Future Directions for Rotavirus Vaccine Research

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Future Directions of Research for Rotavirus vaccines

- International perspective
  - Recommendations from WHO GACVS and SAGE
  - Recommendations from WHO meetings
    - Geneva, March 2006;
    - Geneva, December 2006 and
    - Atlanta, November 2007
- New vaccines
- Surveillance and monitoring
- Programmatic issues
SAGE recommendations

• SAGE recommended **clinical trials to generate efficacy data** in Asia and Africa, where the disease burden is very high.

• SAGE considered that a regional and phased approach could be appropriate in those regions where successful phase III trials have been undertaken, and provided that other elements such as the **appropriate infrastructure** and **financing mechanisms** were available.

• SAGE recommended **post-marketing surveillance for vaccine impact** and **post-marketing surveillance for vaccine safety** in countries that introduce rotavirus vaccines.

• SAGE recommended that **communication strategies** should be established in countries about rotavirus vaccines and diarrhoeal diseases.
Post-marketing surveillance for vaccine safety and vaccine impact (Geneva, December 2006)

• General recommendation that post-marketing surveillance was necessary to assess both vaccine safety with respect to intussusception and other potential rare adverse events
  • Generic Protocol for Post-marketing Surveillance for Vaccine Safety (developed by Julie Bines) for WHO
  • Generic Protocol for measuring vaccine impact (developed by Manish Patel and Umesh Parashar) for WHO
• Consensus to establish a Technical Oversight Committee as a sub-committee of the GACVS to oversee and review data being generated as vaccines are introduced to advise national MOH and industry
• General recommendation that each candidate should be taken forward for clinical evaluation

• Minimum standard of global expectations for rotavirus vaccine clinical development to ensure that there is not a potential spill over effect of "unforeseen" problems or R&D processes

• **Quality-assured phase I and II development programmes** encouraged to ensure overall compliance with international standards

• Encourage development of non-living, inactivated virus approaches

• Recognise that there are National and Institutional prerogatives for rotavirus vaccine R&D

• Role of WHO DCVMN and DCVRN to alert, influence and assist the R&D process, the regulatory process and ultimately pre-qualification of the upstream rotavirus vaccines
Other Candidate Live Oral Rotavirus Vaccines

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Name</th>
<th>Company</th>
<th>Strain(s)</th>
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<tbody>
<tr>
<td>NIH Bovine-human reassortant rotavirus</td>
<td>UK</td>
<td>Butantan, Brazil Wuhan &amp; Chengdu, China SSI, Shanta, Biologicals E, Bharat, India</td>
<td>Bovine (G6) + G1,G2,G3,G4,P[8] + designer reassortants</td>
</tr>
<tr>
<td>Australian neonatal</td>
<td>RV3</td>
<td>MCRI / Biofarma, Australia / Indonesia</td>
<td>G3, P[6]</td>
</tr>
<tr>
<td>Rhesus-human tetravalent rotavirus</td>
<td>RRV-TV</td>
<td>BIOVIRx / USA (IMF) US IDT / Germany</td>
<td>Rhesus (G3) + VP7 (G1,G2,G4)</td>
</tr>
<tr>
<td>Lamb rotavirus -- lamb human reassortant vaccine</td>
<td>LLR</td>
<td>Lanzhou Biologicals / Xinkexian Biological Technology, China</td>
<td>G10,P[12] + G1,G2,G3,G4</td>
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UK Bovine-human Rotavirus Reassortant Vaccine

- Developed by Al Kapikian, NIAID, NIH
- Tetravalent vaccine tested in USA and Finland
- Developed in parallel with RRV-TV
  - Safe and non-reactogenic in phase I trials
  - Satisfactory immunogenicity in phase II trials
  - Efficacy comparable to RRV-TV
- Possible “designer vaccine” for different strains
- Suggested neonatal immunization schedule as RRV-TV neonatal dose protected against fever seen with dose at 2 months
- Licensed by NIH to 7 companies in 3 countries Brazil, China and India


8th International Rotavirus Symposium, Turkey, 2008
Production of reassortant rotavirus vaccines

Human Rotavirus (HRV) x Bovine RV Reassortant Hexavalent Vaccine with VP7 Serotype 1, 2, 3, 4, 8, and 9 Specificities

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

Taka Hoshino & Al Kapikian, NIH
Indian Neonatal Strain 116E

- Naturally reassorted human-bovine rotavirus strain
- Human rotavirus with a bovine rotavirus VP4 gene
- Asymptomatic infection in neonates in Delhi
- Infection rates
  - 50% by day 3
  - 80% by day 5
- Prolonged viral shedding of 7-14 days
- Good immune responses observed in neonates
- Single unusual strain – G9 (P11) human-bovine reassortant
- Children protected from severe RV disease on reinfection

(Bhan et al, 1993)
ORV 116E - Early Clinical Data

• **Safety**
  • Demonstrated in adults, children and infants,
  • Non reactogenic
  • No SAE’s (grade 4 or 5)

