Cholera vaccine update and proposed recommendations

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Advisory Committee on Immunization Practices Meeting • 22 June 2016

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Cholera infection

- Caused by toxigenic *Vibrio cholerae* O1 (>99% of global cases) or O139
- Watery diarrhea that may be severe and rapidly fatal without proper treatment
- Endemic in >50 countries; may also cause epidemics
- Rehydration can reduce fatality rate to <1%

Cholera among US travelers

- In the United States, most cases occur among travelers to cholera-affected areas
- Cholera is rare
  - Increase in cases in travelers from Haiti after epidemic began in October 2010
- Safe food and water and personal hygiene measures are key to prevention

Populations who may be at higher risk of cholera infection

- Travelers visiting friends and relatives
- Long-term travelers
- Travelers who do not follow safe food and water precautions and personal hygiene measures
- Healthcare workers and response workers with direct contact with body fluids from cholera patients

Populations who may be at higher risk of poor outcomes from cholera

- Travelers without ready access to rehydration therapy and medical care
- Travelers with a condition that carries increased risk of poor clinical outcomes from cholera
  - Blood type O
  - Pregnancy
  - Immunocompromising conditions
  - Cardiovascular disease, renal disease

CVD 103-HgR vaccine

- Live attenuated single-dose oral cholera vaccine
- Protects against toxigenic *V. cholerae* O1 infection
- More than 500,000 doses of previous formulation distributed
- Redeveloped as Vaxchora
- Efficacy assessed by immunogenicity and protection against oral cholera challenge

GRADE review

- CVD 103-HgR vaccine safe and effective for prevention of infection with toxigenic *V. cholerae* O1
- Overall evidence type: 2
  - Safety: evidence type 3
  - Efficacy: evidence type 1

Evidence types:
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

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Pregnant or breastfeeding women

- No data exist on use of CVD 103-HgR vaccine in pregnant or breastfeeding women
- Pregnant women are at risk of poor outcomes from cholera infection
- Vaccine not absorbed systemically
- Maternal exposure to CVD 103-HgR not expected to result in exposure of fetus or breastfed infant to vaccine

Immunocompromised populations

- No data exist on use of new CVD 103-HgR formulation in immunocompromised populations
- Study of older vaccine formulation in HIV+ adults in Mali
  - Vibriocidal seroconversion slightly lower among HIV-positive than HIV-negative participants (58% versus 71%)
  - No differences found between vaccinated and comparison populations for any systemic adverse events

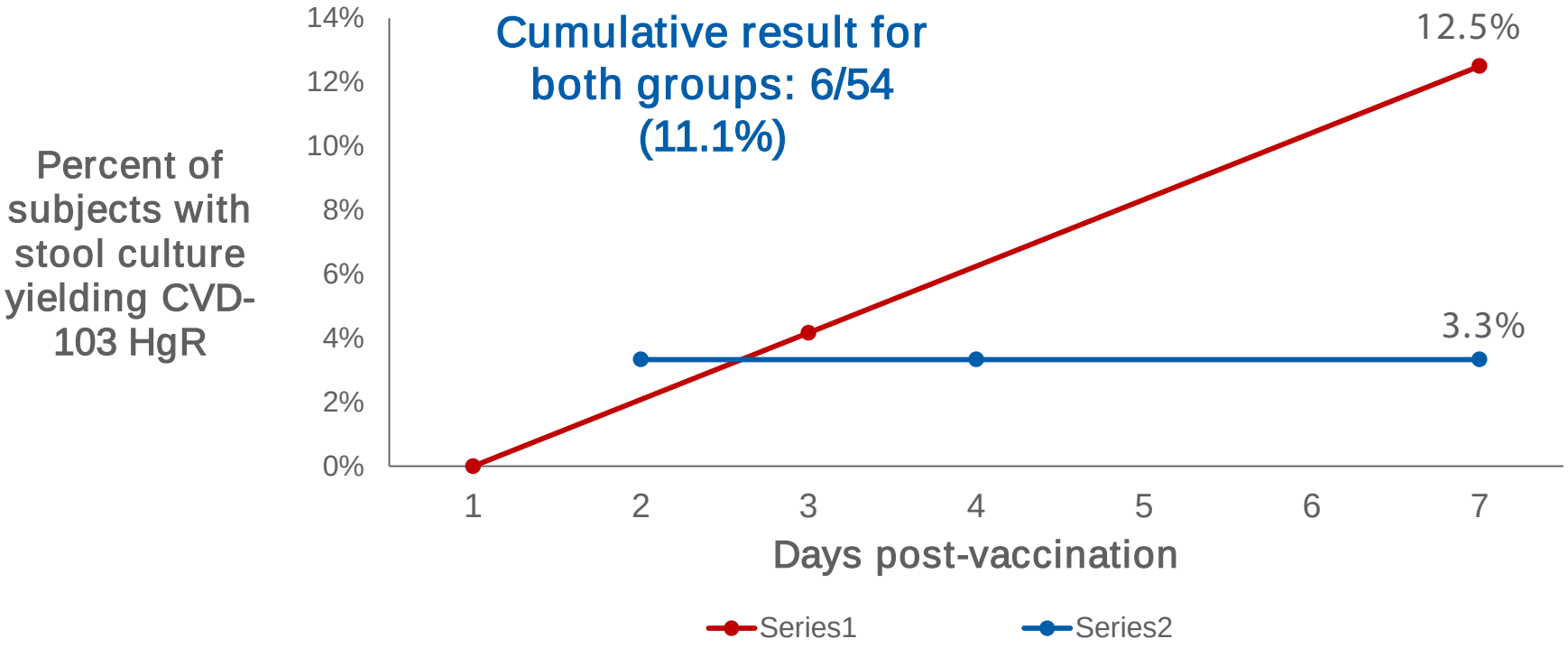
Perry RT et al, Bulletin of WHO. 76(1), 1998, pp. 63-71

