IVI Cholera Activities

5th Initiative Against Diarrheal and Enteric Diseases in Asia (IDEA)
Hanoi, March 6-9, 2017.

Dr. Julia Lynch
Deputy Director General
Development and Delivery
Outline

• Introduce IVI
• Review OCV Development
  • mORCVAX
  • Shanchol
  • Euvichol
  • Cholvax
• Single Dose Study
• Campaigns and Demonstration projects
IVI is a Vaccine R&D center with a Global Health mission

**VISION**
Developing countries free of suffering from infectious diseases

**MISSION**
Discover, develop and deliver safe, effective and affordable vaccines for global public health

International Organization
- UNDP initiative
- First international organization in Korea (1997)
- 35 countries and WHO as state parties

Global Vaccine Research Institute
- HQ and laboratory in Seoul
- Field programs in 29 countries: Asia, Africa, Latin America
IVI Full Spectrum: Bench to Delivery

DISCOVER
- Pathogen genotyping
- Novel antigens
- Novel adjuvants
- New delivery mechanisms
- New routes of administration

DEVELOP
- Laboratory process development
- Assay development
- Technology transfer for large-scale production
- Clinical development
- Regulatory expertise

DELIVER
- Epidemiological and Socioeconomic studies
- Vaccine feasibility/acceptance
- Field effectiveness studies
- Cost-effectiveness and impact analyses
- Dissemination to stakeholders

Safe, effective, affordable and sustainable vaccine introduction
Development of Killed Oral WC Vaccine

- Technology transfer from University of Gothenburg, Professor Jan Holmgren to VABIOTECH in 1980s
  - Inactivated Whole Cell-only vaccine, without CTB component
  - Vaccine reformulated by VABIOTECH, proven safe and effective in Vietnamese people and licensed as ORC-Vax™ in 1997
- IVI engaged VABIOTECH to modify and reformulate vaccine to meet WHO standards (2004)
  - Modification of Strains, Production, Standardization & QC
  - A Safety and Immunogenicity Study of a 2-Dose Regimen of the Reformulated Bivalent Killed Oral Cholera Vaccine in Vietnamese Subjects (NIHE/IVI)
  - Licensed in Vietnam (mORCVAX™)
**Cholera Vaccine (Inactivated Whole Cell Oral Cholera vaccine)**

**IVI Technology Transfers**

<table>
<thead>
<tr>
<th>Company</th>
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<th>Stage of development</th>
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<td>Shantha (India)</td>
<td>Technology transfer May 2008</td>
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</table>

- Because NRA of Vietnam not recognized by WHO at that time, mORCVAX could not be WHO approved and made available on global PH market
- IVI Tech transferred the vaccine to Shantha in 2008 for production in India → Shanchol
Shanchol Trial: Phase III Study of the Reformulated Bivalent Killed Oral Cholera Vaccine in Kolkata (NICED/IVI)

- To assess the protection of a two-dose regimen of the reformulated oral killed WC cholera vaccine against episodes of cholera severe enough to require medical treatment
- A cluster-randomised, double-blind, placebo-controlled trial
  - Cholera endemic urban slums of Kolkata, India
  - 65,000 subjects (3,478 clusters)
  - Age > 1 year (excluding pregnant women)
  - Two doses, 14 days apart
OCV Safety: Shanchol Common Adverse Events

- After Dose 1 Vaccine
- After Dose 1 Placebo

- After Dose 2 Vaccine
- After Dose 2 Placebo

Symbiosis

- Diarrhea
- Vomiting
- Fever
- Abdominal pain
- Rash
- Weakness
- Nausea
- Itching
- Cough
- Dizziness
- No with ≥ one SAE
## Protective Efficacy during Three Years of Follow-up in Per Protocol Analyses, by Year of Follow-up