• **Immunogenicity:** by 4 fold or greater raise in serum IgA from baseline level
  • 20% in the placebo group
  • 73% in the 116E group

• **Rotavirus shedding:** Stool samples day 3 and 7,
  • 6% in the placebo group
  • 40% in 116E group

*Bhandari et al., Vaccine 2006*
Human Neonatal Strain (RV3)

- RV3 neonatal strain
  - Naturally attenuated strain in maternity units
  - Infants followed for 3 years
  - Protected against rotavirus disease
  - G3P[6] - both human rotavirus immunogens

  (Bishop et al, NEJM, 1983)

- Clinical trials with neonatal rotavirus
  - Safe, but low immunogenicity at $10^5$ pfu per dose
  - Infants who sero-converted were protected in following year

  (Barnes et al, Vaccine, 2002)
RV3 Vaccine - Second phase

- Viral titre increased from $6 \times 10^5$ ffu/ml to $1 \times 10^7$ ffu/ml at MCRI
- Cell line changed from AGMK to WHO-approved Vero cells
- Vaccine clinical trial lots being prepared under GMP at Meridian Biologics
- Technology transfer to BioFarma
- Phase I trials planned in Melbourne (regulatory)
- Phase II trials in New Zealand and in Indonesia
  - Meridian vaccine – New Zealand and Jogykarta, Indonesia
  - BioFarma vaccine – Bandung, Indonesia
- Planned neonatal dose arm in studies
- Funding received for development and phase I & II clinical trials

Barnes and Bines, personal communication
Other live oral rotavirus vaccines

- International Medica Foundation, Len Ruiz (poster 57)
- Xinkexian Biological Technology, Yang Li
ARVAC
Advancing Rotavirus Vaccine Development

- Grant from the Bill and Melinda Gates Foundation to PATH (2007-2011)
- Developed by John Boslego, Georges Thiry, Bill Wainwright, Rajat Goyal and John Wecker
- Focused on three initiatives:
  - Support for 116E product development
  - Support for UK bovine human reassortant vaccine
  - Enabling platform for technologies
Objectives of ARVAC - for 116E

- Assist Bharat Biotech International Ltd. (BBIL)
  - the establishment of a cGMP (current Good Manufacturing Practices)
  - the establishment of GLP - compliant assay laboratory
  - stable formulation
  - full-scale manufacturing process
  - complete manufacture of a Ph3 lot of 116E vaccine strain.
- Support BBIL and partners (DBT, SAS, NII) in developing a clinical development plan for vaccine trials up to phase III
Objectives of ARVAC - for UK BRV

- Support development of the US National Institutes of Health bovine-human rotavirus vaccine (BRV) through Phase 2 at two selected manufacturers
  - Shantha Biotechnics, Ltd, India
  - Wuhan Institute of Biological Products (WIBP), China.
- Address key technical development aspects of the reassortant BRV with other manufacturers from emerging countries — Serum Institute of India (SII), BBIL, Chengdu Institute, Butantan Institute, and Biological E.
Enabling Platform of Technologies

• Finalize product development plans
• Produce reagents and reference standards for process and immunology
• Qualify starting materials
• Develop vaccine formulation
• Design final packaging
• Develop large-scale process development
• Number of partners
  • Aridis - formulation
  • Murdoch Children’s Research Institute – reference standards and monoclonal antibodies
  • Charles River – qualified cell banks and virus seeds
  • ATCC – WHO qualified Vero cell lines
Impact of high-volume vaccines on cold chain capacity in developing countries

Vaccine volume per dose

**Polio**: 2.5 cm³/dose (10-dose vial)*

**Measles**: 1.5 cm³/dose (20-dose vial)*

**Rotarix**
- Contents include vaccine, diluent, applicator, connector: 111.6 cm³/dose
- Vaccine only: 11.4 cm³/dose

*Source: WHO. Guidelines on the international packaging and shipping of vaccines. 2002; WHO/V&B/01.05.

2500 doses - measles
1600 doses - OPV
625 doses

Robin Biellik, PATH, 2006
Objectives of ARVAC - for RV3

- Advance the RV3 rotavirus vaccine programme by supporting cGMP manufacture of clinical trial materials with Murdoch Children’s Research Institute (MCRI) and BioFarma, Indonesia
Non-living Rotavirus Vaccine Approaches

- VP6 vaccine candidate (Dick Ward, Cincinnati)
- Virus-like particles (Margaret Conner, Baylor College)
- Inactivated approach (Baoming Jiang, CDC)
- Inactivated approach (Osamu Nakagomi, Akita University)
Summary
Future Rotavirus Research Agenda

• Country decision making processes
  • Cost effectiveness analysis – building the evidence base
  • Rotavirus burden of disease to generate local data
• Introduction of current vaccines
  • Post-marketing surveillance for vaccine safety
  • Post-marketing surveillance for vaccine impact
  • Assessment of programmatic costs and impact
• Surveillance and Monitoring
  • Strain diversity and genotypes
• New vaccines
  • Live oral vaccine candidates
  • Non-living vaccine candidates
• Programmatic questions