacy from two doses of kOCV is significantly less in children under five years old compared to older children and adults.

The choice of using a one- or two-dose regimen, particularly in outbreaks where supplies are limited has been a difficult one.[13,37] Our estimates of the short-term average one- and two-dose effectiveness are similar, however this comparison was not possible for efficacy studies due to limited data. When short-term protection is needed and it is not possible to provide two-doses to all at-risk, our results suggest that a single-dose will provide some if not the same-level of short-term protection. Whether and when to provide a booster dose remains an open question and this may vary by the degree to which the population has previously been exposed to *Vibrio cholerae*. New evidence on the duration of protection of one- and two-dose regimens will enhance the ability to make better decisions on when each should be used and at what intervals booster doses should be provided.

kOCVs, like other oral vaccines,[35] provide less protection to young children than others. This differential protection by age may have implications for deciding between different vaccination strategies, particularly when kOCVs become more broadly used in highly endemic countries, like Bangladesh. Vaccination of young children, despite the lower efficacy, may still have profound impacts on disease burden, due to indirect ('herd') effects.[36] More work is needed to refine estimates of the differential protection by age, to better understanding

the impact of different age-targeted vaccine delivery strategies and to understand whether alternative dosing regimens, such as the provision of a third dose, may enhance protection in young children.

The local epidemiology of cholera, including the pathways of transmission and the transmission intensity can determine which age groups are at highest risk of becoming cases. In highly cholera-endemic settings, like Bangladesh and India, cholera cases tend to be younger, since older adults benefit from protection conferred by previous exposure to *Vibrio cholerae*. Given that efficacy of kOCVs is age-dependent, the distribution of the age of cases likely shape estimates of protection across different areas (Figure S2). This phenomenon in addition to difference in the duration of studies, may explain why the average two-dose effectiveness is higher than that of two-dose efficacy.

We identified moderate to high levels of heterogeneity between individual study estimates of vaccine protection within the primary two-dose efficacy analysis and within the average one-dose effectiveness analysis. While some of the heterogeneity is explained by the duration of the study and the average age of cases, other unidentified factors likely played a role. One outlier in the primary two-dose efficacy analysis, a trial conducted in Peru,[24] found no protection during the 10-months after vaccination, in contrast to almost all other estimates. This study was conducted with an early vaccine variant produced before large-scale dedicated production existed. Also a massive household-based active surveillance campaign combined with low cholera incidence may have influenced the results in unanticipated ways.

This manuscript builds upon the 2011 Cochrane review of OCV efficacy by incorporating the large body of additional evidence generated since 2010 and including field-effectiveness studies, which provide public health-relevant measures of vaccine protection.[11] In addition, we conduct sub-analyses for protection by dose, age, study type, and duration of protection to help explain some of the heterogeneity in estimates seen in the literature. This summarization of the evidence is particularly timely due to the increases in global supply of kOCVs, and the increasing interest in incorporating its use into national cholera control plans in areas that experience cholera regularly.

This review came with multiple limitations. Given few studies and their diversity in study design, duration of follow-up, vaccine type, and in epidemiologic settings, we were unable to fully control for each factor in estimating the true average effect. We presented stratified estimates to help interpret how each factor may influence estimates of kOCV protection. In our analyses of single-dose protection, we combined estimates of 1-dose protection from studies where it was the primary outcome and studies where it was a secondary outcome. Especially in observational settings, these secondary estimates are based on individuals who failed to get the full vaccine regimen, which may be correlated to cholera risk. If this were the case, we would expect that we may have underestimated the average single-dose protection. Similarly, using both vaccine arms from Matlab studies without accounting for correlation between them (shared placebo arm) likely led to slight underestimation of the variance in the average efficacy estimates. Lastly, while no significant differences between protection estimates using different vaccines were detected, the increase in antigen protection over time and the addition of the B-subunit, may account for some undetected differences that this study was underpowered to detect. We conducted sensitivity analyses excluding trials using WC-BC vaccines and found that the overall average two-dose efficacy (57·4%, weighted mean duration=28 months) and effectiveness (72·3%, weighted mean duration=22 months) were similar, although slightly, lower than the combined analyses.

In conclusion, kOCVs are effective in reducing the risk of cholera. While cholera vaccine alone will likely not lead to elimination of this disease, it can provide an important stopgap while improved water, sanitation, and healthcare infrastructure are provided to cholera-vulnerable populations. More work is needed to understand how and when to best use existing vaccines and design new and more effective ones. However, the last three decades of evidence points towards kOCV being a safe, effective, and important tool to fight cholera.

