Evidence to Recommendations: CVD 103-HgR among children and adolescents aged 2–17 years

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Advisory Committee on Immunization Practices
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Background of the work group

- **June 2016**: ACIP recommended the cholera vaccine CVD 103-HgR (Vaxchora) for adult travelers aged 18–64 years from the United States to an area with active cholera transmission.
- **October 2020**: ACIP cholera vaccine work group formed.
- **December 2020**: FDA extended the approved usage to include children and adolescents aged 2–17 years.
- **February 2021**: Work group presented background information and the manufacturer presented pediatric clinical trial data.
Evidence to Recommendation (EtR)
Framework: policy question

- Should ACIP recommend CVD 103-HgR for children and adolescents aged 2–17 years traveling to an area with active cholera transmission?
## PICO components

<table>
<thead>
<tr>
<th>Population</th>
<th>Children and adolescents aged 2–17 years traveling to an area with active cholera transmission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Lyophilized CVD 103-HgR (single-dose, oral, live-attenuated bacterial vaccine*)</td>
</tr>
<tr>
<td>Comparison</td>
<td>No cholera vaccine</td>
</tr>
<tr>
<td>Outcomes</td>
<td>- Cholera diarrhea, moderate or severe</td>
</tr>
<tr>
<td></td>
<td>- Cholera diarrhea, any severity</td>
</tr>
<tr>
<td></td>
<td>- Serious adverse events</td>
</tr>
<tr>
<td></td>
<td>- Non-serious adverse events</td>
</tr>
</tbody>
</table>

*4x10⁸–2x10⁹ colony forming units with buffer (50 ml if 2–5 years; 100 ml if 6–17 years)
### Evidence to Recommendations (EtR) Framework

<table>
<thead>
<tr>
<th>EtR Domain</th>
<th>Question</th>
</tr>
</thead>
<tbody>
<tr>
<td>Public health</td>
<td>Is cholera among children and adolescents aged 2–17 years traveling to an area with active cholera transmission of public health importance?</td>
</tr>
<tr>
<td>benefits and harms</td>
<td>How substantial are the desirable anticipated effects?</td>
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<td>Feasibility</td>
<td>Is CVD 103-HgR feasible to implement among children and adolescents aged 2–17 years traveling to an area with active cholera transmission?</td>
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EtR domain: public health problem
Public health problem questions

- Is cholera among children and adolescents aged 2–17 years traveling to an area with active cholera transmission a public health problem?
  - Are the consequences cholera serious (i.e., severe or important in terms of the potential benefits or savings)?
  - Is cholera urgent?
  - Are many travelers aged 2–17 years from the United States affected by cholera?
  - Is cholera related to emerging diseases, antimicrobial resistance, or epidemic potential?
  - Are disadvantaged groups or populations disproportionately/differentially affected by cholera?

☐ No  ☐ Probably no  ☐ Probably yes  ☐ Yes  ☐ Varies  ☐ Don’t know
- Are the consequences of cholera serious?
- Is cholera urgent?

- Infection with toxigenic *V. cholerae* O1 can cause a range of symptoms

- Cholera gravis is rapidly fatal if untreated
- Fluid management is the primary focus treatment
- Rehydration can reduce the fatality rate to <1%
- Patients with cholera gravis may require up to 350 ml/kg of fluids within the first 24 hours of illness
Are many travelers aged 2–17 years from the United States affected by cholera?

- Most international travelers from the United States do not get cholera\(^1\)
  - do not visit areas with active cholera transmission
  - have good access to safe food and water
- During 2012–2018, 64 cholera cases reported in the United States
  - 5 (8%) aged 2–17 years
  - 2 deaths (adults)
  - 56 (88%) travel associated
- National cholera case counts underestimate the true burden

\(^1\)https://wwwnc.cdc.gov/travel/diseases/cholera#areas
- Is cholera related to emerging diseases, antimicrobial resistance, or epidemic potential?
- Are disadvantaged groups or populations disproportionately/differentially affected by cholera?

