GRADE Review and Work Group Plans

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For the Cholera Vaccine Work Group

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Acknowledgments

**ACIP Cholera Vaccine Work Group**
- Kashmira Date
- Sandra Fryhofer
- Mark Gershman
- Barbara Mahon
- Eric Mintz
- Kathy Neuzil
- Walt Orenstein
- Art Reingold
- Laura Riley
- Ed Ryan
- John Su
- Mary Wilson
- COL Margaret Yacovone

**CDC**
- Erin Burdette
- Sam Crowe
- Caroline Jackman
- Jessica Korona
- Amanda Cohn
- Wendy Carr
CVD 103-HgR is a live attenuated single-dose oral cholera vaccine

- No cholera vaccine currently available in the United States
- Vaccines available outside the United States require two doses
- CVD 103-HgR previously licensed in other industrialized countries, marketed as Orochol/Mutacol
  - Manufacture ceased for business reasons
- PaxVax acquired license to re-develop vaccine as Vaxchora™ (newer formulation)
  - BLA filed October 2015, adults ≥18 years old
  - FDA action date expected in mid-June
Policy question for GRADE review

- Should live attenuated oral cholera vaccine CVD 103-HgRbe recommended for use in adults $\geq 18$ years of age at risk of travel-related exposure to toxigenic *Vibrio cholerae* O1?
  - **Population**: Adults who live in the United States and are traveling to cholera-affected areas.
  - **Intervention**: CVD 103-HgR administered as a single oral dose.
  - **Current Option**: No oral cholera vaccine is currently recommended or available to adults in the U.S.
### Outcome measures included in evidence profile

<table>
<thead>
<tr>
<th>OUTCOME</th>
<th>IMPORTANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benefits</strong></td>
<td></td>
</tr>
<tr>
<td>Prevent cholera death</td>
<td>Critical</td>
</tr>
<tr>
<td>Prevent life-threatening (&gt;5L*) cholera diarrhea</td>
<td>Critical</td>
</tr>
<tr>
<td>Prevent severe (&gt;3L*) cholera diarrhea</td>
<td>Critical</td>
</tr>
<tr>
<td>Prevent cholera diarrhea of any severity</td>
<td>Important</td>
</tr>
<tr>
<td>Induce vibriocidal antibody response</td>
<td>Important</td>
</tr>
<tr>
<td><strong>Harms</strong></td>
<td></td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>Critical</td>
</tr>
<tr>
<td>Systemic adverse events</td>
<td>Critical</td>
</tr>
<tr>
<td>Decrease effectiveness of co-administered vaccines or medications</td>
<td>Critical</td>
</tr>
</tbody>
</table>

*Volume over course of illness*
Evidence retrieval

- Systematic review of PubMed and Embase papers in any language published between 1988, when CVD 103-HgR was first developed, and January 2016
- Efforts made to obtain available unpublished literature
- References of relevant papers reviewed
- Articles included if they presented data on CVD 103-HgR and
  - Involved human subjects
  - Reported primary data
  - Included data relevant to the outcome measures being assessed
  - Included data for a relevant dose (≈4 x 10^8–2 x 10^9 CFU)
Evidence retrieval

- 77 studies identified in initial review
  - 49 excluded
    - 41 either did not include CVD 103-HgR data or any primary data
    - 8 pediatric studies
    - 1 cost-benefit analysis
  - 28 studies in GRADE evaluation
Studies of CVD 103-HgR included in evidence review (n=28)

- Of the 28 studies
  - 3 of newer formulation (Vaxchora™)
    - All randomized controlled trials (RCTs)
  - 25 of older formulation
    - 18 RCTs
    - 7 observational studies

- 5 were challenge studies
  - 3 RCTs (1 new formulation)
  - 2 observational studies
**Evidence related to GRADE outcomes**