Children

- No data exist on use of new CVD 103-HgR formulation in children
- Limited data exist on use of older formulation
  - 10 studies included participants 3 months–17 years old
  - Ecuador, Chile, Indonesia (none in United States)
  - No pediatric challenge studies
  - Vibriocidal antibody response (Inaba) VE 29–98%
  - No association detected between CVD 103-HgR and serious or systemic adverse events

References listed at end of presentation.

Shedding of new CVD 103-HgR formulation strain



Chen WH, Greenberg RN et al. Clin Vaccine Immunol. 2014;21(1):66–73.

Household transmission

- **New CVD 103-HgR formulation**
  - CVD 103-HgR not isolated from stools of 28 household contacts cultured 7 days post-vaccination
- **Older formulation**
  - CVD 103-HgR isolated from stool in <1% of household contacts cultured up to 5 days post-vaccination
  - Seroconversion detected in 3.7% of family contacts at 9 or 28 days

Chen WH, Greenberg RN et al. Clin Vaccine Immunol. 2014;21(1):66–73.
Simanjuntak CH et al. Journal Inf Dis. 1993;168:1169-76

Duration of protection from challenge studies

- **New formulation** vaccine efficacy for protection against severe (>3L) diarrhea

Time post-vaccination	Vaccine	Placebo	VE (95% CI)
10 days	2/35 (5.7%)	39/66 (59.1%)	90.3% (62.7–100%)
3 months	4/33 (12.1%)		**79.5%** (49.9–100%)

Chen WH, Cohen MB et al. Clin Infect Dis. 2016 Jun 1;62(11):1329-35.

- **Older formulation** vaccine efficacy for protection against diarrhea of any severity

Time post-vaccination	Vaccine	Placebo	VE
4–6 months	0/14 (0%)	10/15 (66.7%)	~100%

Tacket CO et al. J Infect Dis. 1992 Oct;166(4):837-41.

Duration of immune response (new vaccine formulation)

Vibriocidal antibody seroconversion

Study	Day 7	Day 10	Day 14	Day 28	Day 90	Day 180
[1] Vaccine (n=54)		83.3%	88.9%	81.5%		
[2] Vaccine (n=94)	79.8%	89.4%		90.4%	90.4%	**90.4%**
[2] Placebo (n=102)	2%	2%		2%	2%	2%

- No data exist on re-immunization with new CVD 103-HgR formulation

[1] Chen WH, Greenberg RN et al. Clin Vaccine Immunol. 2014;21(1):66–73.
[2] Chen WH, Cohen MB et al. Clin Infect Dis. 2016 Jun 1;62(11):1329-35.

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FDA announced Vaxchora approval on June 10, 2016

- Approved for use in adults 18–64y traveling to cholera-affected areas
- Limitations of use
  - Effectiveness not established in persons living in cholera-affected areas
  - Effectiveness not established in persons with pre-existing immunity due to previous exposure to *V. cholerae* or receipt of a cholera vaccine
  - Not shown to protect against disease caused by non-O1 serogroups

FDA announced Vaxchora approval on June 10, 2016

- Safety and effectiveness not established in immunocompromised persons
  - Vaccine strain may be shed in the stool of recipients for at least 7 days.
  - Use caution when considering whether to administer Vaxchora to individuals with immunocompromised close contacts.
- Establishment of pregnancy exposure registry
- Safety and effectiveness not established in persons <18y or ≥65y