- Antibiotic resistance can occur
- Fluids are the mainstay of treatment; antibiotics are adjunctive therapy in moderate to severe illness
- An estimated 1.3–4.0 million cholera cases and 21,000–143,000 deaths occur worldwide each year
- Cholera epidemics are associated with unsafe water and inadequate sanitation
- Secondary cases are rare if sanitation is adequate
- A US outbreak from a returning traveler is unlikely

1 https://www.who.int/health-topics/cholera#tab=tab_1
Is cholera among children and adolescents aged 2–17 years traveling to an area with active cholera transmission a public health problem?

- Cholera is a public health problem for local populations in endemic settings due to unsafe drinking water and inadequate sanitation.
- For travelers from the United States, the risk varies by:
  - travel destination
  - travel activities
  - access to safe water, food, and sanitation
- Cholera may pose a meaningful individual risk for ill travelers with inadequate or delayed access to fluid replacement.
- May become a bigger problem for travelers in the future.
- Having a supply of cholera vaccine for US travelers is important.
Public health problem: work group determination

- Is cholera among children and adolescents aged 2–17 years traveling to an area with active cholera transmission a public health problem?
  - Most members felt probably yes
  - Some felt probably no or varies
EtR domain: benefits and harms
Benefits and harms questions

▪ How substantial are the desirable anticipated effects overall and for each main outcome for which there is a desirable effect?

- Minimal
- Small
- Moderate
- Large
- Varies
- Don’t know

▪ How substantial are the undesirable anticipated effects overall and for each main outcome for which there is an undesirable effect?

- Minimal
- Small
- Moderate
- Large
- Varies
- Don’t know
Benefits and harms questions

- Do the desirable effects outweigh the undesirable effects?

- What is the overall certainty of this evidence for the critical outcomes?

- Favors intervention (CVD 103-HgR)
- Favors comparison (placebo)
- Favors both
- Favors neither
- Unclear

- High
- Moderate
- Low
- Very low
## PICO outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benefits</strong></td>
<td></td>
</tr>
<tr>
<td>Cholera diarrhea, moderate or severe</td>
<td>Critical</td>
</tr>
<tr>
<td>Cholera diarrhea, any severity</td>
<td>Critical</td>
</tr>
<tr>
<td><strong>Harms</strong></td>
<td></td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>Critical</td>
</tr>
<tr>
<td>Non-serious adverse events</td>
<td>Important</td>
</tr>
</tbody>
</table>
GRADE evidence retrieval

- **Databases:** PubMed, Embase, and Cochrane Library, written in English
- **Search terms:** cholera, *Vibrio cholerae*, CVD 103-HgR, cholera vaccine
- **Inclusion:** provided data on the current formulation and dose of CVD 103-HgR and 1) involved human subjects aged 2–17 years, 2) reported primary data relevant to the efficacy and safety outcomes, and 3) conducted in cholera non-endemic settings
- **Titles and abstracts screened by 2 reviewers**
GRADE evidence retrieval

Records identified and screened (n=571)

Records excluded based on title (n=557):
- Published before 2009* (n=404)
- Not a cholera vaccine trial (n=105)
- Different vaccine/setting (n=48)

Records assessed for eligibility (n=14)

Full-text articles excluded (n=11):
- Adult study (n=10)
- Different formulation (n=1)

Articles included in GRADE (n=3)

*The current formulation of CVD 103-HgR was not available before 2009
### Setting
- Seven U.S. sites
- July 2017 – September 2019

### Inclusion
Healthy children and adolescents aged 2–17 years*
- Cohort 1: 12–17 years
- Cohort 2: 6–11 years
- Cohort 3: 2–5 years

### Randomization (6:1 ratio)
CVD 103-HgR $1 \times 10^9$ CFU vs. 0.9% saline placebo (6:1 ratio)

### Optional sweetener
PureVia Stevia**

### Outcomes
Safety and immunogenicity

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*without a significant medical history or physical examination findings at screening. In female participants of childbearing potential, a urine pregnancy test was performed at screening and before vaccine administration.