<table>
<thead>
<tr>
<th>OUTCOME</th>
<th>No. RCTs</th>
<th>No. observational</th>
<th>Data available</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benefits</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevent cholera death</td>
<td>4*</td>
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<td>Yes, limited</td>
</tr>
<tr>
<td>Prevent life-threatening (&gt;5L) cholera diarrhea</td>
<td>1*</td>
<td>0</td>
<td>Yes, limited</td>
</tr>
<tr>
<td>Prevent severe (&gt;3L) cholera diarrhea</td>
<td>3*</td>
<td>0</td>
<td>Yes</td>
</tr>
<tr>
<td>Prevent cholera diarrhea of any severity</td>
<td>4*</td>
<td>3</td>
<td>Yes</td>
</tr>
<tr>
<td>Induce vibriocidal antibody response</td>
<td>19*</td>
<td>3</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Harms</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>20*</td>
<td>4</td>
<td>Yes</td>
</tr>
<tr>
<td>Systemic adverse events</td>
<td>20*</td>
<td>4</td>
<td>Yes</td>
</tr>
<tr>
<td>Decrease effectiveness of co-administered vaccines or medications</td>
<td>3</td>
<td>1</td>
<td>Yes, limited</td>
</tr>
</tbody>
</table>

* Includes ≥1 RCT with the new formulation of CVD 103-HgR vaccine
**GRADE evidence type scoring method**

- **Initial evidence type:**
  - RCT (1), Observational (3)

- **Criteria for moving down** (-1, -2)
  - Risk of bias, inconsistency, indirectness, imprecision, publication bias

- **Criteria for moving up** (+1, +2)
  - Strength of association, dose response gradient, opposing plausible residual confounding

- **Final evidence type**
  1 = RCTs or overwhelming evidence from observational studies
  2 = RCTs with important limitations, or exceptionally strong evidence from observational studies
  3 = Observational studies, or RCTs with notable limitations
  4 = Clinical experience and observations, observational studies with important limitations, or RCTs with several major limitations

Strength of association: May be upgraded by one level for risk ratios >2 or <0.5; may be upgraded by two levels if risk ratio >5 or <0.2.
Evidence of benefits: prevention of cholera death

- Challenge studies not designed to assess this outcome
- One large field study showed no difference in deaths from diarrhea of any etiology between vaccinated and comparison populations
  - Cause of death assessed by verbal autopsy

<table>
<thead>
<tr>
<th>Study</th>
<th>Site</th>
<th>Type</th>
<th>Population</th>
<th>Time post-vaccination</th>
<th>Deaths, vaccinated persons</th>
<th>Deaths, comparison persons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levine 1988</td>
<td>U.S.</td>
<td>RCT</td>
<td>Adults</td>
<td>1 month</td>
<td>0/6</td>
<td>0/8</td>
</tr>
<tr>
<td>Tacket 1992</td>
<td>U.S.</td>
<td>Obs</td>
<td>Adults</td>
<td>4-6 months 8 days</td>
<td>0/14 0/11</td>
<td>0/15 0/11</td>
</tr>
<tr>
<td>Tacket 1999</td>
<td>U.S.</td>
<td>RCT</td>
<td>Adults</td>
<td>3 months</td>
<td>0/28</td>
<td>0/23</td>
</tr>
<tr>
<td>Chen, Cohen 2014*</td>
<td>U.S.</td>
<td>RCT</td>
<td>Adults</td>
<td>10 days 3 months</td>
<td>0/35 0/33</td>
<td>0/66</td>
</tr>
<tr>
<td>Richie 2000</td>
<td>Indonesia</td>
<td>RCT</td>
<td>Adults and children (2–41y)</td>
<td>Up to 4 years surveillance</td>
<td>6/33696 [diarrhea, any etiology]</td>
<td>8/33812 [diarrhea, any etiology]</td>
</tr>
</tbody>
</table>

* New formulation of CVD 103-HgR vaccine
Evidence type: prevention of cholera death (critical outcome)

