Ongoing development of future vaccines against rotavirus disease

Carl Kirkwood
Bill & Melinda Gates Foundation
WHO: Product Development Vaccine Advisory Committee meeting,
Geneva, 8-10th June 2016
Plan

1. Background of rotavirus disease/pathogen
2. Current vaccine efforts: live oral rotavirus vaccines
3. New approaches: non-replicating rotavirus vaccines
Rotavirus disease

• Rotavirus is the leading cause of severe diarrhea among all children below 5 years of age worldwide (20-40%).
• Democratic infection, all children susceptible regardless of socio-economic status.
• Disease burden:
  >100 million cases of diarrhea annually
  215,000 deaths (197-233,000) deaths in 2013
  (declined from >500,000 in 2000).
• Infection causes significant impact on health of all children.

1. Tate et al CID 2016.
Rotavirus vaccines

• Two live attenuated oral rotavirus vaccines developed, WHO pre-qualified & commercially available:

  • Rotarix (GSK) - single human strain (G1P[8])
    - 2 dose schedule (2 & 4 months)
  • RotaTeq (Merck) - 5 human-animal reassortant strains contains human G1, 2, 3, 4 & P[8] proteins
    - 3 dose schedule (2, 4 & 6 months)
  • Phase III clinical trials showed that both highly efficacious in preventing severe rotavirus disease (phase III trials ~ 60,000 participants):
    - 70 - 85% efficacy against rotavirus gastroenteritis of any severity.
    - 80 - 100% efficacy against severe rotavirus gastroenteritis requiring hospitalisation
  • Vaccination is now well established worldwide, resulted in significant reduction in cases of severe diarrhea and deaths due to RV infection.
Rotavirus vaccines – National Introductions By Geographic Region*

* As of 31 January 2016
Oral Rotavirus vaccines: candidate pipeline

- **Discovery & preclinical**
  - Liquid presentation
    - Bharat Biotech
  - Liquid BRV
    - Serum Institute
  - RV3-BB
    - Biofarma, Indonesia

- **Phase 1**
  - Lyophilized BRV
    - Serum Institute
  - Liquid BRV
    - Shantha Biotechnics

- **Phase 2**
  - Bharat Biotech Frozen product licensed in India

- **Phase 3**
  - Phase 3 efficacy
    - RCT in 7500 infants
  - Immunogenicity comparator to RotaTeq

- **Live-attenuated, oral**
  - Human rotavirus
    - Polyvac, Vietnam
  - Lamb rotavirus
    - Lanzhou Institute of Biological Products
### Rotavirus vaccines under current clinical development

<table>
<thead>
<tr>
<th>Candidate</th>
<th>Producer</th>
<th>Strain</th>
<th>Characteristics</th>
<th>Route</th>
<th>Recent Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRV</td>
<td>Serum Institute of India</td>
<td>Pentavalent combination (G1-4, G9)</td>
<td>First presentation – lyo, Phase 1 - liquid presentation</td>
<td>Oral</td>
<td>Phase 3 efficacy of lyo completed, awaiting results. (n=7,500)</td>
</tr>
<tr>
<td>BRV</td>
<td>Shanta Biotechnic, India</td>
<td>Tetravalent combination (G1-4)</td>
<td>Liquid presentation</td>
<td>Oral</td>
<td>Phase 3 non-inferiority study completed (n=1,200)</td>
</tr>
<tr>
<td>BRV</td>
<td>Wuhan Institute of Biological Products, China</td>
<td>Hexaavalent Combination (G1-4, G8, G9)</td>
<td>Liquid presentation</td>
<td>Oral</td>
<td>Phase 1: age descending study approved in China</td>
</tr>
<tr>
<td>BRV</td>
<td>Instituto Butantan, Brazil</td>
<td>Pentavalent combination (G1-4, G9)</td>
<td></td>
<td>Oral</td>
<td>Phase 1 safety in adults completed</td>
</tr>
</tbody>
</table>
## Rotavirus vaccines under current clinical development

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<thead>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Phase 2b immuno &amp; efficacy underway in Indonesia</td>
</tr>
<tr>
<td>LLR</td>
<td>Lanzhou Institute of Biological Products, China</td>
<td>Lamb strain G10P[12]</td>
<td>First generation: Liquid Second generation: multivalent</td>
<td>Oral</td>
<td>Licensed in China Effectiveness study of 35%</td>
</tr>
</tbody>
</table>
Ongoing issues:

Despite enormous success of oral, life attenuated rotavirus vaccines, several issues remain:

- A lower protection (50% or lower) in emerging countries in Asia and Africa against severe diarrhea over the first year of life with no evidence of protection in the second year as compared to the protection in "high-income" countries (>95%)
- Vaccine cost is still relatively high.
- Despite an overall acceptable safety profile, intussusception rate seems to be slightly increased by the ORV vaccination (occurrence 1 to 3 /100 000 ORV vaccine recipients) in developed countries.