<table>
<thead>
<tr>
<th></th>
<th>First Year</th>
<th>Year of Follow-up</th>
<th>Third year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vaccine</td>
<td>Placebo</td>
<td>Vaccine</td>
</tr>
<tr>
<td></td>
<td>n=31,93</td>
<td>n=34,96</td>
<td>n=30,53</td>
</tr>
<tr>
<td>Cholera Episodes</td>
<td>11</td>
<td>23</td>
<td>9</td>
</tr>
<tr>
<td>Incidence (per 100,000 person-days)</td>
<td>.10</td>
<td>.19</td>
<td>.08</td>
</tr>
<tr>
<td>Protective Efficacy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(95% CI lower boundary)</td>
<td>41%</td>
<td>(-13%)</td>
<td>76%**</td>
</tr>
</tbody>
</table>

* *p<.05; ** p<.01
5 year efficacy of a bivalent killed whole-cell oral cholera vaccine in Kolkata, India: a cluster-randomised, double-blind, placebo-controlled trial

Saikat K Bhattacharjee, Dipakun Saha, Mohammad Ali, Samiran Konar, Young Ae You, Jayaprakash Manca, Sowmya Subramanian, Sowjanya K Niyogi, Jan K Kiyeng, Sameer Satpute, Mahesh K Puri, Derek Ryan Kim, Jacqueline D. Dews, Jan Holmgren, Rodney Cushions, Manpreet Singh Dhingra, Adrian Danner, G Bhakta, Ana Lora Lopez, Thomas F Wierzba, John D Clemens

Summary

Background Efficacy and safety of a two-dose regimen of bivalent killed whole-cell oral cholera vaccine (Shantha Biotechnics, Hyderabad, India) to 5 years is established, but long-term efficacy is not. We aimed to assess protective efficacy up to 5 years in a slum area of Kolkata, India.

Methods In our double-blind, cluster-randomised, placebo-controlled trial, we assessed incidence of cholera in non-pregnant individuals older than 1 year residing in 1911 dwellings (clusters) in Kolkata, India. We randomly allocated participants, by dwelling, to receive two oral doses of modified killed bivalent whole-cell cholera vaccine or heat-killed Escherichia coli K12 placebo, 14 days apart. Randomisation was done by use of a computer-generated sequence in blocks of four. The primary endpoint was prevention of episodes of culture-confirmed Vibrio cholerae O1 diarrhea severe enough for patients to seek treatment in a health-care facility. We identified culture-confirmed cholera cases among participants seeking treatment for diarrhea at a study clinic or government hospital between 14 days and 1825 days after receipt of the second dose. We assessed vaccine protection in a per-protocol population of participants who had completed two doses of assigned study treatment.

Findings Of 31932 recipients of vaccine and 219 of 34968 recipients of placebo developed cholera during 5 years follow-up (incidence 2.2 per 1000 in the vaccine group and 6.3 per 1000 in the placebo group). Cumulative protective efficacy of the vaccine at 5 years was 65% (95% CI 52.74%; p<.001), and point estimates by year of follow-up suggested no evidence of decline in protective efficacy.

Interpretation Sustained protection for 5 years at the level we reported has not been noted previously with other oral cholera vaccines. Established long-term efficacy of this vaccine could assist policy makers formulate rational vaccination strategies to reduce overall cholera burden in endemic settings.

 Funding Bill & Melinda Gates Foundation.

Introduction

Cholera is a serious global public health problem because clean drinking water and sanitation are not universally available, and appropriate case management is not accessible to many patients. In endemic countries alone, about 1-4 billion people are at risk of cholera and an estimated 2-8 million cases and 91000 deaths occur each year. More than half these cases and deaths occur in cholera-endemic countries in Asia and Africa.1 Furthermore, recent outbreaks in Cuba, Haiti, and Zimbabwe show the ability of this disease to spread rapidly to new areas and to produce outbreaks with substantial morbidity and mortality. Because of their capacity to spread rapidly, cholera outbreaks can overwhelm existing public health infrastructures and require substantial resources. The economic burden of cholera in African countries alone in 2005-07 ranged from US$39 million to US$156 million per year, dependent on the estimate of average life expectancy used.2 Additional preventive interventions are needed.

