# 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.<br>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 |

| | | | | |
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| | | | 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.<br>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.<br>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. | |

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| | 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 systematic 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 vaccination campaigns. 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. |

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| EQUITY | What would be the impact on health inequities? | *Increased* ☐ *Probably increased* ☐ *Uncertain* ☐ *Probably reduced* ☐ *Reduced* ■ *Varies* ☐ | 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* ■ *Varies* ☐ | 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 International Coordinating Group (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* ■ *Varies* ☐ | 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<br><br>☐ | We suggest considering the option<br>☐ Only in the context of rigorous research<br>☐ Only with targeted monitoring and evaluation<br>☐ Only in specific contexts | We recommend the option<br><br>■<br><br>**The recommendation applies to specific contexts, in specific (sub) populations and in conjunction with other prevention and control measures.** |
|---|---|---|---|

| | |
|---|---|
| Recommendation | Given the current availability of prequalified whole-cell, 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.<br><br>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.<br><br>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.<br><br>Further assessment of herd protection is needed.<br><br>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.<br><br>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.<br><br>More information is needed on co-administration of OCV with other vaccines, especially with oral vaccines such as oral polio vaccine 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/ other prevention and control measures (e.g. water, sanitation and hygiene (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.

**References**


1. Concha A et al. Safety and immunogenicity of oral killed whole cell recombinant B subunit cholera vaccine in Barranquilla, Colombia. *Bull Pan Am Health Organ* 1995; 29(4):312-321.
2. Trach DD et al. Investigations into the safety and immunogenicity of a killed oral cholera vaccine developed in Viet Nam. *Bull Pan Am Health Organ* 2002; 80(1):2-8.
3. Anh DD et al. Safety and immunogenicity of a reformulated Vietnamese bivalent killed, whole-cell, oral cholera vaccine in adults. *Vaccine* 2007; 25(6):1149-1155.
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5. Sur D 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.
6. Saha A 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. Qadri 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.
8. Desai SN.et al. 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
9. Baik YO 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.
10. Qadri et al. Efficacy of a Single-Dose, Inactivated Oral Cholera Vaccine in Bangladesh. *N Engl J Med* 2016: 374: 1723-32.

**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/ other prevention and control measures (e.g. WASH)
**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 priori 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).

**References**


1. Grout L 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
2. Hashim R et al. Safety of the recombinant cholera toxin B subunit, killed whole-cell (rBS-WC) oral cholera vaccine in pregnancy. *PLoS Negl Trop Dis* 2012; 6(7): e1743.
3. Ali M 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 AI 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/ 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 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 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 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 et al. Field trial of a locally produced, killed, oral cholera vaccine in Vietnam. *Lancet* 1997; 349(9047): 231-235.
5. Sur D 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.
6. Bhattacharya SK, 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.
7. Desai SN et al. 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 et al. Efficacy of a Single-Dose, Inactivated Oral Cholera Vaccine in Bangladesh. *NEJM* 2016; 374: 1723-1732.
9. Baik YO 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.
10. Qadri 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.
11. van Loon FPL 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 et al. Effectiveness of Mass Oral Cholera Vaccination in Beira, Mozambique. *NEJM* 2005; 352: 757-767.
13. Khatib AM 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 et al. Effectiveness of an oral cholera vaccine campaign to prevent clinically-significant cholera in Odisha State, India. *Vaccine* 2015; 33(21): 2463-2469.
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16. Severe K et al. Effectiveness of Oral Cholera Vaccine in Haiti: 37-Month Follow-Up. *Am J Trop Med Hyg* 2016; 94(5): 1136-1942.
17. Luquero FJ et al. Use of Vibrio cholerae vaccine in an outbreak in Guinea. New England Journal of Medicine 2014; 370(22): 2111-20.
18. Thiem VD 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/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 et al. Field trial of oral cholera vaccines in Bangladesh: results from three-year follow-up. *Lancet* 1990; 335(8684): 270-273.
2. Taylor DN 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 et al. Field trial of a locally produced, killed, oral cholera vaccine in Vietnam. *Lancet* 1997; 349(9047): 231-235.
4. Qadri F et al. Efficacy of a Single-Dose, Inactivated Oral Cholera Vaccine in Bangladesh. *NEJM* 2016; 374: 1723-1732.
5. Qadri 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 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/ 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 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 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 et al. Field trial of a locally produced, killed, oral cholera vaccine in Vietnam. *Lancet* 1997; 349(9047): 231-235.
4. Sur D 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 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 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 et al. 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 et al. Efficacy of a Single-Dose, Inactivated Oral Cholera Vaccine in Bangladesh. *NEJM* 2016; 374: 1723-1732.
9. Bhattacharya SK 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 et al. Effectiveness of Mass Oral Cholera Vaccination in Beira, Mozambique. *NEJM* 2005; 352: 757-767.
11. Ivers LC 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/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 | | | 3 |
| 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 et al. Efficacy of a Single-Dose, Inactivated Oral Cholera Vaccine in Bangladesh. *NEJM* 2016; 374: 1723-1732.
2. Qadri 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/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 5-14 years of age old?*** | | | | |
|---|---|---|---|---|
| | | | Rating | Adjustment to Rating |
| Quality of Evidence | No. of studies/starting rating | | 7 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 that of the estimate on the effect of the health outcome. |
| | Conclusion | | | 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. |

**References:**


1. Taylor DN 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 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 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 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 et al. 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 et al. Efficacy of a Single-Dose, Inactivated Oral Cholera Vaccine in Bangladesh. *NEJM* 2016; 374: 1723-1732.
7. Bhattacharya SK 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/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 et al. Efficacy of a Single-Dose, Inactivated Oral Cholera Vaccine in Bangladesh. *NEJM* 2016; 374: 1723-1732.
2. Qadri 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/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 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 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 et al. Field trial of a locally produced, killed, oral cholera vaccine in Vietnam. *Lancet* 1997; 349(9047): 231-235.
4. Sur D 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 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 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 et al. 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 et al. Efficacy of a Single-Dose, Inactivated Oral Cholera Vaccine in Bangladesh. *NEJM* 2016; 374: 1723-1732.
9. van Loon FPL 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 et al. Effectiveness of Mass Oral Cholera Vaccination in Beira, Mozambique. *NEJM* 2005; 352: 757-767.
11. Ivers LC 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/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 et al. Efficacy of a Single-Dose, Inactivated Oral Cholera Vaccine in Bangladesh. *NEJM* 2016; 374: 1723-1732.
2. Qadri 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/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 et al. Efficacy of a Single-Dose, Inactivated Oral Cholera Vaccine in Bangladesh. *NEJM* 2016; 374: 1723-1732.
2. Khatib AM 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.
3. Wierzba TF et al. Effectiveness of an oral cholera vaccine campaign to prevent clinically-significant cholera in Odisha State, India. *Vaccine* 2015; 33(21): 2463-2469.
4. Ivers LC 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/ 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/ 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.