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Declaration of Interests:
We declare no competing interests.

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Figures:

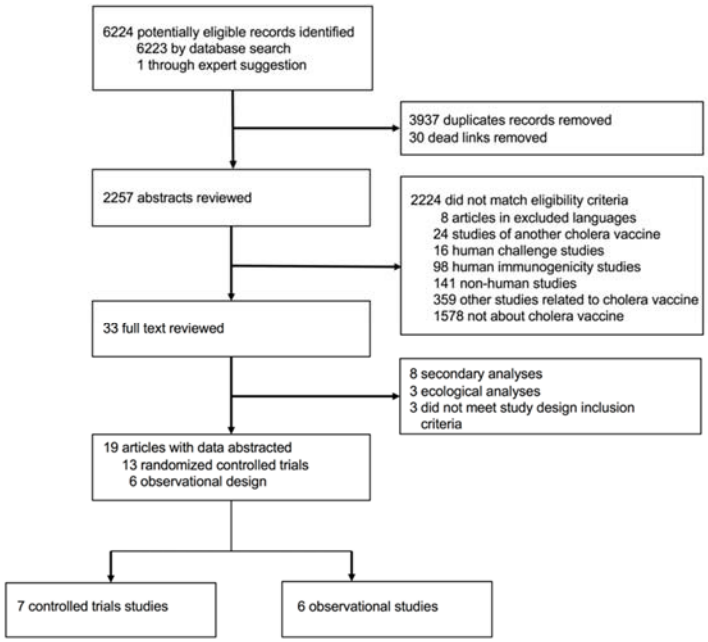

Figure 1: PRISMA flow chart highlighting details of the systematic review and data-abstraction process. Of the three studies estimating effectiveness that did not meet the study design inclusion criteria; one was due to a non-standard study design,[31] the others only used suspected,[32,33] not confirmed cholera, as the study endpoint.

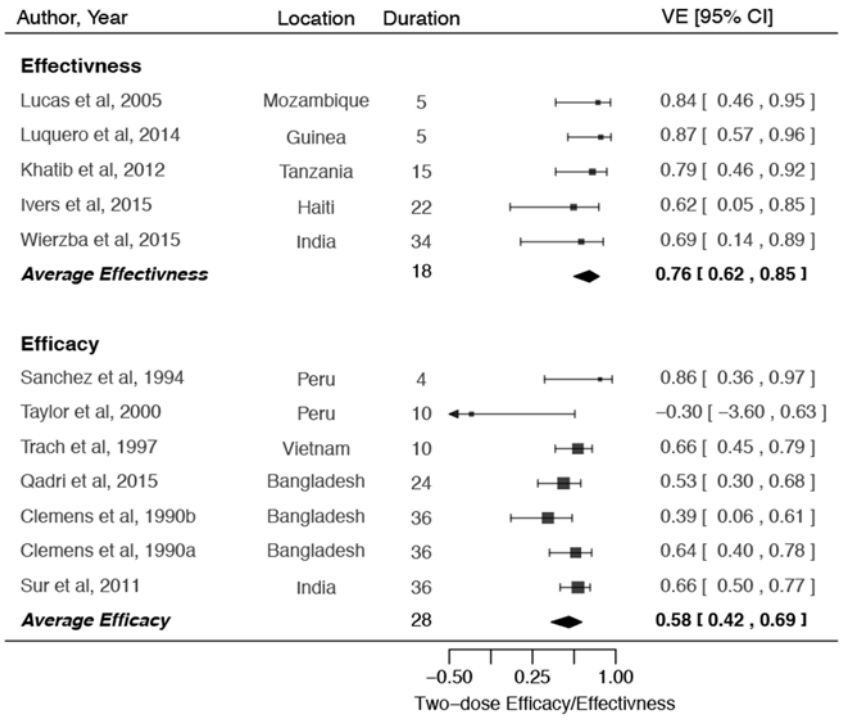

Figure 2: **Effectiveness and Efficacy Main Pooled Analyses for two doses kOCV**. Individual estimates, location, duration, efficacy/effectiveness estimate, and accompanying 95% confidence intervals presented in each row, with the top portion of each panel representing estimates of effectiveness and bottom portions efficacy. Average (pooled) estimates of effectiveness and efficacy are presented below individual estimates for each study type. Confidence intervals presented in figure and used for meta-analyses are not necessarily the same as the original study as they were based on a reconstruction of a 2-sided 95% confidence interval from estimates of the standard error of the estimate from each study. All estimates included except for those from Clemens et al, 1990a and 1990b use

the main vaccine dose used in the study. Qadri et al estimate[28] is an estimate of total protection including both direct and indirect effects.

