New and Underused Vaccines, Rotavirus

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Outline

- Burden of Rotavirus Disease
- Rotavirus vaccine Paradigm
- Vaccines in Use
- New vaccines in Development
- Rotavirus vaccine Pipeline

Tate JE, Burton AH, Boscho-Pinto C et al. Lancet Infect Dis 2010
Rotavirus is the most common cause of diarrhoeal death in young children

Global rotavirus surveillance: 39-40% of diarrhoeal hospitalizations

10 countries account for ~85% of rotavirus associated mortality

Tate JE, Burton AH, Boscho-Pinto C et al. Lancet Infect Dis 2010
Rotavirus epidemiology and burden in Africa

- ~39% of children hospitalized with acute diarrhoea were excreting rotaviruses

- Rotavirus occurred in:
  - 36% of infants <6 months of age
  - 75% of infants <12 months of age
  - 83% of children <18 months of age
  - Peak Infection in 6-18 months old

- Rotavirus infection occurs commonly in children in the community

Rotavirus Morphology and Major Viral Antigens

- VP7
  - Neutralization Antibodies
  - Glycoprotein [G]

- VP4
  - Neutralization Antibodies
  - Virulence
  - Cellular Attachment
  - Protease Sens. [P]
Rotavirus Vaccine Paradigms

Human monovalent vaccines
- Natural infection offers protection
- High replication in the host - attenuated by TC passage
- Broad immunity is acquired through various immune effector mechanisms
- Heterotypic protection is gained through broad immune response

Animal reassortant vaccines
- Naturally attenuated strains in humans – lower replication
- Higher titres required
- Expectation that neutralizing antibody in the gut lumen is required
- Reassortant vaccine constructs to include the common human rotavirus antigens
Rotavirus Vaccine Paradigms

- Clinical immunity after neonatal rotavirus infection
- Primary infection usually symptomatic and protects against severe re-infection
- VP7 elicits production of neutralizing antibodies in host
- Animal viruses are often naturally attenuated in humans
- Evidence that protection against rotavirus diarrhea after natural infection is not dependent on serotype-specific neutralizing antibody
- Vaccines developed based on classical “Jennerian” approach
- Heterotypic vs homotypic immunity basis of different approaches to vaccine candidates
- Mucosal immunity is believed to be important in protection
## Consequences of this Rotavirus Vaccine Paradigm

<table>
<thead>
<tr>
<th>RotaTeq™, Merck</th>
<th>Rotarix™, GSK Bio</th>
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<tbody>
<tr>
<td>G1</td>
<td>G1P[8]</td>
</tr>
<tr>
<td>G2</td>
<td></td>
</tr>
<tr>
<td>G3</td>
<td></td>
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<tr>
<td>G4</td>
<td></td>
</tr>
<tr>
<td>G6</td>
<td></td>
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<tr>
<td>P[5]</td>
<td></td>
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</table>

### Five bovine-human rotavirus strains


GSK Rotarix™
Human, monovalent, oral Rotavirus Vaccine

- Lyophilized vaccine reconstituted with CaCO₃ buffer
  - human G1P[8] strain
  - cross-protective of multiple strains
  - high efficacy and safety, no interference with OPV or other vaccines
  - 2-doses, given <24 weeks of age

- Current presentation:
  - mono-dose, 1 ml/dose
  - +2°C to +8°C, must not freeze
  - non-standard handling
  - large per-dose volume
  - VVM on UNICEF-supplied vaccine
  - WHO prequalified Jan 2007
Merck RotaTeq®
Pentavalent, reassortant, oral Rotavirus Vaccine

- Liquid vaccine, 5 human-bovine reassortant strains:
  - G serotypes - human G1, G2, G3 and G4; bovine G6
  - cross-protective of multiple strains
  - high efficacy and safety, no interference with OPV or other vaccines
  - 3-doses, given <32 weeks of age

- Current presentation:
  - mono-dose, 2 ml/dose
  - +2°C to +8°C storage
  - administered like OPV,
  - large per-dose volume
  - VVM to be developed
  - WHO prequalified: October 2008
Global introduction of Rotavirus vaccines in childhood immunization programme

- Global Recommendation in 2009
- 70 Countries globally
- Sudan in 2011
- 27 countries introduces in Africa
### Why the need for New vaccines?

