Background on cholera and CVD 103-HgR

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Advisory Committee on Immunization Practices
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Background on cholera

- Toxin-mediated, acute watery diarrheal illness
- Caused by **toxigenic Vibrio cholerae O1 or O139**
  - Curved, motile, Gram-negative rods
- Can be severe and rapidly fatal without proper treatment
- Endemic in >50 countries
- Can cause large epidemics
Microbiology and pathogenesis
Vibrio cholerae is a diverse species with pathogenic and non-pathogenic variants.

V. cholerae (>200 serogroups)
Vibrio cholerae is a diverse species with pathogenic and non-pathogenic variants

V. cholerae (>200 serogroups)

O1
biotypes: El Tor, classical
serotypes: Inaba, Ogawa
Vibrio cholerae is a diverse species with pathogenic and non-pathogenic variants.

- Toxigenic O1
- Toxigenic O139

V. cholerae (>200 serogroups)

Cholera epidemics
Vibrio cholerae is a diverse species with pathogenic and non-pathogenic variants. *V. cholerae* (>200 serogroups) includes:
- **Toxigenic O1**
- **Toxigenic O139**
- **Non-toxigenic O1, O139**
- Other pathogenic serogroups (± toxigenic)

These variants can lead to:
- Cholera epidemics
- Gastroenteritis
Cholera epidemics are associated with unsafe water and inadequate sanitation

- *V. cholerae* has an aquatic reservoir
- Human infection
  - ingestion of contaminated water or food
  - direct fecal-oral transmission
  - secondary cases rare if sanitation adequate
  - incubation period: hours to 5 days
Cholera is a toxin-mediated disease.
Cholera is a toxin-mediated disease.

Unusual ability to survive and replicate in the small intestine.
Cholera is a toxin-mediated disease.

Non-invasive (do not enter the intestinal epithelium)
Cholera is a toxin-mediated disease

Produce cholera toxin
Cholera toxin subunit A enters the cytoplasm and causes secretory diarrhea.

Cholera is a toxin-mediated disease.
Epidemiology
Cholera can cause explosive epidemics

- Seven pandemics have been reported since 1817
- The **current global pandemic (El Tor O1)** began in 1961
- Serogroup O139 first emerged in 1992, in Asia
  - first non-O1 cause of epidemic cholera
  - now causes a small portion of cases
Asia and sub-Saharan Africa have the highest burden of cholera deaths

Countries reporting cholera deaths and imported cases to the World Health Organization (WHO), 2019

Cholera cases reported to WHO increased during 2017–2019

Annual cholera cases and mortality reported by year –WHO, 1989–2019

Cholera in the United States and other high-income countries is primarily travel-associated

- Most international travelers from the United States do not get cholera
  - Do not visit areas with active cholera transmission
  - Have good access to safe food and water
- CDC monitors areas with active cholera transmission

https://wwwnc.cdc.gov/travel/diseases/cholera#areas
Like most infections, cholera is underreported in the United States.
Cholera in the United States, 2001–2011

- 111 cholera cases over 11-year period
- Age
  - 1–85 years (median 44 years)
  - 15 (14%) 2–19 years old
- 108 diagnosed by stool culture; 107 were *V. cholerae* O1
- No deaths

90 (81%) cases associated with international travel, 2001–2011

Oct 2010: onset of epidemic cholera in Haiti

Cholera in the United States, 2012–2018

- 64 patients with cholera reported
- Age
  - 11 months–87 years (median 51 years)
  - 5 (8%) 2–17 years old
- All *V. cholerae* O1
- 2 deaths (adults)
## Cholera in the United States, 2012–2018

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*International travel in the 7 days before illness began*
56 (88%) cases were travel-associated

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5 (8%) cases in children and adolescents 2–17 years old

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*International travel in the 7 days before illness began
Annual case counts 15 or fewer during 2012–2018
Clinical manifestations and diagnosis
Clinical manifestations of cholera infection vary

Asymptomatic ~75%

Cholera gravis ~10%

Risk factors:
- High dose exposure
- Low gastric acidity
- Blood group O
Cholera gravis is rapidly fatal if untreated

- Profuse watery diarrhea
- “Rice-water stools” flecked with mucus and epithelial cells
- Vomiting
- Leg cramps
- Severe dehydration
  - loss of skin turgor
  - hypotension
  - weak pulse
  - altered mental status
A definitive diagnosis of cholera is based on culture of stool or rectal swab

- Transport media and selective culture media needed
- Other stool tests
  - Rapid antigen
  - Darkfield microscopy
  - Molecular assays
- Acute/convalescent serology sometimes used
Fluid management is the primary focus of cholera treatment

- Patients with cholera gravis may require up to 350 mL/kg of fluids within the first 24 hours of illness
- Moderately to severely ill patients should receive antibiotic therapy
Immune response and vaccines
Immune response to cholera is serogroup-specific (O1 or O139)

- El Tor O1 and O139
  - genomes are very similar
  - identical cholera toxin genes
- Immune responses targeting cholera toxin common after cholera; do not mediate long-term protection
- Vibriocidal antibodies are best marker for protection against *V. cholerae* infection
  - Every two-fold increase associated with ~40% reduction in risk of cholera*
- Lipopolysaccharide-specific memory B cells may play role in mediating long-term protection**

CVD 103-HgR was derived from wild-type V. cholerae O1

- Single-dose, live, attenuated oral vaccine
  - Inaba serotype, classic biotype
  - Cross-protective against other O1 serotypes and biotypes
  - 94% of gene encoding enterotoxin subunit A deleted
  - Expression of non-toxic B subunit left intact
  - Contains a marker to differentiate from wild-type Vibrio