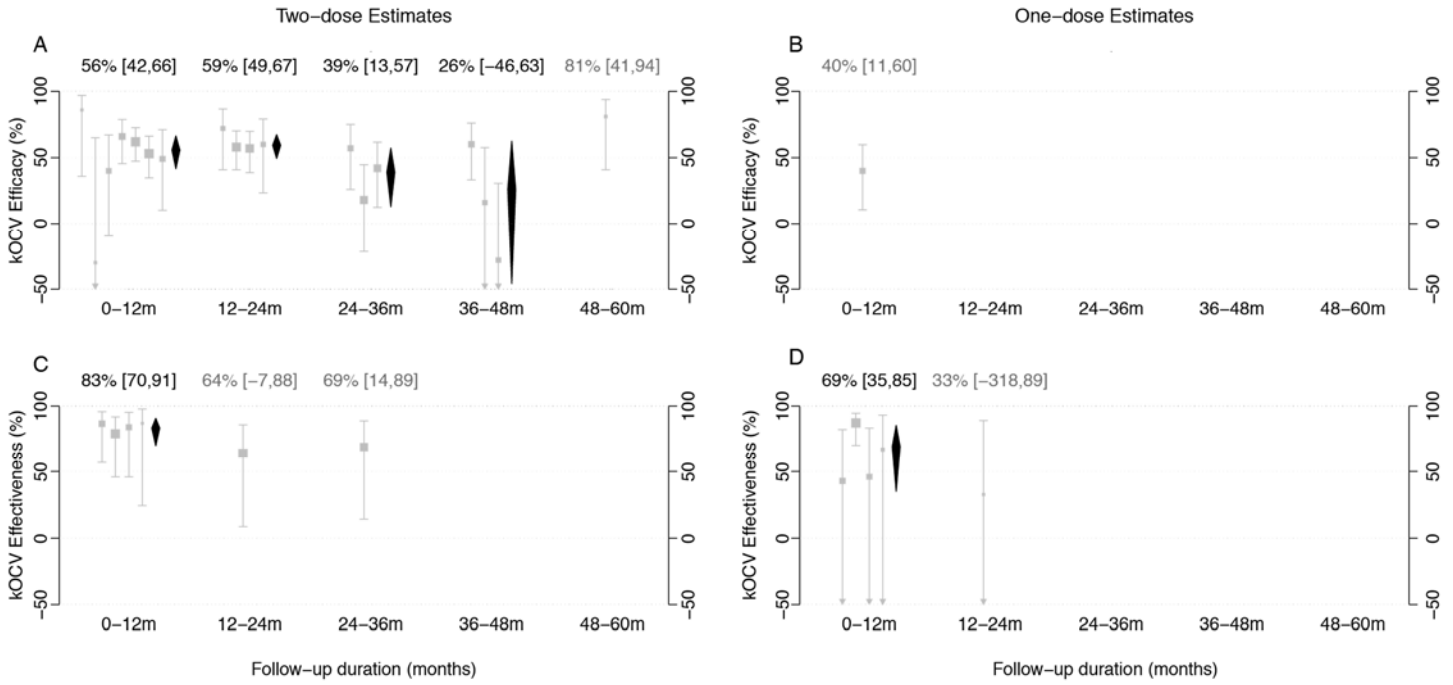

Figure 3: Efficacy (Panels A and B) and effectiveness (Panels C and D) by time since vaccination and dose. Estimates are grouped per the timeframe of analysis with zero representing the day of last dose of vaccine (dose dependent). Light grey bars and squares represent the 95% confidence intervals and point estimates of efficacy from the literature. The black diamonds represent the average efficacy and 95% confidence interval. Note that studies were grouped into time-period bins and not all studies cover the entire 12-months period. Also, we included one estimate,[8] which is cumulative over 22-months after vaccination and categorized it as 0-12 months to be conservative.