To complement improvements in access to water and sanitation and rehydration therapies, much attention has been given to development of a cholera vaccine. After several studies in the 1960s showed that injectable whole-cell cholera vaccines conferred only modest protection of short duration, often with significant side-effects, researchers focused on oral vaccines that could efficiently stimulate local immunity in the gut.3 The first oral cholera vaccine to be prequalified by WHO for purchase by UN agencies contains a mixture of killed Vibrio cholerae O1 bacteria and the non-toxic B subunit of cholera toxin, and is marketed under the trade name Dukoral ( Crucell, Netherlands). This vaccine was licensed largely on the basis of studies done more than 20 years ago in Bangladesh4 and Peru5 that showed 85% protection for the first 4-6 months and 60% protection for 2 years after a primary regimen of two or three doses. The protection declined substantially in the third year and was evident against V cholerae O1 El Tor only in the first year for individuals younger than 5 years.6 The vaccine is used primarily by people travelling from

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>Crude protective efficacy (PE)</td>
<td>Adjusted protective efficacy (95%CI; p-value)</td>
</tr>
<tr>
<td>N</td>
<td>Cases</td>
</tr>
<tr>
<td>31,932</td>
<td>69</td>
</tr>
<tr>
<td>66% (53-75%; &lt;·001)</td>
<td>65% (52-74%; &lt;·001)*</td>
</tr>
</tbody>
</table>

Protocol (1)

Vaccines and Immunotherapies

cumpulative protective efficacy of

Adjusted protective efficacy (95%CI; p-value)

65% (52-74%; <·001)*

ratified point estimates of efficacy not statistically different between age groups, however, suggest reduced cases were prevented in children than other age groups.
Herd Effect:
Re-analysis of the Bangladesh Field Trial of Killed, Oral Cholera Vaccines (Ali, Lancet, 2005)

- A re-analysis of the 1985 trial of killed whole cell-based oral cholera vaccines found:
  - Non-vaccinees were protected against cholera if they lived in neighborhoods with high levels of vaccine coverage
  - Vaccinated persons had higher levels of protection if they lived in highly vaccinated neighborhoods
No Vaccination
11.2 cases/1000

14% Vaccination
Unvacc. 7.6 cases/1000
Vacc. 2.7 cases/1000

38% Vaccination
Unvacc. 3.7 cases/1000
Vacc. 1.3 cases/1000

58% Vaccination
Unvacc. 1.8 cases/1000
Vacc. 0.6 cases/1000
## Cholera Vaccine (Inactivated Whole Cell Oral Cholera vaccine)

### IVI Technology Transfers

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“OCV should be used in endemic areas and should be considered for use in areas at risk for outbreaks in conjunction with other prevention and control strategies”
• IVI engaged Eubiologics in a tech transfer Euvichol® Development Strategy
- Tech Transfer of identical process and materials
- Conduct comparative biophysical and quality analysis
- Conduct clinical trials to evaluate safety and immunogenicity (non-inferiority) compared to Shanchol™
Each oral dose of 1.5mL contains

<table>
<thead>
<tr>
<th>Vaccine Strain</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>V. cholera</em> O1 Inaba E1 Tor strain Phil 6973 formaldehyde killed</td>
<td>600 Elisa Units (EU) of lipopolysaccharide (LPS)</td>
</tr>
<tr>
<td><em>V. cholera</em> O1 Ogawa classical strain Cairo 50 heat killed</td>
<td>300 EU of LPS</td>
</tr>
<tr>
<td><em>V. cholera</em> O1 Ogawa classical strain Cairo 60 formaldehyde killed</td>
<td>300 EU of LPS</td>
</tr>
<tr>
<td><em>V. cholera</em> O1 Inaba classical strain Cairo 48 heat killed</td>
<td>300 EU of LPS</td>
</tr>
<tr>
<td><em>V. cholera</em> O139 strain 4260B formaldehyde killed</td>
<td>600 EU of LPS</td>
</tr>
<tr>
<td>Thiomersal B.P.</td>
<td>Not more than 0.02% (w/v)</td>
</tr>
<tr>
<td>Buffer</td>
<td>q.s to 1.5mL</td>
</tr>
<tr>
<td>VVM</td>
<td>13</td>
</tr>
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</table>

