RV3 Rotavirus Vaccine:

A human neonatal rotavirus vaccine to protect against rotavirus disease from birth
Rotavirus Vaccine efficacy varies markedly between high and low income countries

Nelson & Glass; Lancet 2010
Challenges to the success of Rotavirus Vaccines

1. Lower efficacy in developing countries

2. Challenges for implementation
   • Timely access to infants at high risk of RV disease
   • Cold chain: requirement & volume required, implications for transport and secure storage
   • Age restrictions: implications for catch-up vaccination strategies

3. Safety concerns
   • Intussusception: real vs perception, accept of any risk?
   • Contaminants: porcine circonovirus

4. Cost
   • Vaccine
   • Implementation
   • Post-licensure surveillance: safety, efficacy
Is it possible to protect babies against rotavirus disease from birth?
Rationale for a birth dose strategy for a rotavirus vaccine

- **First rotavirus infection**
  - most severe
  - produces a strong immune response that limits disease on re-infection

- **Younger age at first infection in developing countries**
  - Is a first dose at 6-8 weeks with completion of course (max protection) at 5-6 month of age too late to protect some infants?
  - Gap in the first 6-8 weeks – no protection

- **Birth is “best” immunization opportunity**
  - Established EPI time-point in many developing countries (OPV, BCG)

- **Intussusception is extremely rare**
  - improved safety profile
Potential interference from maternal and breast milk antibodies
Potential interference from maternal and breast milk antibodies

• Which factor is most important?
  – IgA, IgG, Neutralising Abs
  – Serum vs breast milk

• Breast milk has a number of other anti-infective and anti-inflammatory properties
  – Lactoferrin
  – Cytokines and cytokine receptors, TLR agonists and antagonists
  – Hormones, nucleotides, complex carbohydrates

Every day severe rotavirus infection occurs despite the presence of maternal and breast milk antibodies
Potential interference from maternal and breast milk antibodies

- 100 maternal and infant pairs in Jogjakarta, Indonesia
  - Cord and maternal sera
  - Colostrum (1-3 days) and transitional breast milk (7-10 days post-partum)

<table>
<thead>
<tr>
<th>Rotavirus specific IgG</th>
<th>N</th>
<th>No. pos (%)</th>
<th>Median</th>
<th>IGR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal serum</td>
<td>99</td>
<td>99 (100)</td>
<td>2200</td>
<td>1148-3920</td>
</tr>
<tr>
<td>Cord serum</td>
<td>94</td>
<td>94 (100)</td>
<td>2646</td>
<td>1276-5760</td>
</tr>
<tr>
<td>Rotavirus specific IGA</td>
<td>N</td>
<td>No. pos (%)</td>
<td>Median</td>
<td>IGR</td>
</tr>
<tr>
<td>Maternal sera</td>
<td>99</td>
<td>56 (56.6)</td>
<td>100</td>
<td>50-400</td>
</tr>
<tr>
<td>Cord sera</td>
<td>94</td>
<td>0 (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colostrum</td>
<td>96</td>
<td>75 (78.1)</td>
<td>640</td>
<td>160-2560</td>
</tr>
<tr>
<td>Transitional BM</td>
<td>99</td>
<td>64 (66.6)</td>
<td>160</td>
<td>40-640</td>
</tr>
<tr>
<td>Neutralising antibodies</td>
<td>N</td>
<td>No. pos (%)</td>
<td>Median</td>
<td>IGR</td>
</tr>
<tr>
<td>Colostrum</td>
<td>34</td>
<td>19 (56%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transitional BM</td>
<td>34</td>
<td>14 (41%)</td>
<td></td>
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</tbody>
</table>

Chan J, et al, Vaccine 2011
To avoid potential interference from maternal and breast milk antibodies

- **Timing of vaccination**

  *Ideal opportunity to deliver rotavirus vaccine is at birth*
  
  - No maternal IgA antibodies transferred across the placenta
  - Before breast feeding is established, particularly exposure to colostrum

- **Selection of the ideal vaccine strain**
  
  - Use a vaccine strain known to less susceptible or resistant to maternal and/or breast milk antibodies
Selecting the best vaccine candidate to target neonatal administration

- Critical elements
  - Safety
  - Effective in neonates
- Insight from wild-type rotavirus infection

**Neonatal rotavirus strains**
- Replicate well in the neonatal gut
- Asymptomatic infection (or low incidence of disease)
- Natural infection has been associated with protection against rotavirus disease in later infancy (RV3)

*Target neonatal administration strategy using innate advantages offered by a neonatal rotavirus strain*
What makes neonatal rotavirus infection different from infection later in life?

- Gut factors
- Virus factors

What makes neonatal rotavirus infection different from infection later in life?

The newborn gut has distinct structural and functional differences to mature gut that effect:

– Gut barrier function
– Mucosal immunity
– Impacted by factors:
  • Bacterial colonization
  • Method of feeding
  • Interventions: medications, surgery
  • Environment
  • Genetics
What makes neonatal rotavirus infection different from infection later in infancy?

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The newborn gut has distinct structural and functional differences to mature gut that effect:

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- Mucosal immunity
- Impacted by environmental factors

Insoft RM, Sanderson IR, Walker WA. Pediatric Nth America 1996; 43: 551-571
What makes neonatal rotavirus strains different from other rotavirus strains?