- Lyophilized (freeze-dried powder)
- Reconstituted with a buffer solution to neutralize stomach acid
Commercial formulations of CVD 103-HgR

- Orochol, Mutacol (Berna)
  - $5 \times 10^8$ colony-forming unit (CFU) dose
  - Licensed in non-US countries in the 1990s
  - Production discontinued in 2004
Commercial formulations of CVD 103-HgR

- **Vaxchora** (Emergent BioSolutions)
  - Dose range: $4 \times 10^8$–$2 \times 10^9$ CFU
  - Volume with buffer
    - 100 ml if ≥6 years
    - 50 ml if 2–5 years
  - Licensed by FDA
    - Adults 18 – 64 years (June 2016)
    - Children 2–17 years (December 2020)
Current ACIP recommendations for lyophilized CVD 103-HgR

Recommendations of the Advisory Committee on Immunization Practices for Use of Cholera Vaccine

Weekly / May 12, 2017 / 66(18);482-485

Karen K. Wong, MD¹; Erin Burdette, MPH¹; Barbara E. Mahon, MD¹; Eric D. Mintz, MD¹; Edward T. Ryan, MD²; Arthur L. Reingold, MD³ (View author affiliations)
Work group findings — efficacy & immunogenicity

- Efficacy against severe diarrhea (fecal output >3L/24 hours) after oral toxigenic V. cholerae O1 challenge*
  - Current formulation: estimated to be 90% at 10 days, 80% at 3 months
  - Similar efficacy in studies of the previous formulation

- Vibriocidal antibody response
  - Both formulations of the vaccine effectively induce these

*GRADE evidence type 1
Work group findings — adverse events

- Adverse events**
  - No vaccine-related serious adverse events for either formulation
  - Current formulation: slightly higher prevalence of diarrhea (mostly mild) among vaccine vs. placebo recipients (3.8% vs. 1.6%)
  - No other differences between vaccinated and unvaccinated groups
ACIP currently recommends CVD 103-HgR for adult travelers (18–64 years old) from the United States to an area of active cholera transmission.
ACIP currently recommends CVD 103-HgR for adult travelers (18–64 years old) from the United States to an area of active cholera transmission.

Policy topic under consideration:
Should ACIP cholera vaccine recommendations be expanded to include children and adolescents 2–17 years old?
Recently published pediatric studies

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

James M. McCarty,1* Emma C. Gierman,2 Lisa Bedell,2 Michael D. Lock,2 and Sean Bennett2
1Stanford University School of Medicine, Stanford, California; 2PaxVax, Inc., Redwood City, California

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
Studies of prior formulation of CVD 103-HgR among children

Safety and immunogenicity of single-dose live oral cholera vaccine CVD 103-HgR in 5-9-year-old Indonesian children

Suharyono CYRUS SIMANJUNTAK NANCY WITHAM NaraIn PUNJABI D. Gray Heffner GenevieVe losonSky HARDJINING TOTOSUDIRJO ATTI R. Rifai JOHN CLEMENS YU LEUNG LIM DONALD BURR STEVEN S. Wasserman JAMES KAPER KURT SORENSON STANLEY CRYZ MYRON M. LEVINE


Tolerancia, immunogenicidad, excreción y transmisión de la vacuna anti-cólera oral viva, CVD 103-HgR. Estudio paralelo doble ciego en niños chilenos de 24 a 59 meses.

Safety, Immunogenicity, and Transmissibility of Single-Dose Live Oral Cholera Vaccine Strain CVD 103-HgR in 24- to 59-Month-Old Indonesian Children


Efficacy trial of single-dose live oral cholera vaccine CVD 103-HgR in North Jakarta, Indonesia, a cholera-endemic area

Emily Richie,*, NaraIn H. Punjabi, Yuwono Sihardha, Kenny Pecotusan, Melane Sukandar, Steven S. Wasserman, Murad Lesmana, Ferry Wangauputra, Sri Pandam, Myron M. Levine**, Peter O'Hanley*, Stanley J. Cryz, Cyrus H. Simanjuntak*

Adverse events after oral vaccination against cholera with CVD103-HgR

Gerhard Wiedermann,1 Herrwig Kollaritsch,2 Eva Jeschké,1 Michael Kundi,1 Christian Herzog,1 and Bernhard Wegmüller1

1 Institute for Specific Prophylaxis and Tropical Medicine, and 2 Institute for Environmental Hygiene, University of Vienna, Austria

2 Swiss Serum and Vaccine Institute (SSVI), Berne, Switzerland
Studies of prior formulation of CVD 103-HgR among children

- **5x10^8 CFU dose** was much less immunogenic among children in Indonesia than among adults in industrialized countries*

- **5x10^9 CFU dose**
  - 51–81% vibriocidal seroconversion
  - Shedding of vaccine strain was infrequent
  - Vaccine generally well tolerated; fever more common among vaccine recipients in one study (18 vs. 9%)**
  - Single-dose did not confer long-term protection***
  - **Dose was higher than Vaxchora (4x10^8–2x10^9 CFU)**

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** Simanjuntak et al. *JID.* 1993;168:1169-76
*** Richie et al. *Vaccine.* 2000; 18; 2399-2410
Summary

- Cholera
  - Toxin-mediated, acute watery diarrheal illness that can be severe and rapidly fatal without proper treatment
  - Endemic in >50 countries and can cause explosive epidemics
  - Most US cases occur among travelers to cholera-endemic areas
  - Immune response is serogroup-specific (O1 or O139)
- CVD 103-HgR
  - Single-dose, live, attenuated serogroup O1 oral vaccine
  - ACIP currently recommends for adult travelers (18–64 years old) from the United States to an area of active cholera transmission
Thank you!

For more information, contact CDC
1-800-CDC-INFO (232-4636)

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.