**Sweetener added for 437/471 (93%) CVD 103-HgR and 73/79 (92%) placebo recipients
Outcomes 1 and 2:
- Cholera diarrhea, moderate to severe
- Cholera diarrhea, any severity

NO PEDIATRIC STUDIES DIRECTLY ASSESSED VACCINE EFFECTIVENESS

- Assessment based on immunobridging to adults
  - Oral wild-type *Vibrio cholerae* O1 administered to participants aged 18–45 years following vaccine or placebo
  - Correlation coefficient between cumulative diarrhea (in L) and fold-increase in serum vibriocidal antibody:
    • -0.75 at 10 days
    • -0.69 at 3 months
- In endemic settings, fold-increases in SVA correlated with protection in both adults and children

# GRADE evidence table:

**Cholera diarrhea, moderate to severe* **OR **any severity***

Assessed via SVA seroconversion (≥4-fold rise in titer) on day 11

<table>
<thead>
<tr>
<th>Certainty assessment</th>
<th>Summary of findings</th>
</tr>
</thead>
<tbody>
<tr>
<td># studies</td>
<td>Study design</td>
</tr>
<tr>
<td>2</td>
<td>RCT</td>
</tr>
<tr>
<td>393/399 (98.5%)</td>
<td>1/67 (1.5%)</td>
</tr>
</tbody>
</table>

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*a Loss to follow-up for SVA at day 11: 2–5 year cohort (CVD 103 HgR: 47/150 (32%); Placebo: 6/26 (24%)), 6–11 year cohort (CVD 103-HgR 25/321 (8%); Placebo: 6/53 (11%)).

*b Serious concern for indirectness because efficacy is inferred from immunobridging. SVA seroconversion is an indirect correlate of protection with biologic plausibility. Dichotomous definition of seroconversion (≥4-fold rise in titer) is different than fold-increases in SVA. In an adult challenge study (Chen, 2016), the correlation coefficient between cumulative diarrhea (L) and fold-increase in serum-vibriocidal antibodies was -0.75 at day 10 and -0.69 at 3 months.

*c The RCTs enrolled healthy children and adolescents aged 2–17 years and may not represent all children and adolescents in this age group, such as those with immunocompromising conditions.

*d Seroconversion on day 11 occurred among 292/296 (98.6% [98.3% CI: 95.9–99.6%]) of CVD 103-HgR recipients aged 6–17 years and among 101/103 (98.1% [98.3% CI: 91.5–99.6%]) of CVD 103-HgR recipients aged 2–5 years. Seroconversion in each of these age groups met prespecified non-inferiority criteria (lower limit of the 96.7% CIs on the difference between the groups exceeding -10) compared with adults 18–45 years from a phase 3 lot consistency study.
### GRADE evidence table: serious adverse events

Assessed via serious adverse events (through day 181)

<table>
<thead>
<tr>
<th>Certainty assessment</th>
<th>Summary of findings</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td># studies</td>
<td>Study design</td>
<td>Risk of bias</td>
</tr>
<tr>
<td>2</td>
<td>RCT</td>
<td>Not serious</td>
</tr>
</tbody>
</table>

- **CVD 103-HgR**
- **# patients**: CVD 103-HgR: n/N (95% CI)
- **Effect**: Placebo: n/N % (95% CI)
- **Relative risk**: (95% CI)
- **Absolute risk**: (95% CI)

**Certainty assessment notes**

- **a** Loss to follow-up for serious adverse events: CVD 103-HgR: 3/471 (0.6%), placebo: 4/79 (5%).
- **b** No SAEs were attributed to the vaccine in either study.
- **c** The RCTs enrolled healthy children and adolescents aged 2–17 years and may not represent all children and adolescents in this age group, such as those with immunocompromising conditions.
- **d** Very serious concern for imprecision based on the small sample size to assess rare serious adverse events, the small number of events, and the wide 95% confidence interval that crosses the line of no effect.
## GRADE evidence table: non-serious adverse events
Assessed via any solicited adverse event, day 1–8

<table>
<thead>
<tr>
<th>Certainty assessment</th>
<th>Summary of findings</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td># studies</td>
<td>Study design</td>
<td>Risk of bias</td>
</tr>
<tr>
<td>2</td>
<td>RCT</td>
<td>Not serious(^a)</td>
</tr>
</tbody>
</table>

\(^a\)Loss to follow-up for solicited adverse events CVD 103-HgR: 3/471 (0.6%), placebo: 4/79 (5%).