#### Efficacy of rotavirus vaccines by mortality stratum and country

<table>
<thead>
<tr>
<th>Mortality rate defined by WHO</th>
<th>RV vaccine efficacy estimates</th>
<th>Countries where studies were performed</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIGH</td>
<td>50–64%</td>
<td>Ghana, Kenya, Malawi, Mali</td>
</tr>
<tr>
<td>INTERMEDIATE</td>
<td>46–72%</td>
<td>Bangladesh, South Africa</td>
</tr>
<tr>
<td></td>
<td>72–85%</td>
<td>Vietnam, countries in the Region of the Americas</td>
</tr>
<tr>
<td>LOW</td>
<td>85–100%</td>
<td>Countries in the Region of the Americas, Europe, Western Pacific</td>
</tr>
</tbody>
</table>

**Vaccine Efficacy Lower in Developing Countries with Higher Rotavirus Mortality Rates**
Challenges to RV vaccination

Hurdles to Immunization for a Live Oral Rotavirus Vaccine

Factors that lower viral titer
- Breast milk
- Stomach acid
- Maternal antibodies
- OPV

Factors that impair immune response
- Malnutrition - Zn, Vit A
- Interfering microbes- viruses and bacteria
- Other infections - HIV, malaria, TBC

Umesh Parashar, 2014
New Vaccine Concepts

- Human monovalent vaccines
- Animal reassortant vaccines
- Non replication rotavirus vaccines
The human monovalent rotavirus vaccines

RotaVac
RotaVin-M1
RV3
Indian Neonatal Strain 116E

- Naturally reassorted human-bovine rotavirus strain
- Human rotavirus with a bovine rotavirus VP4 gene
- Asymptomatic infection in neonates in Delhi - good immune responses observed in neonates
- Phase 1 and 2 studies completed in India showed robust immune response to the vaccine
- Phase 3 safety and efficacy demonstrated efficacy similar to other licensed vaccines
- Licensed as RotaVac™ by Bharat Biotech International, Ltd., India and introduced into the EPI in 2014
- Supported by the Indo-US Vaccine Action Program and PATH (with BMGF funding) and Dept of Biotechnology (DBT), India

Phase 3 efficacy study of ROTAVAC® completed in late 2013, which involved 6,799 infants enrolled across three sites in India.

The trial data showed the vaccine to have an excellent safety and efficacy profile.

ROTAVAC® significantly reduced severe rotavirus diarrhea by more than half—56% of children during the first year of life, with protection continuing into the second year of life.

Compares favorably with the efficacy of globally available rotavirus vaccines in low-resource countries. ROTAVAC® also showed impact against severe diarrhea of any cause.

Collaboration between CDC and national institute of vaccines and Biologicals, Vietnam since 1998

- 2 dose vaccine given 2 months apart at 6-12 weeks of age
- Safe and efficacious
- Seroconversion >75%

Development of Rotavin-M1

- Originated from stool of a child with acute gastroenteritis in Khanh Hoa in 2003
- “Attenuated” by serial passages (x40) in cell culture
- Tested for safety and immunogenicity in mice, rabbits and monkeys

Anh, DD: Vaccine 2012
Human Neonatal Strain (RV3)

- Naturally attenuated strain isolated in maternity units in Melbourne
- Infants followed up for 3 years
- No diarrhoeal symptoms in siblings aged 1-2 years
- Never identified in children with community acquired diarrhoea
- Protected against rotavirus disease in the cohort
- G3P[6] - both human rotavirus immunogens
- G3 epitopes cross-reactive with G1 and G9.
- P[6] epitopes appear adapted to neonatal gut and high maternal antibody titres

RV3-BB Vaccine Clinical Development

- Phase 1 trial completed in Melbourne (TGA)
  - Adults, toddlers, infants
  - No safety concerns
- Phase 2 trial completed in New Zealand for proof of principle of immunogenicity at higher titre
- Phase 2b study for immunogenicity and efficacy is ongoing in Indonesia
  - Immune responses with IPV and OPV
  - Neonatal immunization schedule and EPI schedule
The animal strain reassortant rotavirus vaccines
Construction of NIH bovine – human reassortant rotavirus vaccines