- Insufficient evidence to assess prevention of cholera death

<table>
<thead>
<tr>
<th>Studies</th>
<th>Initial evidence</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Publication bias</th>
<th>Other</th>
<th>Final evidence</th>
<th>Overall evidence type</th>
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<tbody>
<tr>
<td>4 RCTs*</td>
<td>1 N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Very serious (-2)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
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* Includes ≥1 study with new formulation of CVD 103-HgR vaccine
Evidence of benefits: prevention of life-threatening (>5L) cholera diarrhea

- 1 RCT addressed outcome (new formulation of vaccine)
- Challenge with toxigenic *V. cholerae*O1 performed at 10 days or 3 months after vaccination
Evidence type: prevention of life-threatening (>5L) cholera diarrhea (critical outcome)

- Strong evidence from 1 RCT with newer formulation of vaccine that CVD 103-HgR prevents life-threatening cholera diarrhea

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<tbody>
<tr>
<td>1 RCT</td>
<td>1</td>
<td>No serious</td>
<td>No serious</td>
<td>No serious</td>
<td>No serious</td>
<td>No serious</td>
<td>Strength of assoc. (+2)</td>
<td>1</td>
<td>1</td>
</tr>
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Evidence of benefits: prevention of severe (>3L) cholera diarrhea

- 3 RCTs addressed outcome
- 2 challenge RCTs showed a strong consistent reduction in severe cholera diarrhea among vaccinated vs. comparison individuals

Note: Chen, Cohen 2014 study assessed outcome at multiple time points after vaccination
Evidence of benefits: prevention of severe (>3L) cholera diarrhea

- Field RCT: No significant difference in severe cholera diarrhea in vaccinated vs. comparison individuals
  - Conducted in Indonesia among children and adults
  - Individuals rather than clusters randomized
  - Cholera outcomes assessed by sentinel surveillance over 4 years
  - Incidence of cholera low during study period

Note: Chen, Cohen 2014 study assessed outcome at multiple time points after vaccination
Evidence type: prevention of severe (>3L) cholera diarrhea (critical outcome)

- Downgraded for inconsistency: 1 large field trial showed no effect
- Strong evidence from studies with old and new vaccine formulations that CVD 103-HgR prevents severe (>3L) cholera diarrhea

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* Includes ≥1 study with new formulation of CVD 103-HgR vaccine
Evidence of benefits: prevention of cholera diarrhea of any severity

- 4 RCTs, 3 observational studies addressed outcome

Note: Chen, Cohen 2014 and Tacket 1992 studies assessed outcome at multiple time points after vaccination
Evidence of benefits: prevention of cholera diarrhea of any severity

- 5 challenge studies
- 4 showed significant reduction in proportion developing cholera diarrhea (VE 51–100%)

Note: Chen, Cohen 2014 and Tacket 1992 studies assessed outcome at multiple time points after vaccination
Evidence of benefits: prevention of cholera diarrhea of any severity

- **1 field RCT:** No difference between vaccinated and comparison populations in cholera diarrhea detected by sentinel surveillance over 4 years
- **1 mass vaccination campaign during outbreak:** Incidence of cholera diarrhea lower in vaccinated vs. comparison populations

Note: Chen, Cohen 2014 and Tacket 1992 studies assessed outcome at multiple time points after vaccination
Evidence type: prevention of cholera diarrhea of any severity (important outcome)

- Downgraded for inconsistency: 1 large field trial showed no effect
- Strong evidence from studies with old and new vaccine formulations that CVD 103-HgR prevents cholera diarrhea of any severity

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<td>1</td>
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* Includes ≥1 study with new formulation of CVD 103-HgR vaccine
Evidence of benefits: vibriocidal antibody response

- **Vibriocidal antibodies**
  - best available marker for protection against cholera
  - serogroup-specific (O1 or O139) protection
  - protect against both biotypes (El Tor, Classical) and both serotypes (Inaba, Ogawa)

- **19 RCTs, 3 observational studies assessed immunogenicity**
Vibriocidal antibody response (Inaba)