\(^b\)Solicited adverse events were reported by a lower percentage of study participants aged 2–5 years (CVD 103-HgR: 40.4%, placebo: 34.6%) than aged 6–17 years (CVD 103-HgR: 61.8%, placebo: 59.2%). This may relate to limited language skills in the younger age group and was deemed not serious.

\(^c\)The RCTs enrolled healthy children and adolescents aged 2–17 years and may not represent all children and adolescents in this age group, such as those with immunocompromising conditions.

\(^d\)Serious concern for imprecision because the wide confidence intervals cross the line of no effect.
# Benefits and Harms: Summary of GRADE

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Importance</th>
<th>Design (# studies)</th>
<th>Findings</th>
<th>Evidence type*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benefits</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholera diarrhea, moderate to severe</td>
<td>Critical</td>
<td>RCT (2)</td>
<td>CVD 103-HgR effectively induces SVA seroconversion, <em>an imperfect correlate of protection</em> against cholera</td>
<td>Type 2 (moderate)</td>
</tr>
<tr>
<td>Cholera diarrhea, any severity</td>
<td>Critical</td>
<td>RCT (2)</td>
<td>CVD 103-HgR effectively induces SVA seroconversion, <em>an imperfect correlate of protection</em> against cholera</td>
<td>Type 2 (moderate)</td>
</tr>
<tr>
<td><strong>Harms</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>Critical</td>
<td>RCT (2)</td>
<td>No SAEs were judged to be related to the vaccine.</td>
<td>Type 3 (low)</td>
</tr>
<tr>
<td>Non-serious adverse events</td>
<td>Important</td>
<td>RCT (2)</td>
<td>Frequency of non-serious adverse events was not meaningfully different among CVD 103-HgR versus placebo recipients</td>
<td>Type 3 (low)</td>
</tr>
</tbody>
</table>
Benefits and harms: work group determination

- How substantial are the desirable anticipated effects overall and for each main outcome for which there is a desirable effect?

- How substantial are the undesirable anticipated effects overall and for each main outcome for which there is an undesirable effect?
Benefits and harms: work group determination

- Do the desirable effects outweigh the undesirable effects?

- What is the overall certainty of this evidence for the critical outcomes?

- Favors intervention (CVD 103-HgR)
  - High
  - Moderate
  - Low (marked)
  - Very low

- Favors comparison (placebo)
  - Favors both
  - Favors neither
  - Unclear
EtR domain: values
Values questions

- 1. Does the target population feel the desirable effects are large relative to the undesirable effects?
- 2. Is there important uncertainty about, or variability in, how patients value the outcomes?

Minimal  Small  Moderate  Large  Varies  Don’t know
Values

- No research evidence identified
- Cholera vaccines are optional
- Individuals can decide whether to get it based on their values
Values: work group determination

1. Does the target population feel the desirable effects are large relative to the undesirable effects?

2. Is there important uncertainty about, or variability in, how patients value the outcomes?

[☐ Minimal] [☐ Small] [☐ Moderate] [☐ Large] [☐ Varies] [☒ Don’t know]
EtR domain: acceptability
Acceptability questions

- Is the intervention acceptable to key stakeholders?
  - Are there key stakeholders that would not accept the distribution of benefits, harms, and costs?
  - Are there key stakeholders that would not accept the costs or undesirable effects in the short term for the desirable effects in the future?

☐ No  ☐ Probably no  ☐ Probably yes  ☐ Yes  ☐ Varies  ☐ Don’t know
Acceptability

- No research evidence identified
- Travel medicine providers and medical associations (IDSA, AAP, PIDS) are likely to find it acceptable to administer CVD 103-HgR to children and adolescents aged 2–17 years traveling to an area with active cholera transmission
Acceptability: work group determination

- Is the intervention acceptable to key stakeholders?