- Thus non-replicating rotavirus vaccines may provide alternative
Non-replicating rotavirus vaccines: candidate pipeline

- **Expressed VP6 protein**
- **VLP VP2/6; VP2/6/7**
- **Combo-VP6 with norovirus VLP**
- **Inactivated Rotavirus CDC**
- **NRRV (P2-VP8*) PATH**
## Non–replicating vaccine candidates

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Characteristics</th>
<th>Developer</th>
<th>Development</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inactivated rotavirus vaccine</strong> <em>(IRV)</em></td>
<td>Heat inactivated human rotavirus <em>(G1P[8])</em> - grows to high titre</td>
<td>CDC, USA</td>
<td>Preclinical: mice/monkeys Immunogenic Protective in animal model - clinical lot prepared, - Process development</td>
</tr>
<tr>
<td><strong>Expressed proteins</strong> <em>(based on VP6 inner capsid)</em></td>
<td>Truncated VP6</td>
<td>Cincinnati Children’s Hospital Med Cent, USA</td>
<td>Animal studies - immunogenic - Protected in challenge - low yields</td>
</tr>
<tr>
<td></td>
<td>VP6 combined with norovirus VLP</td>
<td>University of Tampere School of Medicine, Finland.</td>
<td></td>
</tr>
<tr>
<td><strong>Virus like particles</strong></td>
<td>Virus-like particles VP2/6/7; VP2/4/6/7</td>
<td>Baylor College of Medicine, USA</td>
<td>Animal studies - Immunogenic - Protective small animals (predom. Homotypic) - Low yields/process difficult</td>
</tr>
<tr>
<td><strong>VP8 expressed proteins</strong> <em>(NRRV)</em></td>
<td>Trivalent Truncated VP8: P[4], P[6] and P[8]</td>
<td>PATH, National Institutes of Health, USA.</td>
<td>Human Phase I/II studies ongoing</td>
</tr>
</tbody>
</table>
Non-replicating rotavirus vaccine candidates in human studies

<table>
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<tr>
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<th>Route</th>
<th>Recent Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>P2-VP8* (NRRV)</td>
<td>PATH (commercial partner to be identified)</td>
<td>Trivalent, truncated VP8* of P[4], P[6] and P[8]</td>
<td>NIH developed the constructs, and provided license for use.</td>
<td>Parenteral</td>
<td>Phase 2a immunogenicity of monovalent</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Phase 2 of trivalent ongoing in South Africa</td>
</tr>
</tbody>
</table>
NRRV: based on P2-VP8* rotavirus protein

- Developed at NIH (USA) by Y Hoshino
- Truncated VP8* subunit, synthetic genes from human G1 P[8], G2P[4], G3P[6], expressed in E.coli (T5 promoter).
- Fused to the tetanus toxin P2 CD4 epitope via a linker region.
- No unexpected toxicity in rabbits at doses up to 60 µg
- Liquid formulation, adsorbed to aluminum hydroxide
- No intellectual property concerns
- Likely need for a trivalent combination:
  - Circulating genotypes,
  - homotypic and heterotypic neutralizing anti- [P] abs.

Distribution of human rotavirus VP4 (P) genotypes

- Sequence homology among clinical isolates
  - P8 and P4: ~85%
  - P8 and P6: ~65%
- Immunological relatedness
- Neutralization and protection
  - In animal models extensive cross-neutralization between P8 and P4, modest for P6
- Suggests bivalent P8-P6 vaccine
  - may confer protection against >90% of field isolates, however, post vaccine surveillance suggested P[4] & P[6] are emerging.

Santos and Hoshino, 2004
Phase 1: Safety and immunogenicity study (Vac 009)

A phase 1 double-blinded, randomized, placebo-controlled dose escalation study:

• First-in-human testing of the monovalent P2-VP8 subunit rotavirus vaccine

• Enrollment: Dec 2012 – Feb 2013

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Dosing Groups</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10 µg vaccine with Al(OH)₃</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>30 µg vaccine with Al(OH)₃</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>60 µg vaccine with Al(OH)₃</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>12 vaccine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12 placebo</td>
<td></td>
</tr>
</tbody>
</table>

Vaccine Schedule: Days 0, 28 and 56
Highest level of any reactogenicity per subject (Vac 009) (local and systemic combined)

<table>
<thead>
<tr>
<th></th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Any</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>3 (25.0)</td>
<td>2 (16.7)</td>
<td>0</td>
<td>5 (41.7)</td>
</tr>
<tr>
<td>10 µg</td>
<td>7 (58.3)</td>
<td>2 (16.7)</td>
<td>0</td>
<td>9 (75.0)</td>
</tr>
<tr>
<td>30 µg</td>
<td>6 (50.0)</td>
<td>0</td>
<td>0</td>
<td>6 (50.0)</td>
</tr>
<tr>
<td>60 µg</td>
<td>6 (50.0)</td>
<td>2 (16.7)</td>
<td>0</td>
<td>8 (67.7)</td>
</tr>
</tbody>
</table>
Phase 1 study: Immune responses P2-VP8* rotavirus vaccine (Vac 009)