- Consistent vibriocidal antibody response seen with older and newer formulation of vaccine

Note: Some studies assessed outcome in >1 group and/or at multiple time points after vaccination
Vibriocidal antibody response (Inaba)

- VE with new formulation $\geq 98$

Note: Some studies assessed outcome in >1 group and/or at multiple time points after vaccination
Evidence type: vibriocidal antibody response (important outcome)

- Observational studies with older vaccine downgraded for indirectness
- Strong evidence from studies with old and new formulations that CVD 103-HgR vaccine induces vibriocidal antibody response

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<td>Strength of assoc. (+2)</td>
<td>2</td>
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* Includes ≥1 study with new formulation of CVD 103-HgR vaccine
Evidence of harms: serious and systemic adverse events

- 20 RCTs, 4 observational studies, and post-marketing surveillance data

- **Serious adverse events**
  - 1 field RCT: No difference in overall mortality in vaccinated vs. comparison population over 4 years
  - No differences detected between vaccinated and comparison populations for any serious adverse events

- **Systemic adverse events**
  - 1 unpublished RCT with new formulation found slightly higher proportion with diarrhea in vaccinated vs. comparison persons (0.8% vs. 0)
  - Systemic adverse events occur at similar rates in vaccinated and comparison populations
Orochol® Post-marketing, spontaneously reported, serious unexpected adverse events, 1994–2004

- Of 528,765 Orochol® doses distributed:
  - Hospitalization with fever, gastroenteritis, vomiting, hemorrhagic CSF in 11-mo infant (1)
  - Guillain-Barre syndrome (1)
    - Received CVD 103-HgR, YFV, Ty21a, diphtheria, polio vaccines
  - Angioedema (1)
  - Loss of hair (1)

- Of 276,564 Orochol® E doses distributed (higher dose formulation):
  - No spontaneously reported adverse reactions
Evidence type: serious and systemic adverse events (critical outcome)

- Most evidence from studies of older formulation of vaccine (downgraded for indirectness)
- Relatively few recipients of newer formulation of vaccine (downgraded for imprecision)
- Serious adverse events uncommon
- Studies with old and new formulations of vaccine suggest adverse events occur at similar rates in vaccinated and comparison populations

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<td>20 RCTs*</td>
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<td>None</td>
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<tr>
<td>4 Obs</td>
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<td>No serious</td>
<td>Serious (-1)</td>
<td>No serious</td>
<td>No serious</td>
<td>None</td>
<td>4</td>
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* Includes ≥1 study with new formulation of CVD 103-HgR vaccine
Evidence of harms: decrease effectiveness of co-administered vaccines and medications

- 3 RCTs, 1 observational study evaluated outcome

- No effect identified on antibody response to live attenuated oral typhoid vaccine (Ty21a)
  - 62–83% given both vaccines (n=425) developed anti-Typhi antibodies vs. 66% given typhoid vaccine alone

- No effect identified on antibody response to yellow fever vaccine (17D)
  - 100% given both vaccines (n=58) developed anti-YF antibodies
Evidence of harms: decrease effectiveness of co-administered vaccines and medications

- 1 additional study evaluated CVD 103-HgR in combination with Ty21a, yellow fever vaccine, oral polio vaccine, mefloquine, chloroquine, and proguanil

- Lower vibriocidal seroconversion when chloroquine co-administered with CVD 103-HgR (67%) vs. CVD 103-HgR alone (91%)
Evidence type: decrease effectiveness of co-administered vaccines or medications (critical outcome)

- For typhoid or yellow fever vaccine: downgraded for indirectness (older formulation vaccine)
- No suggestion that CVD 103-HgR decreases effectiveness of typhoid (Ty21a) or yellow fever (17D) vaccines
- Insufficient evidence to determine effect on other co-administered vaccines or medications

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<td>4</td>
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## GRADE summary