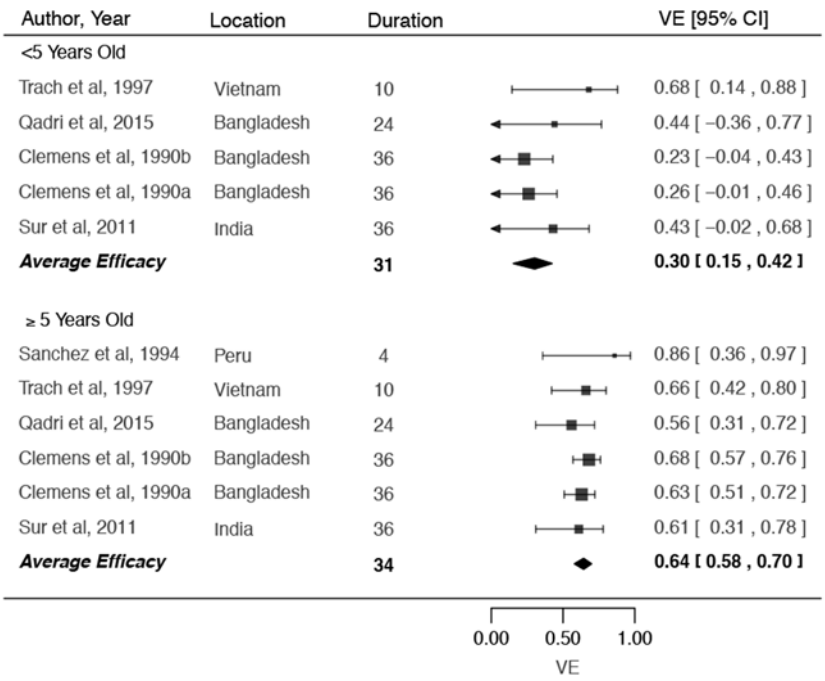

Figure 4: kOCV Efficacy by Age Group. Estimates of efficacy for under 5-year olds on the top and over 5-year olds (including estimates that only include 15 years and up, when 5 years and up not available). Light lines and bars represent estimates from the literature and their 95% confidence intervals. Diamonds represent average estimate and 95% confidence intervals.