[ ] No    [ ] Probably no    [ ] Probably yes    [X] Yes   [ ] Varies   [ ] Don’t know
EtR domain: resource use
Resource use questions

- Is CVD 103-HgR among children and adolescents aged 2–17 years traveling to an area with active cholera transmission a reasonable and efficient allocation of resources?
  - What is the cost-effectiveness of the vaccination?
  - How does the cost-effectiveness of the vaccination vary in any sensitivity analyses?
  - How does the cost-effectiveness change in response to changes in context, assumptions, model structure, across different studies, etc.?
Resource use: work group determination

- No research evidence identified
- Cost-analysis was not conducted given optional nature of CVD 103-HgR among travelers
Resource use: work group determination

- Is CVD 103-HgR among children and adolescents aged 2–17 years traveling to an area with active cholera transmission a reasonable and efficient allocation of resources?

[ ] No  [ ] Probably no  [ ] Probably yes  [ ] Yes  [ ] Varies  [x] Don’t know
EtR domain: equity
Equity questions

- What would be the impact on health equity of CVD 103-HgR among children and adolescents aged 2–17 years traveling to an area with active cholera transmission?
  - Are there any groups or settings that might be disadvantaged in relation to the problem or options that are considered?
  - Are there plausible reasons for anticipating differences in the relative effectiveness of the option for disadvantaged groups or settings?
  - Are there different baseline conditions across groups or settings that affect the absolute effectiveness of the option or the importance of the problem for disadvantaged groups or settings?
  - Are there important considerations that should be made when implementing the intervention (option) in order to ensure that inequities are reduced, if possible, and that they are not increased?
Equity

- No research evidence identified
- Concern for possible inequity
- Underserved populations may have difficulty accessing and paying for the vaccine
  - Travelers visiting friends and relatives (VFR) in cholera endemic areas are likely highest risk for illness but are often uninsured
  - For other travel vaccines, VFR travelers are often less likely than other travelers to come to travel clinics and receive pre-travel vaccines
Equity: work group determination

- What would be the impact of CVD 103-HgR among children and aged adolescents 2–17 years traveling to an area with active cholera transmission on health equity?

- Minimal
- Small
- Moderate
- Large
- Varies
- Don’t know
EtR domain: feasibility
Feasibility questions

- Is CVD 103-HgR feasible to implement among children and adolescents aged 2–17 years traveling to an area with active cholera transmission?
  - Is the intervention sustainable?
  - Are there important barriers that are likely to limit the feasibility of implementing the intervention or that require consideration when implementing it?
  - Is access to the vaccine an important concern?
  - Would the vaccine recommendation have any impact on health equity?
  - Are there important considerations when implementing the intervention in order to ensure that inequities are reduced, if possible, and that they are not increased?

[Box with options: No, Probably no, Probably yes, Yes, Varies, Don’t know]
Feasibility

- Likely feasible to administer to children and adolescents aged 2–17 years in a travel clinic
  - Dose preparation is more complicated than routine childhood vaccines
    - Requires reconstitution in bottled purified/spring water
    - Half of buffer is discarded for children aged <6 years
  - May be optimally ingested with specific sweeteners
    - >92% of trial participants used PureVia Stevia
    - 89% of study participants consumed the complete dose
    - SVA seroconversion with partial dosing
      - 18/26 (69.2%) who consumed <50% of dose
      - 7/7 (100%) who consumed 50 – <80% of dose
- The recommendation may impact health equity
Feasibility questions

▪ Is CVD 103-HgR feasible to implement among children and adolescents 2–17 years traveling to an area with active cholera transmission?

- No
- Probably no
- **Probably yes**
- Yes
- Varies
- Don’t know

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Summary
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<thead>
<tr>
<th>EtR Domain</th>
<th>Question</th>
<th>Work group determination</th>
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<tbody>
<tr>
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<tr>
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<td>Moderate</td>
</tr>
<tr>
<td></td>
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<td>Small</td>
</tr>
<tr>
<td></td>
<td>Do the desirable anticipated effects outweigh the undesirable effects?</td>
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**EtR framework summary: work group interpretations**

*CVD 103-HgR for children and adolescents aged 2–17 years traveling to an area with active cholera transmission*