Work group considerations for formulating recommendation option

- Evidence supports safety and efficacy of vaccine
- Cholera among travelers is rare, though can be severe
- Most travelers to cholera-affected areas are at low risk of severe infection
- Category A recommendation for a clearly defined population will be easier for clinicians to interpret and implement

Work group approach to recommendation option

- Category A recommendation for a defined subpopulation of travelers
- Recommendation requires assessment of the individual traveler's risk factors and travel plans
- Recommendation should be clear that vaccine is not routinely recommended for most travelers due to low risk of cholera

Work group approach to recommendation option

- Duration of protection beyond 3–6 months not known at this time
- No formal recommendations for re-immunization in the proposed option
- Assess data on re-immunization as it becomes available and update recommendation

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Recommendation for prevention of severe cholera among travelers

- Personal protective measures

- Use of CVD 103-HgR vaccine (Category A recommendation)

Overview of vaccine recommendation

Travel to an area of active toxigenic *V. cholerae* O1 transmission

AND

Increased risk of exposure to toxigenic *V. cholerae* O1

OR

Increased risk of poor outcome if infected

Personal protective measures

- All travelers to cholera-affected areas should follow safe food and water precautions and proper sanitation and personal hygiene measures as primary prevention strategies against cholera infection.
- Travelers who develop severe diarrhea should seek medical attention, particularly rehydration therapy, promptly.

Use of CVD 103-HgR vaccine

1. Vaccination against cholera is not routinely recommended for most travelers who are at low risk of exposure to toxigenic *V. cholerae* O1. Prevention of cholera and other diarrheal diseases primarily depends on following safe food and water precautions and personal hygiene measures.
2. The decision to vaccinate should be made after detailed assessment of the individual traveler's risk of exposure to toxigenic *V. cholerae* O1 and the traveler's risk of severe outcomes if infected.

Use of CVD 103-HgR vaccine

3. CVD 103-HgR vaccine is recommended for travelers to an area of active cholera transmission
   a. who are at increased risk of toxigenic *V. cholerae* O1 exposure, or
   b. whose individual risk factors or travel situations carry increased risk of poor clinical outcome if infected.

Use of CVD 103-HgR vaccine

3c. These populations include:

- People with increased risk of exposure to toxigenic *V. cholerae* O1
  - Travelers, including those visiting friends and relatives, who are unable to consistently follow safe food and water precautions and personal hygiene measures in an area of active toxigenic *V. cholerae* O1 transmission
  - Healthcare personnel and others who have direct contact with body fluids (vomitus or stool) from cholera patients

Use of CVD 103-HgR vaccine

3c. (continued)

- People with increased risk of poor clinical outcome if infected
  - Travelers who may be without rapid access to adequate rehydration and medical care
  - Travelers with a condition known to carry increased risk of poor clinical outcomes from cholera, such as low gastric acidity or blood type O
  - Travelers with chronic medical conditions, including but not limited to travelers with conditions such as cardiovascular or kidney disease who would tolerate dehydration poorly.

Footnotes

"CVD 103-HgR vaccine is recommended for travelers to an area of active cholera transmission[1]"

1 An **area of active cholera transmission** is defined as a province, state, or other administrative subdivision within a country with endemic or epidemic cholera caused by toxigenic *V. cholerae* O1 and includes areas with cholera activity within the last 1 year that are prone to recurrence of cholera epidemics; it does not include areas where rare sporadic cases have been reported. Most travelers from the United States do not visit areas with active cholera transmission. The vaccine is not routinely recommended for most travelers from the United States.

Footnotes

[People with increased risk of exposure to toxigenic V. cholerae *O1]*

"Travelers, including those visiting friends and relatives, who are unable to consistently follow safe food and water precautions and personal hygiene measures in an area of active toxigenic V. cholerae *O1 transmission*[2]*"*

[2] Long-term travelers and frequent travelers to areas of active cholera transmission may also be at increased risk of exposure, because the cumulative risk of exposure to unsafe food or water is presumed to be higher with longer duration of travel. However, data are limited on the duration of protection beyond 3–6 months afforded by vaccination with CVD 103-HgR.

Review: Recommendation for prevention of severe cholera among travelers

Personal protective measures

- Food, water, hygiene precautions
- Seek medical attention for diarrhea

Use of vaccine

- Not routinely recommended for most travelers
- Detailed assessment of traveler's risk of exposure and risk of severe outcomes
- CVD 103-HgR vaccine is recommended for travelers to an area of active cholera transmission
  - who are at increased risk of toxigenic *V. cholerae* O1 exposure, or
  - whose individual risk factors or travel situations carry increased risk of poor clinical outcome if infected.

Questions and discussion

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Pediatric studies

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