The composition in 1.5mL:

<table>
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<tr>
<th>Description</th>
<th>V. Cholerae O1 and O139 bivalent inactivated vaccine</th>
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<tr>
<td><strong>Composition</strong></td>
<td><strong>Quantity</strong></td>
</tr>
<tr>
<td>V. Cholerae O1 Inaba Cairo 48, Heat inactivated</td>
<td>300 L.E.U*</td>
</tr>
<tr>
<td>V. Cholerae O1 Phil 6973 El Tor, Formalin inactivated</td>
<td>600 L.E.U</td>
</tr>
<tr>
<td>V. Cholerae O1 Ogawa Cairo 50, Formalin inactivated</td>
<td>300 L.E.U</td>
</tr>
<tr>
<td>V. Cholerae O1 Cairo 50, Heat inactivated</td>
<td>300 L.E.U</td>
</tr>
<tr>
<td>V. Cholerae O139 4260B, Formalin inactivated</td>
<td>600 L.E.U</td>
</tr>
<tr>
<td>Phosphate buffered saline (pH 7.3)</td>
<td>20mM</td>
</tr>
<tr>
<td>Thimerosal</td>
<td>0.15 mg</td>
</tr>
<tr>
<td>VVM</td>
<td>VVM 30</td>
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# Cholera Vaccine (Inactivated Whole Cell Oral Cholera vaccine)

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<td>Eubiologics (Korea)</td>
<td>Euvichol</td>
<td>Korean export license 2014 WHO prequalified Dec 2015</td>
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<td></td>
<td>Technology transfer 2010-11</td>
<td></td>
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Euvichol® (Eubiologics, Korea)

100L Formulation
• Market authorization from Korean FDA Jan 2015
• WHO PQ obtained Dec 2015

600L/no-thimerosal variation $\rightarrow$ capacity up to 25M doses/year
Bridging trial (100L to 600L) in the Philippines May 5, 2016
  442 participants: Age 1-40y
• Variation Approval from WHO received Sept 2016

Eubiologics expected to be the major supplier of OCV to the WHO stockpile

(Funder: BMGF)
Thermostability: currently VVM 30 (30 days at 37C)
Easier administration
Lower production cost
Lower cost of delivery
## Cholera Vaccine (Inactivated Whole Cell Oral Cholera vaccine)
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<td><strong>Eubiologics</strong></td>
<td>Technology transfer 2010-11</td>
<td>Korean export license 2014 WHO prequalified Dec 2015</td>
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<tr>
<td>(Korea)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Incepta</strong></td>
<td>Technology transfer May 2014</td>
<td>IVI conducting clinical trials in Bangladesh, license in Bangladesh expected 2017/18.</td>
</tr>
<tr>
<td>(Bangladesh)</td>
<td></td>
<td></td>
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<tr>
<td><strong>Shanchol</strong></td>
<td></td>
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<tr>
<td><strong>Euvichol</strong></td>
<td></td>
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<tr>
<td><strong>Cholvax</strong></td>
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Cholvax® (Incepta, Bangladesh) : Supply

- OCV Tech Transfer to Incepta 2014
- GMP Support (ongoing)

- Clinical Trial: Non-inferiority to Shanchol (icddr,b)
  - Safety, Immunogenicity, lot-to-lot consistency
  - 2,052 subjects (3 age cohorts)

- Challenges to achieve WHO PQ
  - Recognition of NRA (~2020)

(Funder: BMGF)
Single Dose Study (icddr,b): Flexibility

An individually randomized, placebo controlled trial of a single dose of Shanchol in an endemic setting