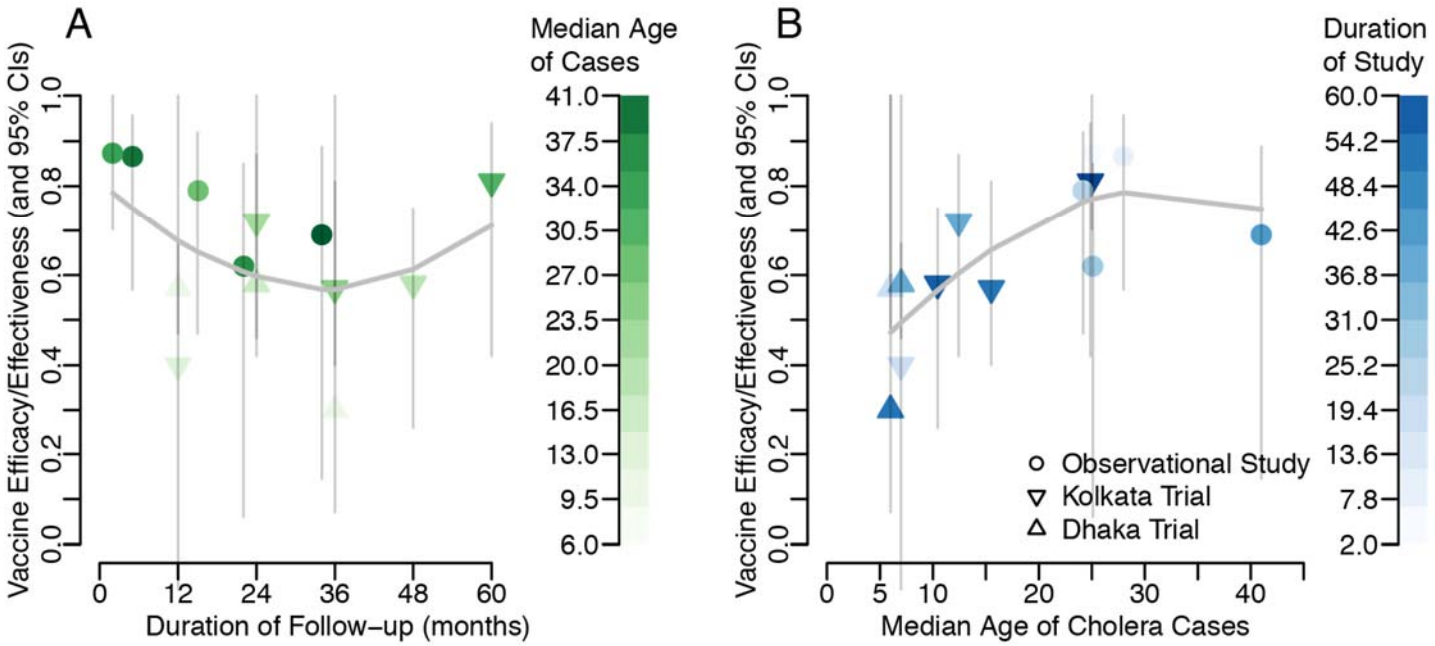

Figure 5: Relationship between protection, duration of follow-up and median age of cholera cases. Panel A illustrates the relationship between protection (y-axis) and months of follow-up (x-axis), with median age of cases highlighted by shades of green. Panel B illustrates the relationship between protection (y-axis) and the median age of cases (x-axis), with the duration of follow-up highlighted by shades of blue. Lines in grey were fit with a polynomial spline with 3 degrees of freedom as implemented. Note these plots only include a subset of data where the age-distribution of cases were available.[6,7,8,22,23,25,28]

***Tables*:**

Table 1. Overview of Primary Efficacy Studies Meeting Inclusion Criteria in Main Analyses.

Continent	Location	Study Design	Vaccine	Duration of Estimate(s) ¶	Doses	Study Population	Serotypes	Number of Cases	Reference(s)
Asia	Kolkata, India	Cluster Randomized Placebo-Controlled Trial	WC	2-, **3-**, and 5-years	2	All nonpregnant individuals ≥1 years old	Inaba & Ogawa	168	[6,30,38]
South America	Lima, Peru	Individually Randomized Placebo-Controlled Trial	WC-BS	2-years	3	All individuals nonpregnant 2-65 years old	Inaba & Ogawa	7	[5]
South America	Lima, Peru	Individually Randomized Placebo-Controlled Trial	WC-BS	5-months	2	Male military recruits 17-65 years old	NA	16	[24]
Asia	Matlab, Bangladesh	Individually Randomized Placebo-Controlled Trial	WC/WC-BS	6-months, 1-, **3-**, and 5-years	3	Children 2-15 years old and all women >15, non-pregnant	Inaba & Ogawa	81/68§	[9,10,34,39]
Asia	Dhaka, Bangladesh	Cluster Randomized Trial*	WC	2-years	2	All non-pregnant individuals ≥1 years old	Inaba & Ogawa	139	[28]
Asia	Dhaka, Bangladesh	Individually Randomized Placebo-Controlled Trial	WC	6-months	1	All individuals ≥1 years old, nonpregnant	Inaba & Ogawa	101	[29]
Asia	Hue, Vietnam	Household Randomized Trials without Placebo	WC	10-months	2	All individuals ≥1 years old	Ogawa	117	[26]

¶ When multiple durations are presented, bolded number indicates primary duration that the study design was based on.
§ VE of at least one dose estimated in this study
§ Numbers for WC and WC-BS arm respectively
* The protective estimate in Qadri et al 2015 was characterized as protective efficacy due to the cluster randomized trial design. The study had no placebo arm, and the non-intervention group was used as the comparison group.

Table 2. Overview of Primary Effectiveness Studies Meeting Inclusion Criteria in Main Analyses.

Continent	Location	Study Design	Vaccine	Duration of Estimate	Doses	Study Population	Serotypes	Number of Cases	Reference(s)
Asia	Puri District, India	Case-Control	WC	3-years	2	All non-pregnant individuals 1 and older seeking care at health facilities	Ogawa	35	[25]
North America	Artibonite Department, Haiti	Case-Control	WC	2-years	2	All individuals 1 year and older seeking care at health facilities	Inaba & Ogawa	44	[8]

Africa	Boffa and Forecariah Districts, Guinea	Case-Control	WC	4-months	2	All individuals >1 seeking care at health facilities	Ogawa	66	[7]
Africa	Zanzibar, Tanzania	Cohort	WC-BS	15-months	2	All non-pregnant healthy individuals 2-year and older	Ogawa	39	[22]
Africa	Beira, Mozambique	Case-Control	WC-BS	4-months	2	All non-pregnant healthy individuals 2-year and older	Ogawa	88	[23]
Africa	Juba, South Sudan	Case-Cohort	WC	2-months	1	All individuals 1-year and older	Inaba	34	[27]

§ VE of at least one dose estimated in this study

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Supplement

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Table S1. Specific searches and terms used in review.

