Update on Cholera Vaccines

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“A fresh outbreak of cholera has killed five people from more than 100 recorded cases, state media reported on Tuesday, raising fears of a repeat of last year's epidemic that claimed more than 4,000 lives. The southern African country suffered the continent's worst cholera outbreak in 15 years between August 2008 and June this year after its public health and water and sanitations systems collapsed”.

Reuters
Outline of presentation

Currently licensed Cholera Vaccines
- Dukoral – Crucell, available and WHO pre-qualified
- Orochol – Crucell, no longer produced
- Shanchol – Shantha Biotechnics, WHO pre-qualification pending
  - ORC-VAX (and mORC-VAX) – VaBiotech (Vietnam); licensed and used nationally

New cholera vaccines under clinical development (not discussed today)
- Peru-15 (US/China)
- V. cholerae 638 (Cuba)
- VA1.4 (India)
# Vaccine Landscape – licensed vaccines

<table>
<thead>
<tr>
<th>Supplier</th>
<th>Crucell / SBL Vaccine</th>
<th>Shantha Biotech</th>
<th>Crucell / Berna</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine</td>
<td>Dukoral</td>
<td>Shanchol</td>
<td>Orochol / Mutachol</td>
</tr>
<tr>
<td>Strain / Antigen</td>
<td>Killed <em>Vibrio cholerae</em> O1 strains (serotypes: Inaba &amp; Ogawa; biotypes: El Tor &amp; classical) + rCTB</td>
<td><em>Vibrio cholerae</em> O1 &amp; O139 without CTB</td>
<td>Reformulated Bivalent <em>Vibrio cholerae</em> O1 (same formulation as in Dukoral) &amp; O139, without CTB</td>
</tr>
<tr>
<td>Adjuvant / Platform</td>
<td>Killed <em>Vibrio cholerae</em> + rCTB</td>
<td>Killed <em>Vibrio cholerae</em></td>
<td>Live attenuated <em>Vibrio cholerae</em> + CTB</td>
</tr>
<tr>
<td>Administration Route</td>
<td>Oral</td>
<td>Oral</td>
<td>Oral</td>
</tr>
<tr>
<td>Formulation</td>
<td>Liquid</td>
<td>Liquid</td>
<td>Lyophilized</td>
</tr>
<tr>
<td>Presentation</td>
<td>2 unit-dose vials + 2 sachets of buffer</td>
<td>Single dose vial</td>
<td>Double-chambered aluminum foil sachet containing CVD103-HgR and buffer</td>
</tr>
<tr>
<td>Dosing Schedule</td>
<td>2 doses (0, 1-2wks), Single dose booster every 3 yrs (for 2-5y 3 doses and single dose boosting after 6 mo are recommended in licensure brochure)</td>
<td>2 doses (1-2wks apart) revaccination expected every 3 yrs</td>
<td>Single dose</td>
</tr>
<tr>
<td>Target Population for Licensure</td>
<td>≥ 2yo (safety and immunogenicity tested down to 6 mo)</td>
<td>≥ 1yo</td>
<td>≥ 2yo</td>
</tr>
<tr>
<td>Safety</td>
<td>Very safe</td>
<td>No major safety concerns</td>
<td>No major safety concerns</td>
</tr>
<tr>
<td>Efficacy</td>
<td>56-95% protection</td>
<td>68% protection</td>
<td>60-90% protection</td>
</tr>
<tr>
<td>Duration of Protection</td>
<td>3 yrs</td>
<td>At least 2 years</td>
<td>~3mo</td>
</tr>
<tr>
<td>Licensure Date (Location)</td>
<td>1991 (Sweden)</td>
<td>2009 (India)</td>
<td>1993 (Switzerland)</td>
</tr>
<tr>
<td>Estimated WHO Prequalification Date</td>
<td>2004</td>
<td>2011 (?)</td>
<td>(no longer manufactured)</td>
</tr>
</tbody>
</table>
The Dukoral® oral cholera vaccine

- Dosage:
  - 2 doses, 1-week interval
  - children 2-5 years: 3 doses

- Booster dose after 2-3 years in subjects ≥6 years
  - children, booster after 6 months

- 3 ml vaccine is dissolved in 150 ml buffer solution
  - Chlorinated water can be used

- The interval between the two doses of Dukoral® is a minimum of 7 days

- Full protection is expected one week after the 2nd dose, i.e. two weeks after the 1st dose
**Protective efficacy against cholera**

- 85% short term protection
  - Protection for 3 years in adults and children ≥6 years
  - Children 2-5 years protected for 6 months
- 78% protection (CI 39-92%) in African population in Moçambique for at least 5 months

**Added value protection against ETEC**

- 67% protective efficacy against LT and LT/ST ETEC for at least 3 months
# The Bangladesh Field Trial (1985)