- **Primary Objective:**
  Protective efficacy of a single dose of Shanchol™ during initial 6 months following dosing

- **Secondary Objective:**
  Protective efficacy of a single dose of Shanchol™ at 12, 18, and 24 months following dosing

6 Month vaccine protective efficacy (PE)

- 40% (95% CI lower-bound (LB)=16%; P=.006) against all cholera cases
- 63% (95% CI=24%-82%; P=.007) against severely dehydrating cholera cases
- Efficacy only in >5 years of age

2 Year follow-up being analyzed now (Funder: BMGF)
### Vaccination campaigns 2015/16

Demonstrate feasibility, cost effectiveness in different settings

<table>
<thead>
<tr>
<th>Year</th>
<th>Location/Type</th>
<th>Target #</th>
<th>Coverage</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>2016/17</td>
<td>Nepal Pre-emptive</td>
<td>25,000</td>
<td>90%</td>
<td>M&amp;E In progress</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Expect Cost of Delivery and assessment of Choltool</td>
</tr>
<tr>
<td>2015</td>
<td>Nsanje, Malawi Reactive</td>
<td>160,000</td>
<td>1st 98%</td>
<td>Acceptability, feasibility, Effectiveness (on going)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2nd 68%</td>
<td>Delivery and Cost of Illness (COI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cost-Effectiveness Analysis</td>
</tr>
<tr>
<td>2015</td>
<td>Shashemene Ethiopia</td>
<td>~62,000</td>
<td>1st 76%</td>
<td>Acceptability</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2nd 65%</td>
<td>Feasibility</td>
</tr>
<tr>
<td>2015</td>
<td>Newakot and Dhading, Nepal Pre-emptive</td>
<td>10,000</td>
<td>1st 105%</td>
<td>Feasibility of delivering OCV in earthquake affected districts (during monsoon season) using government infrastructure</td>
</tr>
</tbody>
</table>
• 10 February 2015: 1st cholera case lab confirmed in Nsanje District
• 4 March 2015: 72 cases, 2 deaths
• 50,000 person pre-emptive campaign became a 160,000 person reactive effort (collaboration with WHO, MoH)
  ✓ Camps hosting the internally displaced populations and surrounding villages
• 320,000 doses
  ✓ 110,000 redirected from planned pre-emptive campaign
  ✓ 210,000 dispatched via the ICG Stockpile

Coverage: 1st dose 98%, 2nd dose 68%
Cholera Surveillance in Malawi (CSIMA)

Goal: To determine the 2-year protective effectiveness of OCV delivered through a reactive campaign in Nsanje District and increase the capacity for diarrheal surveillance in Nsanje and Chikwawa Districts

- Vaccine Effectiveness (VE): case-control study design
- Vaccination campaign delivery costs (Choltool)
- Cost of illness: public and private expenditures for treatment and productivity losses associated with cholera
- Cost-effectiveness
- Capacity building and strengthening surveillance system: support of Nsanje/Chikwawa laboratories

(Funder: BMGF)
Rotary Nepal Project: Cholera Prevention and Control (CCPC) in Nepal

Preemptive Campaign in rural “hot spot” in Nepal

Banke District, (Terai plain): 25,000 target population
2 doses of Euvichol®

Funders: Rotary International, IVI Korean Support Committee

Partners:
– Rotary Korea and Rotary Nagarjun Nepal
– JHUSPH-M&E
– GoN, MOH (EDCD)
– District Public Health Office

Outcomes:
– Feasibility
– Assessment of Choltool
  • comparison of the prediction of campaign costs with actual costs

Vaccination: Dec 2016 – Jan 2017
(~90% coverage)

M&E: ongoing
Thank You

IVI website
www.ivi.int

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Follow us
https://twitter.com/IVIHeadquarters
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Bangladesh  Bhutan  Brazil  China  Ecuador  Egypt  India  Indonesia