<table>
<thead>
<tr>
<th>Balance of consequences</th>
<th>Undesirable consequences clearly outweigh desirable consequences in most settings</th>
<th>Undesirable consequences probably outweigh desirable consequences in most settings</th>
<th>The balance between desirable and undesirable consequences is closely balanced or uncertain</th>
<th>Desirable consequences probably outweigh undesirable consequences in most settings</th>
<th>Desirable consequences clearly outweigh undesirable consequences in most settings</th>
<th>Evidence to determine the balance of consequences is insufficient</th>
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**EtR framework summary: work group interpretations**

*CVD 103-HgR for children and adolescents aged 2–17 years traveling to an area with active cholera transmission*

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<td>probably outweigh</td>
<td>is closely balanced or uncertain</td>
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<td>probably outweigh</td>
<td>insufficent</td>
</tr>
<tr>
<td></td>
<td>desirable consequences</td>
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<td></td>
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<td>undesirable consequences</td>
<td>in most settings</td>
</tr>
<tr>
<td></td>
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*Note: The table only includes one row for clarity.*
## EtR framework summary: work group interpretations

*CVD 103-HgR for children and adolescents aged 2–17 years traveling to an area with active cholera transmission*

<table>
<thead>
<tr>
<th>Type of recommendation</th>
<th>We do not recommend the intervention*</th>
<th>We recommend the intervention* for individuals based on shared clinical decision-making</th>
<th>We recommend the intervention*</th>
</tr>
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**EtR framework summary: work group interpretations**

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</thead>
</table>

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Acknowledgements

ACIP members
- Pablo Sanchez (chair)
- Matt Daley (member)

Ex officio members
- Bill Alexander (NIH)
- Tina Mongeau (FDA)

ACIP liaisons
- Carol Baker (IDSA)
- Elizabeth Barnett (ISTM)
- Adam Ratner (AAP)

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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.
Extra slides: GRADE assessment
**GRADE certainty of evidence**

Reflects the extent to which confidence in an estimate of the effect is adequate to support a particular recommendation

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1 (high)</td>
<td>Further research is <em>unlikely</em> to change our confidence in the estimate or effect</td>
</tr>
<tr>
<td>Type 2 (moderate)</td>
<td>Further research is <em>likely to have an important impact</em> on our confidence in the estimate of effect and may change the estimate</td>
</tr>
<tr>
<td>Type 3 (low)</td>
<td>Further research is <em>very likely to have an important impact</em> on our confidence in the estimate of effect and is likely to change the estimate</td>
</tr>
<tr>
<td>Type 4 (very low)</td>
<td>Any estimate of effect is <em>very uncertain</em></td>
</tr>
</tbody>
</table>
GRADE certainty of evidence

- **Initial type determined by study design**
  - Type 1 (high) – randomized control trials
  - Type 3 (low) – observational studies

- **Factors that can downgrade evidence profile**
  - **Risk of bias** – failure to conceal allocation, failure to blind, loss to follow-up. Risk of bias may vary across outcomes.
  - **Inconsistency** – criteria for evaluating include similarity of point estimates, extent of overlap of confidence intervals, statistical tests of heterogeneity including chi-square and I².
  - **Indirectness** – Considers the generalizability of the evidence to the original PICO components (i.e., do study patients, intervention, comparison, or outcomes differ from those of interest?)
  - **Imprecision** – Considers the fragility of the relative and absolute effect measures based on the interpretation of the 95% CIs and the optimal information size

- Other factors can downgrade or upgrade evidence: publication bias, dose-response gradient, large magnitude of effect, opposing residual confounding
Safety and Immunogenicity of Live Oral Cholera Vaccine CVD 103-HgR in Children Aged 2–5 Years in the United States

James M. McCarty,¹* David Cassie,² Lisa Bedell,² Michael D. Lock,² and Sean Bennett²
¹Stanford University School of Medicine, Stanford, California; ²Emergent Travel Health, Inc., Redwood City, California

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Safety and Immunogenicity of Live Oral Cholera Vaccine CVD 103-HgR in Children and Adolescents Aged 6–17 Years

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Long-Term Immunogenicity of Live Oral Cholera Vaccine CVD 103-HgR in Adolescents Aged 12–17 Years in the United States