<table>
<thead>
<tr>
<th>Follow-up period</th>
<th>Protective efficacy % (95% confidence interval)</th>
<th>WC-only vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>rCTB-WC vaccine*</td>
<td>All ages</td>
</tr>
<tr>
<td>6 months</td>
<td>85% (56-95%)</td>
<td>100%</td>
</tr>
<tr>
<td>1st year</td>
<td>64% (50-74%)</td>
<td>44%</td>
</tr>
<tr>
<td>2nd year</td>
<td>52% (30-76%)</td>
<td>33%</td>
</tr>
<tr>
<td>3rd year</td>
<td>19% (&lt;0-46%)</td>
<td>-</td>
</tr>
</tbody>
</table>

* The B subunit added significantly to protection for the first 9 months of follow-up

Clemens JD et al. Lancet 1986; 19:124-7;
The Moçambique case control study

- Vaccination campaign during December-January 2004, in Beira
- 14,164 subjects received at least one dose
- Case-control study during January-May

Effectiveness:
- 78% protection (CI: 39%-92%) in ITT-population
- 89% (CI: 7%-99%) against severe dehydration
- 84% (CI: 43%-95%) in PP-population

Vaccine equally effective in children <5 years

Oral killed WC cholera vaccines confer herd protection to non-vaccinated individuals

- Incidence of cholera among placebo recipients inversely related to levels of vaccine coverage

- Vaccine coverage ranged from 4% to 65%

- Incidence of cholera among children <2 yr ranged from 18.9 to 8.6 per 1,000

- Significant protective efficacy remained after adjustment for level of vaccine coverage [55% (CI 41-66% - p <0.001)]

Orochol®: Oral Cholera Vaccine

- Active immunization against cholera (Vibrio cholerae)
- CVD 103-HgR, based on Classical Inaba
- Children ≥2 years and adults
- Liquid formulation
- Two different potencies
  - Travelers: Orochol®, 2-10x10^8 CFU
  - Endemic regions: Orochol E®, 2-10x10^9 CFU
- Single dose
- Start of protection ≥ 8 days, booster at 6 months

Not currently produced
Ad-hoc group of experts on cholera vaccines
28 October 2009

Efficacy in a double-blind, placebo-controlled challenge trials in US volunteers

Protective efficacy: 91% (P<0.01)

- A single dose of 2-8x10^8 live vaccine cells confers 80-100% protection against challenge with wild type Vibrios administered with buffer, 3 months later
- Protection from 1 week to 6 months (longest interval tested)

Orochol®: Protective efficacy in the field

- Immunogenicity observed lower in certain developing countries
  - development of Orochol® E (10⁹ CFU/g)

- Field trial in North Jakarta, Indonesia
  - >67,000 people, 2-41 years of age
  - not significant protective efficacy, but very low incidence of cholera

- Mass vaccination after outbreak (El Tor) in Micronesia
  - protective efficacy 79% (95% CI 72-84)
  - retrospective cohort analysis, under real field conditions

Shanchol™: Oral cholera Vaccine

- Five strains of *V. cholerae* (similar to the Dukarol® vaccine)
- Increased LPS content in this vaccine
  - Doubled El Tor content to $5 \times 10^{10}$ cells
  - Added $5 \times 10^{10}$ formalinized *V. cholerae* O139 cells
- Two dose vaccine,
- Licensed in India in February 2009
- WHO application for pre-qualification in September 2009
Development of the Bivalent Cholera Vaccine (O1 and O139)

- Changed strains to remove residual toxicity
- Added O139 strain
- Increased LPS content of the vaccine


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SHANCHOL™: Interim Analysis after 2 years

- Randomized, placebo-controlled study
  - >67,000 young children / adults enrolled
  - Two doses of vaccine

- Results
  - Safe and immunogenic
  - Confers 68% protection overall over 2 years
  - Protection seen in all age groups

- Surveillance continuing to assess longer term protection and potential herd protection

<table>
<thead>
<tr>
<th>Age Group (yrs)</th>
<th>Protective Efficacy (95% CI)</th>
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<tbody>
<tr>
<td>1 - &lt;5</td>
<td>53% (50-86)</td>
</tr>
<tr>
<td>5 - &lt; 15</td>
<td>88% (36-74)</td>
</tr>
<tr>
<td>≥15</td>
<td>66% (40-73)</td>
</tr>
<tr>
<td>All age groups</td>
<td>68%</td>
</tr>
</tbody>
</table>
Summary

● Oral Cholera Vaccines
  ● One WHO pre-qualified, two-dose oral cholera vaccine – expensive but available
  ● One two-dose oral cholera vaccine - within sight of WHO PQ – less expensive
  ● One single-dose, live oral cholera vaccine – no longer produced
  ● One two-dose nationally produced vaccine in Vietnam, administered to millions of people since 1997

● All have good safety profiles

● All have good to moderate efficacy in the field setting
  ● Protection is against Classical and El Tor strains
  ● Protective efficacy is observed in young children (~1 year olds) and adults
  ● Duration of protection is from 6 months to at least 2 years
  ● Anticipated to exert a major impact on cholera through both direct and herd protective effects