Israel  Jamaica  Kazakhstan  Kyrgyzstan  Lebanon  Liberia  Malta  Mongolia

Myanmar  Nepal  Netherlands  Oman  Pakistan  Panama  Papua New Guinea  Peru

Philippines  Republic of Korea  Romania  Senegal  Sri Lanka  Sweden  Tajikistan  Thailand

Turkey  Uzbekistan  Vietnam  World Health Organization
### Development and Delivery

<table>
<thead>
<tr>
<th>Strategic Goals</th>
<th>Program Objectives</th>
<th>Key Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OCV Supply</strong></td>
<td>Increasing the availability of OCV</td>
<td>• Partnership with manufacturers for TT, GMP, GCP, Clinical Development</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Two OCVs licensed and WHO-PQed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• One more OCV (Cholvax) in development</td>
</tr>
<tr>
<td><strong>Easier OCV Delivery</strong></td>
<td>Flexibility of Use</td>
<td>• Alternative dosing schedule (14 vs 28)</td>
</tr>
<tr>
<td><strong>OCV Use &amp; Introduction</strong></td>
<td>Expand the use of OCV and gather evidence for introduction</td>
<td>• Efficacy of a Single Dose of OCV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Vaccination Campaigns</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Feasibility, Safety, Effectiveness of OCV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Delivery Costs and Cost of Illness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Cost-Effectiveness Analysis</td>
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</tbody>
</table>
Comparison of Reformulated vs Vietnamese Oral Killed WC Vaccines

<table>
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<th>Strain</th>
<th>Vietnamese Vaccine</th>
<th>Reformulated Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formalin-Killed El Tor Inaba (Phil 6973)</td>
<td>$5 \times 10^{10}$ cells</td>
<td>600 EU LPS</td>
</tr>
<tr>
<td>Heat-Killed Classical Ogawa (Cairo 50)</td>
<td>$2.5 \times 10^{10}$ cells</td>
<td>300 EU LPS</td>
</tr>
<tr>
<td>Formalin-Killed Classical Inaba (569B)</td>
<td>$2.5 \times 10^{10}$ cells</td>
<td>-</td>
</tr>
<tr>
<td>Formalin-Killed Classical Ogawa (Cairo 50)</td>
<td>-</td>
<td>300 EU LPS</td>
</tr>
<tr>
<td>Heat-Killed Classical Inaba (Cairo 48)</td>
<td>-</td>
<td>300 EU LPS</td>
</tr>
<tr>
<td>0139 (4260B)</td>
<td>$5 \times 10^{10}$ cells</td>
<td>600 EU LPS</td>
</tr>
</tbody>
</table>
WHO pre-qualified and available OCVs 2010-11

Dukoral

- Killed whole cell vaccine + B (binding) subunit of cholera toxin
- Requires buffer (75-150 ml)
- 2 doses for age>5 yrs. and 3 doses for age 2-5 yrs.
- Vaccine efficacy of 60% sustained over 2 years
- High vaccine price, mainly for travelers
- Monovalent (O1)

Shanchol

- Killed whole cell vaccine (no cholera toxin subunit)
- Buffer is not required
- 2 doses for all age groups (1+ years)
- Efficacy of 66% for 3 years
- Low-cost
- Bivalent (both O1 and O139)
WHO pre-qualified and available OCVs 2010-11

Dukoral
- Killed whole cell vaccine + B (binding) subunit of cholera toxin
- Requires buffer (75-150 ml)
- 2 doses for age >5 yrs. and 3 doses for age 2-5 yrs.
- Vaccine efficacy of 60% sustained over 2 years
- High vaccine price, mainly for travelers
- Monovalent (O1)

Shanchol
- Killed whole cell vaccine (no cholera toxin subunit)
- Buffer is not required
- 2 doses for all age groups (1+ years)
- Efficacy of 66% for 5 years
- Low-cost
- Bivalent (both O1 and O139)
IVI’s Cholera Program Activities Overview
(Supply, Flexibility of Use, Introduction)