Clinical development of NIH bovine-human reassortant vaccine

- Bovine-human rotavirus reassortant strain (UK – G6P[7])

- Quadrivalent reassortant vaccine (with human rotavirus VP7 genes for G1-G4)
  - Safe and non-reactogenic in phase I trials
  - Satisfactory immunogenicity in phase II trials

- Immunogenicity trial in infants administered concomitantly with childhood vaccines
  - Safe and well tolerated after 3 doses at $10^5$ ffu
  - Non-inhibitory to other routine childhood vaccine immune responses
  - 95% of infants developed serum neutralizing antibody responses

Clinical development of NIH bovine-human reassortant vaccine

- Quadrivalent vaccine (G1, G2, G3 and G4) compared to RotaShield® in infants in Finland

- Demonstrated safety and immunogenicity of Dyncorp produced quadrivalent vaccine (FRhL-2 cell line) in infants (2 months old)
  - Two doses – $1.7 \times 10^6$ total virus (frozen) with antacid.
  - RRV-TV associated with transient and generally low-grade fever in up to one third of vaccinees.
  - Bovine rotavirus based vaccine characteristically non-reactogenic

- Immunogenicity and Efficacy of BRV is similar to the licensed RotaShield®

Vesikari et al, J Infect Dis 2006; 194: 370-6
Bovine-human Rotavirus Reassortant Vaccine Manufacturers

- Licensed by Office of Technology, NIH, Bethesda to multiple manufacturers
  - Shantha Biotechnics, India (Phase 2 immunogenicity complete);
  - Butantan, Brazil (Phase 1 safety complete);
  - Wuhan Institute of Biologicals Products, China (pre-clinical)

- Serum Institute of India, Pune, India
  - Pentavalent vaccine construct (G1, G2, G3, G4, G9)
  - Completed Phase 2 immunogenicity study
  - Started Phase 3 safety and efficacy study in multiple sites in India in 2014
## New Rotavirus Vaccines in Development

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Product</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Institute of India</td>
<td>Human-Bovine Reassortant, Pentavalent (G1-G4, G9)</td>
<td>Phase 3 ongoing</td>
</tr>
<tr>
<td>Shantha Biotechnics</td>
<td>Human-Bovine Reassortant Tetravalent (G1-4)</td>
<td>Phase 2 complete; Phase 3 proposed</td>
</tr>
<tr>
<td>Biofarma and MCRI</td>
<td>Human (G3P[6])</td>
<td>Phase 2b ongoing</td>
</tr>
<tr>
<td>Medica International Foundation</td>
<td>Rhesus-human rotavirus reassortant Tetravalent</td>
<td>Phase 2b complete</td>
</tr>
<tr>
<td>Butantan Institute</td>
<td>Human-Bovine Reassortant (G1-4,9) Pentavalent</td>
<td>Phase 2 ongoing</td>
</tr>
<tr>
<td>Wuhan Institute of Biological Products</td>
<td>Bovine Reassortant (G1-4,8,9) Hexavalent</td>
<td>Preclinical; Phase 1 in preparation</td>
</tr>
</tbody>
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Status of Rotavirus Vaccine Development
Serum Institute – BRV-PV

Live, oral, lyophilized BRV vaccine
- (G 1, 2, 3, 4 & 9)
- Phase 3 efficacy study under way, expected completion March 2017
- EPI non-interference / lot consistency trial expected to begin early 2015

Liquid formulation under development
- Tox studies to be completed by October 2014
- Phase 1 targeted to begin Q2 2015; immuno bridging study planned

WHO PQ to be sought for both presentations

Live-attenuated Tetravalent Bovine-Human Reassortant Rotavirus vaccine

- G1, G2, G3, G4 strains
- Ready-to-administer liquid presentation
- Recently completed Phase I and II safety and immunology studies
- Results showed that all three dose levels tested were safe, well tolerated and displayed good immunogenicity (sero-conversion and GMTs) in Indian infants
- Proposed non-inferiority single-blind immunogenicity study with RotaTeq in multiple sites in India
- DCGI approvals pending
- WHO PQ support will be sought