ANTI-P2-VP8* IgG EIA TITERS

ANTI-P2-VP8* IgA EIA TITERS

Neutralizing antibody to other rotavirus genotypes (≥4-fold increase 28 days after 3\textsuperscript{rd} dose)

<table>
<thead>
<tr>
<th>Strain</th>
<th>10 µg % (CI)</th>
<th>30 µg % (CI)</th>
<th>60 µg % (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wa (G1P[8])</td>
<td>67 (35, 90)</td>
<td>42 (15, 72)</td>
<td>58 (28, 85)</td>
</tr>
<tr>
<td>89-12 (G1P[8])</td>
<td>83 (52, 98)</td>
<td>67 (35, 90)</td>
<td>83 (52, 98)</td>
</tr>
<tr>
<td>P (G3P[8])</td>
<td>58 (28, 85)</td>
<td>67 (35, 90)</td>
<td>83 (52, 98)</td>
</tr>
<tr>
<td>DS1 (G2P[4])</td>
<td>0 (0, 26)</td>
<td>50 (21, 79)</td>
<td>58 (28, 85)</td>
</tr>
<tr>
<td>ST3 (G4P[6])</td>
<td>0 (0, 26)</td>
<td>8 (0, 38)</td>
<td>17 (2, 48)</td>
</tr>
</tbody>
</table>

Conclusion: phase 1 trial P2-VP8* rotavirus vaccine (Vac 009)

- Vaccine safe and well tolerated
- Vaccine elicits a robust antibody response to several homologous P[8] strains of rotavirus

- Response rates lower in those with high levels of pre-existing antibody

- Need to add P[4] & P[6] component to cover >90% of genotypes observed in the field
Unpublished NRRV clinical studies (Vac 013) – Confidential

**Phase I/II:** Double blinded, placebo controlled dose escalation study to examine safety, immunogenicity of monovalent P2-VP8 candidate in toddlers and infants in South Africa

- Study design: 10, 30 and 60 μg dose regime of P2-VP8 monovalent vaccine, delivered in a 3 dose schedule: 0, 28 and 56 days in toddlers and infants (N= 42 toddlers (24-35 mths), 162 infants (6-8wks))

**Safety profile** – vaccine well tolerated at all doses, no dose dependent increase in AE observed.

**Immunogenicity data:** Serology:

- Neutralization responses:
Unpublished NRRV clinical studies (Vac 013)

Challenge study:

- Reduction in shedding of Rotarix as surrogate marker of vaccine efficacy.
- Rotarix is shed in the stool by a variable percentage (30-75%) of vaccinees after first dose, and peaks between 5-9 days after primary immunization.
- Absolute shedding rate dependent upon geographical location and assay method used.

Study:

Rotarix vaccine administered 28 days post 3rd dose of monovalent P2-VP8 or placebo.

- stool collected on 5-9 days post dose 1 vaccination
- shedding evaluated by ELISA.
Conclusion: NRRV clinical trial (Vac 013)

• Vaccine is generally well tolerated at all doses tested.
  - No dose dependent increase in AEs observed
Ongoing clinical studies of NRRV (Vac 041):

Phase I/II: Double blinded, placebo controlled dose escalation study to examine safety, immunogenicity of trivalent P2-VP8 candidate in toddlers and infants in South Africa

- P4, P6 and P8 VP8 subunits (each at 5, 10 & 30ug)

- 15, 30 and 90ug dose regime, delivered in 3 dose schedule, 0, 28 and 56 days.

(N = 30 adults, 30 toddlers (24-35 months), 616 infants (6-8 weeks)
Vac 041: Study sites and time line

South African Study Sites:
- RMPRU, Soweto. Site where VAC013 was performed
- FAM-CRU, Tygerburg
- Shandukani, Johannesburg

Time Line:
- Adult, toddler and pilot infant cohorts will be immunized only at RMPRU started in February, 2016
- Expanded infant cohorts will be immunized at all 3 study sites will start in August/September 2016 after rotavirus season.
- Enrollment and collection of blood samples due to be completed, July 2017 and analysis completed by end of 2017
Summary

- Current live attenuated oral rotavirus vaccines provide excellent effectiveness in developed countries, however, the effectiveness is less in developing settings.
- Thus despite enormous success of live rotavirus vaccines, several issues remain:
  - A lower protection (50% or lower) in emerging countries in Asia and Africa against severe diarrhea over the first year of life with no evidence of protection in the second year as compared to the protection in "high-income“ countries (>95%)
  - Vaccine cost is still relatively high.
  - Despite an overall acceptable safety profile, intussusception rate seems to be slightly increased by the ORV vaccination (occurrence 1 to 3 /100 000 ORV vaccine recipients) in developed countries
- Thus non-replicating rotavirus vaccines may provide alternative to help reduce these issues. Several candidates have animal data, however only one is currently in human trials.
- NRRV P2-VP8 (monovalent & trivalent) is only candidate in human studies, early clinical data shows some promise.