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¹Stanford University School of Medicine, Stanford, California; ²Emergent BioSolutions Canada, Inc., Winnipeg, Canada; ³Emergent Travel Health, Inc., Redwood City, California
### Phase 4, randomized, double-blind placebo-controlled trial: analysis endpoints

<table>
<thead>
<tr>
<th>Safety</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Adverse events</td>
</tr>
<tr>
<td></td>
<td>• Solicited (study day 1–8)</td>
</tr>
<tr>
<td></td>
<td>• Unsolicited (through day 29)</td>
</tr>
<tr>
<td></td>
<td>• Serious (through day 181)</td>
</tr>
<tr>
<td></td>
<td>• Safety monitoring committee reviewed blinded data on adverse events Q6 months</td>
</tr>
</tbody>
</table>

| Immunogenicity                                                        | Classic Inaba serum vibriocidal antibodies (SVA)*                |
|                                                                      | • All participants: day 1, 11, and 29 (±2)                       |
|                                                                      | • Cohort 1 (12–17 years): Day 91 (±7) and 181 (±7)              |

| Dosing                                                                | % dose consumed                                                 |
|                                                                      | 5-point hedonic scale 30 minutes after consumption              |

*Sample size calculated for independent evaluation of 2 objectives in each age cohort: noninferiority to adults in seroconversion rate (96.7% CI = 2/3 of alpha), and minimum seroconversion rate of 70% (98.3% CI = 1/3 of alpha)
**INDIRECT EVIDENCE FOR**

- Cholera diarrhea, moderate to severe
- Cholera diarrhea, any severity

<table>
<thead>
<tr>
<th>Age</th>
<th>Evaluable N</th>
<th>Seroconverted N</th>
<th>% (98.3% CI)</th>
<th>Non-inferior to 18–45 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>18–45 years</td>
<td>2,687</td>
<td>2513</td>
<td>93.5 (92.3–94.6%)</td>
<td>REF</td>
</tr>
<tr>
<td>6–17 years</td>
<td>296</td>
<td>292</td>
<td>98.6 (95.9–99.6%)</td>
<td>YES</td>
</tr>
<tr>
<td>2–5 years</td>
<td>103</td>
<td>101</td>
<td>98.1 (91.5–99.6%)</td>
<td>YES</td>
</tr>
</tbody>
</table>

*a*≥4-fold rise in serum vibriocidal antibody titer. Seroconversion among 6–17 year and 2–5 year age groups was non-inferior to adults 18–45 years from a phase 3 lot consistency study based on prespecified 96.7% confidence interval (2/3 of alpha).

*b*In an oral challenge study of adults 18–45 years old: correlation coefficient between cumulative diarrhea (L) and fold-increase in SVA was -0.75 at 10 days and -0.69 at 3 months.

---

INDIRECT EVIDENCE FOR
- Cholera diarrhea, moderate to severe
- Cholera diarrhea, any severity

<table>
<thead>
<tr>
<th>Age</th>
<th>Day</th>
<th>CVD 103-HgR N</th>
<th>Placebo N</th>
<th>CVD 103-HgR GMT (95% CI)</th>
<th>Placebo GMT (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6–17 years</td>
<td>1</td>
<td>296</td>
<td>47</td>
<td>32 (29–35)</td>
<td>39 (30–53)</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>296</td>
<td>47</td>
<td>8,531 (7,270–10,009)</td>
<td>41 (29–58)</td>
</tr>
<tr>
<td></td>
<td>29</td>
<td>294</td>
<td>46</td>
<td>2,341 (2,031–2,697)</td>
<td>41 (29–59)</td>
</tr>
<tr>
<td>2–5 years</td>
<td>1</td>
<td>103</td>
<td>20</td>
<td>27 (24–30)</td>
<td>26 (19–36)</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>103</td>
<td>20</td>
<td>4,852 (3,445–6,832)</td>
<td>28 (20–39)</td>
</tr>
<tr>
<td></td>
<td>29</td>
<td>98</td>
<td>18</td>
<td>1,014 (741–1,387)</td>
<td>27 (21–36)</td>
</tr>
</tbody>
</table>