Date of Query	Engine	Language Restrictions	Date Restrictions	Exact Search Query
9-July-2016	Pubmed	None	None	cholera*[Title/Abstract] AND(vaccin*[Title/Abstract]) AND (effect*[Title/Abstract] OR efficacy[Title/Abstract] OR protect*[Title/Abstract])
9-July-2016	Embase	None	None	cholera*:ab,ti AND vaccin*:ab,ti AND (efficacy:ab,ti OR effect*:ab,ti OR protect*:ab,ti)
9-July-2016	Scopus	None	None	TITLE-ABS(cholera*) AND TITLE-ABS(vaccin*) AND TITLE-ABS(efficacy OR effect* OR protect*)
11-July-2016	ISI Web of Science	None	None	TI=(cholera* AND vaccin*) AND TS=(efficacy OR effect* OR protect*)
9-July-2016	Cochrane Review Library	None	None	cholera* AND vaccin* AND (efficacy OR effect* OR protect*)

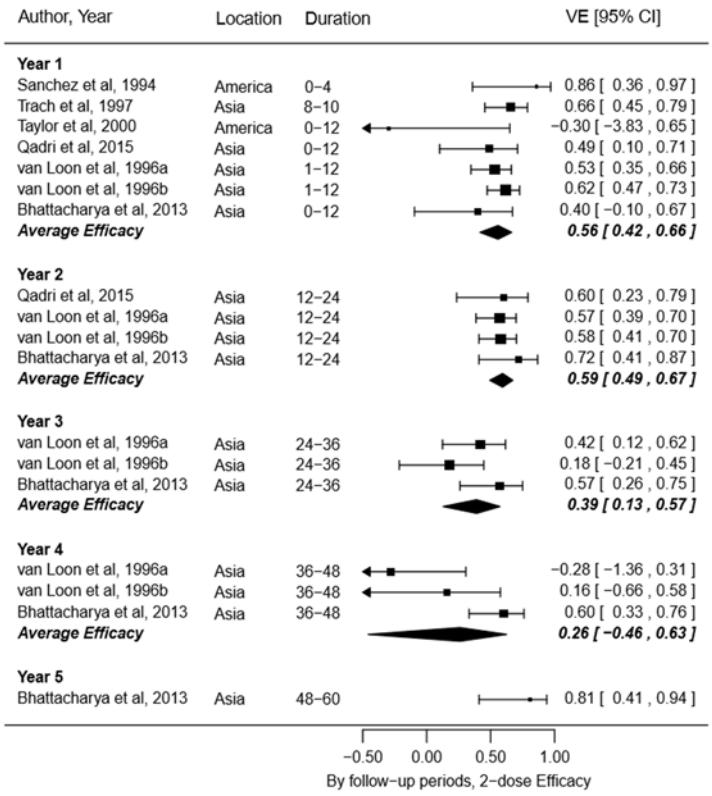

Figure S1. Two-dose vaccine efficacy by years since vaccination.

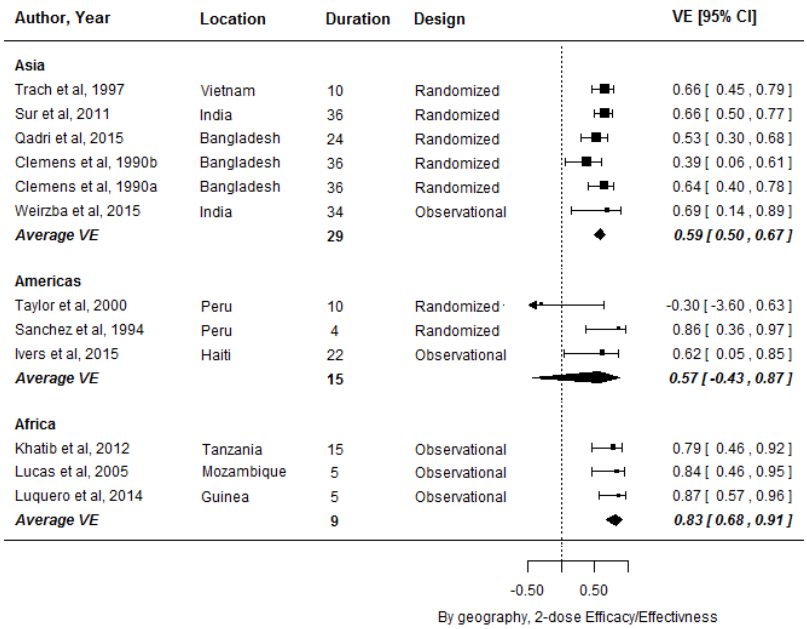

Figure S2. Two-dose pooled vaccine efficacy/effectiveness estimates by location of study.