<table>
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<tr>
<th>Outcome</th>
<th>Studies</th>
<th>Initial evidence</th>
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<tr>
<td>Prevent life-threatening cholera diarrhea</td>
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<td>Strength of assoc. (+2)</td>
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<tbody>
<tr>
<td>Serious/systemic adverse events</td>
<td>20 RCTs</td>
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<td>No serious</td>
<td>Serious (-1)</td>
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<td>Serious (-1)</td>
<td>No serious</td>
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<td>Decrease effectiveness of co-administered vaccines and medications</td>
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<td>Serious (-1)</td>
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</tr>
<tr>
<td></td>
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<td>3</td>
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<td>None</td>
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</tr>
</tbody>
</table>
CONSIDERATIONS FOR FORMULATING RECOMMENDATIONS FOR USE
Cholera epidemiology, United States

- Cholera rare in the United States
- Fewer than 25 cases per year reported since 2012
  - 42 cases in 2011, during cholera epidemic in Haiti
  - Large outbreak on flight from Argentina → Peru → U.S. (1992)
- Cholera cases in United States likely underreported
- Infections that occur while traveling that resolve before return to the U.S. are not captured by U.S. surveillance
  - Short incubation period
  - Little information is available about cases that occur while traveling
Clinical features and risk factors

- Cholera can be severe and rapidly life-threatening
- Overall risk of cholera is very low for most U.S. travelers
- Treatable if medical services readily available
- Certain populations at higher risk of exposure
  - May include healthcare personnel, outbreak response workers, persons visiting friends or relatives, persons traveling or living in cholera-affected areas for extended periods
- Certain populations at higher risk of poor outcomes
  - Low gastric acidity, blood type O
  - Persons without ready access to medical services
- Note: Sanitation, hygiene, safe water/food remain critical to preventing cholera and other enteric infections
Evidence type for benefits and harms

- Overall evidence type 1 for prevention of cholera diarrhea and induction of vibriocidal antibody response
- Overall evidence type 3 for safety (assessed by serious/systemic adverse events) and 2 for decreasing the effectiveness of co-administered vaccines and medications
- Insufficient data to evaluate whether CVD 103-HgR prevents death from cholera
- No data available on safety and efficacy in pregnant women
Balance between benefits and harms

- Strong evidence that CVD 103-HgR prevents cholera diarrhea
- Serious adverse events uncommon with older formulation of vaccine; limited evidence with newer formulation
- Systemic adverse events occur at similar rates in vaccinated and comparison groups
Values related to outcomes

- Prevent a severe, life-threatening illness in travelers at risk of cholera exposure or severe cholera illness, especially if medical care not readily accessible
Cost-effectiveness

- Not evaluated
- Risk of cholera is very low for most travelers to cholera-affected areas
- Travel vaccines are paid for by employers or by the travelers themselves, depending on the circumstances
Options for draft recommendations

- **Broad**: Recommend or consider for adults ≥18 years age planning to travel to a cholera-affected area
- **Targeted**: Recommend or consider for adults ≥18 years of age at high risk of exposure (e.g., cholera outbreak response workers) or severe illness
Next steps

- Based on review of the evidence for critical and important outcomes, WG concludes that vaccine is safe and effective
- WG continuing to discuss category A versus category B recommendation and whether specific risk groups should be emphasized in the recommendations
- WG evaluating evidence for duration of protection and for re-immunization
- WG evaluating evidence from selected subgroups, such as immunocompromised persons, separately from GRADE review
- WG evaluating pediatric studies separately from GRADE review, as a summary of these data may be helpful to clinicians considering off-label use in persons <18 years of age

Category A recommendations are made for all persons in an age- or risk-factor-based group. Category B recommendations are made for individual clinical decision making.
Discussion

- **Policy question:** Should CVD 103-HgR be recommended for use in adults at risk of travel-related exposure to toxigenic *Vibrio cholerae* O1?
  - Should specific risk groups be emphasized?

- **Are there additional data that would be helpful to ACIP to inform future discussions?**