Secondary endpoint: GMTs

GMT: geometric mean titer

## INDIRECT EVIDENCE FOR
- Cholera diarrhea, moderate to severe
- Cholera diarrhea, any severity

<table>
<thead>
<tr>
<th>Age</th>
<th>Day</th>
<th>CVD 103-HgR N</th>
<th>Placebo N</th>
<th>CVD 103-HgR GMT (95% CI)</th>
<th>Placebo GMT (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Secondary endpoint: GMT mean fold increase</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6–17 years</td>
<td>11</td>
<td>296</td>
<td>47</td>
<td>268 (229–315)</td>
<td>1 (1–1)</td>
</tr>
<tr>
<td></td>
<td>29</td>
<td>294</td>
<td>46</td>
<td>73 (64–85)</td>
<td>1 (1–1)</td>
</tr>
<tr>
<td>2–5 years</td>
<td>11</td>
<td>103</td>
<td>20</td>
<td>182 (131–252)</td>
<td>1 (1–1)</td>
</tr>
<tr>
<td></td>
<td>29</td>
<td>98</td>
<td>18</td>
<td>38 (28–51)</td>
<td>1 (1–1)</td>
</tr>
</tbody>
</table>

GMT: geometric mean titer

## Outcome 3: serious adverse events$^a$

<table>
<thead>
<tr>
<th>Age</th>
<th>CVD 103-HgR N</th>
<th>Placebo N</th>
<th>CVD 103-HgR SAEs N</th>
<th>Placebo SAEs N</th>
</tr>
</thead>
<tbody>
<tr>
<td>6–17 years</td>
<td>303</td>
<td>48</td>
<td>1$^b$</td>
<td>0</td>
</tr>
<tr>
<td>2–5 years</td>
<td>123</td>
<td>103</td>
<td>0</td>
<td>1$^c$</td>
</tr>
</tbody>
</table>

$^a$Serious adverse events (SAEs) were collected through study day 181. SAE definition: an AE that met any of the following criteria: resulted in death, was life-threatening, required hospitalization or the prolongation of an existing hospitalization, resulted in a persistent or significant disability or incapacity, resulted in a congenital anomaly or birth defect, required medical or surgical intervention to prevent impairment or damage, other serious important medical event.

$^b$Right leg fracture determined to be unrelated to the vaccine

$^c$Pneumonia and asthma requiring hospitalization determined to be unrelated to placebo

### Outcome 4: non-serious adverse events

<table>
<thead>
<tr>
<th>Age</th>
<th>CVD 103-HgR</th>
<th>Placebo</th>
<th>CVD 103-HgR AEs</th>
<th>Placebo AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>N</td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>Solicited adverse events(^a) (day 1–8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6–17 years</td>
<td>322</td>
<td>49</td>
<td>199 (61.8%)</td>
<td>29 (59.2%)</td>
</tr>
<tr>
<td>2–5 years</td>
<td>146</td>
<td>26</td>
<td>59 (40.4%)(^b)</td>
<td>9 (34.6%)</td>
</tr>
<tr>
<td>Unsolicited adverse events(^c) (through day 29)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6–17 years</td>
<td>322</td>
<td>49</td>
<td>79 (24.5%)</td>
<td>16 (32.7%)</td>
</tr>
<tr>
<td>2–5 years</td>
<td>146</td>
<td>26</td>
<td>38 (26.0%)</td>
<td>6 (23.1%)</td>
</tr>
</tbody>
</table>

\(^a\)Includes tiredness, headache, abdominal pain, lack of appetite, nausea, vomiting, fever, and diarrhea. Frequencies of individual symptoms did not differ between vaccine and placebo groups, except among 2–5 year cohort: vomiting was significantly more frequent in the placebo group.

\(^b\)Includes one case of potentially life-threatening fever T>40°C

\(^c\)Most considered unrelated to study treatment per manufacturer.

---

Outcome 4: non-serious adverse events

- Solicited events
  - Each participant or parent/guardian recorded on a diary card on study day 1–8
  - On study day 11, blinded study staff reviewed diary cards with them and assigned a grade

- Unsolicited adverse events collected through day 29