Serum IgA anti-rotavirus antibody sero-response (four fold or more rise over baseline after each dose). Group A: Placebo, Group B: BRV-TV 105.0FFU, Group C: BRV-TV 105.8FFU, Group D: BRV-TV 106.4FFU, Group E: RotaTeq.
Rotashield: the Ghana Neonatal trials

- Double-blind, placebo-controlled trial of RRV-TV (Rotashield®)
- 2 doses given at 0-28 days and 30-59 days of age, with routine EPI vaccines, including oral polio vaccine (OPV), when possible
- No exclusions for HIV
- No restriction on breastfeeding
- Safety Follow up: 2 and 4 days post any vaccination and then weekly thereafter till 1 year old
- Primary efficacy period: 14 days following the second dose until end of study follow-up

<table>
<thead>
<tr>
<th>RVGE</th>
<th>Any Serotype (95% CI)</th>
<th>Serotypes in RRV-TV (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe*</td>
<td>57.6% (&lt;0, 83.6)</td>
<td>60.5% (&lt;0., 87.5)</td>
</tr>
<tr>
<td>Any severity</td>
<td>60.7% (29.5, 78.1)</td>
<td>63.1% (24.6, 82.0)</td>
</tr>
</tbody>
</table>
Comparison of the Efficacy of RotaTeq, Rotarix, and RRV-TV Against Severe Rotavirus Gastroenteritis (≥11 Vesikari Scale) during first year of life

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Dosage (Ref.)</th>
<th>% Efficacy (95% CI)</th>
<th>Location(s)</th>
<th>Surveillance Period (&gt;14 days after last dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RotaTeq¹</td>
<td>6, 10, 14 weeks (3 doses)</td>
<td>51.0 (12.8-73.3)</td>
<td>Bangladesh and Vietnam combined</td>
<td>Up to one year of age</td>
</tr>
<tr>
<td>RotaTeq²</td>
<td>6, 10, 14 weeks (3 doses)</td>
<td>64.2 (40.2-79.4)</td>
<td>Kenya, Ghana, and Mali combined</td>
<td>Up to one year of age</td>
</tr>
<tr>
<td>Rotarix³</td>
<td>10, 14 weeks or 6, 10, 14 weeks (2 or 3 doses)</td>
<td>61.2 (44.0-73.2)</td>
<td>South Africa and Malawi combined</td>
<td>Up to one year of age</td>
</tr>
<tr>
<td>RRV-TV</td>
<td>0-29 days, 30-59 days (2 doses)</td>
<td>60.5 (&lt;0 - 87.5)</td>
<td>Ghana</td>
<td>Up to one year of age</td>
</tr>
</tbody>
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¹Zaman et al; lancet 2010; 376:615-23  ; ²Armah et al; lancet 2010;376-606-14  
³Madhi et al; NEJM;2 010,362:289-98
Novel approach of non-replicating rotavirus vaccine candidates

- Inactivated rotavirus particles
- Subunit vaccines – VP8* subunit; VP6 subunit
- Virus-like particles (VLPs)
Leading NRRV Candidate – P2-VP8* particle (NIH)

- Fusion protein of the P2 universal T-cell epitope of tetanus toxin and a subunit of the VP8
- Phase 1 safety study complete
- Phase 2 immunogenicity and age descending study ongoing in South Africa
Conclusions from Phase 1 Trial

- Vaccine safe and well tolerated
- Vaccine elicits a robust antibody response to several homologous P[8] strains of rotavirus
  - Modest response to a P[4] strain
  - Meager response to a P[6] strain
- Response rates lower in those with high levels of pre-existing antibody
- Performance of the vaccine in immunologically naïve subjects remains to be determined
Rotavirus vaccine pipeline

Research

Phase 1

Phase 2

Phase 3

Licensure

Market

BB
IL
E

Lanzhou

PolyVAC

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## Other Nationally Licensed Rotavirus Vaccines

<table>
<thead>
<tr>
<th>Manufacturer, Country</th>
<th>Product</th>
<th>Specifications</th>
<th>Date Licensed</th>
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</table>