1. Differences in structural proteins

1. Differences in integrin recognition
What makes neonatal rotavirus strains different from other rotavirus strains?

1. Differences in structural proteins
   - Relationship between VP4 sequence and neonatal infection
   - Residues of VP4 attachment protein correlate with the capacity of some P[6] strains to infect newborns versus older infants
   - VP4 amino acid changes may confer binding to alternative carbohydrate molecules or to proteins present on the surface of neonatal enterocytes

Location of the surface exposed P[6] VP8* residues that correlate with neonatal infection

CM Rippenger et al, Virology 2010
What makes neonatal rotavirus strains different from other rotavirus strains?

2. Differences in integrin recognition

- Many disease causing rotaviruses of human, rhesus and bovine can use sequences on VP4 and VP7 to employ cellular integrins to establish infection
- Integrins α2β1, αXβ2, αVβ3 have been implicated in RV cell attachment and entry
- Integrin usage is related to viral P serotype
- Integrins α2β1, β2, αVβ3 are used by a number of disease causing rotaviruses of children but strains causing asymptotically infection in neonates (including RV3) may be integrin independent.

Graham et al, J of Virology 2003
Are all neonatal rotavirus strains similar?

- Human (RV3: G3P[6])
  Natural human-bovine reassortant (116E: G9P[11])
- Structural differences between neonatal strains
  - Surface exposed VP7 amino acids unique to RV3 or 116E
  - Integrin dependence:
    - RV3 is integrin independent
    - 116E used integrins α2β1, β2, αVβ3
To maximise chances for success for a newborn rotavirus vaccine strategy

- **Timing of vaccination**

  *Ideal opportunity to deliver rotavirus vaccine is at birth*

  - No maternal IgA antibodies transferred across the placenta
  - Before breast feeding is established, particularly exposure to colostrum

- **Selection of the ideal vaccine strain**

  *Target neonatal administration strategy using intrinsic advantages offered by a neonatal rotavirus strain*
What is RV3?

- Rotavirus isolated from healthy newborns in Melbourne in 1975
- In the first 3 years of life, natural asymptomatic infection was associated with
  - 100% protective against SEVERE rotavirus gastroenteritis
  - 75% protective against MODERATE rotavirus gastroenteritis
  - 56% protective against ANY rotavirus gastroenteritis
- NEVER identified in a child admitted to the RCH with gastroenteritis
Natural infection with RV3 appears to offer heterotypic protection

- Humoral immune responses in 3 years after wild-type RV3 infection
  - 3 months: persisting levels of neutralising antibodies to G1, G3, G4 in 50-75%
  - Re-infection with G1, G2, G4 resulted in strong heterotypic responses

- Decrease in gastroenteritis hospitalizations during period of endemic RV3 infection in Neonatal nurseries when main circulating serotype was G2P4
RV3-BB Rotavirus Vaccine

• Single human neonatal rotavirus strain: G3P[6]
• Developed from RV3 rotavirus strain obtained from an newborn with an asymptomatic RV3 infection in Melbourne
• Previous Phase I/II trials of “low titre” RV3 vaccine demonstrated it was well tolerated in infants
• Higher titre (~8.3 x 10^6f cfu/ml) RV3-BB vaccine developed in WHO prequalified vero cells under GMP: Meridian Life Sciences, Memphis
• Developed in collaboration with a developing country vaccine manufacturer, Bio Farma Indonesia
The RV3 Rotavirus Vaccine Program

Develop an affordable human neonatal rotavirus vaccine to provide protection from rotavirus disease from birth
Phase I Safety Trial

- Primary objective: assess tolerability and safety
- Blinded, randomized, placebo control study
- Single dose RV3-BB vaccine (1ml: $\sim 8.3 \times 10^6$ ffu/ml)
- 20 adult, 20 children (3-8 years) and 20 infants (6-8 weeks)
- 10 active, 10 placebo in each arm
- Follow up to 28 days post-dose for solicited and unsolicited adverse events

Last participant completed March 2011
Phase I Safety Trial

• Well tolerated in adults, children and infants
• No adverse events with a definite or probable relationship to study vaccine
• Vaccine take demonstrated in 8/9 (89%) infants
• Funded by Australian National Health and Medical Research Council
• **Presentation on 20th September at 15:50**
RV3 Phase II Clinical Trial: Safety and Immunogenicity Trial

**Primary objective**
To assess cumulative vaccine take following administration of RV3-BB vaccine compared to placebo, when:
1) administered using a neonatal vaccine schedule
2) administered using an infant vaccine schedule.

**Collaboration**
MCRI and the University of Otago

**Site**
Dunedin, New Zealand

**Study commencement**
December 2011

**Funding**
Australian National Health and Medical Research Council
New Zealand Health Research Council
RV3 Phase II Clinical Trial: Safety, Immunogenicity & Efficacy Trial

Site
2 provinces in Indonesia; Yogyakarta, Central Java

Collaboration
Murdoch Childrens Research Institute
Gadjah Mada University
Bio Farma

Funding
National Health & Medical Research Council, Australia
Bill and Melinda Gates Foundation
Bio Farma
RV3 Phase II Clinical Trial: Safety, Immunogenicity & Efficacy Trial

**Primary objective**
To assess the efficacy of three doses of RV3-BB vaccine against severe rotavirus gastroenteritis, up to 18 months of age, compared with placebo.

**Secondary Objectives**
To describe the safety, tolerability and reactogenicity of RV3-BB in each of the neonatal and infant schedules, compared with placebo.

To assess the efficacy of the neonatal schedule, infant schedule, and the combined neonatal and infant schedules of RV3-BB, compared with placebo, against:

- rotavirus gastroenteritis of any severity
- all-cause severe gastroenteritis
- all-cause gastroenteritis of any severity

**Sub-studies embedded within the main trial**
Immunogenicity, Co-administration with OPV
Is it possible to protect babies against rotavirus disease from birth?
Strengths of RV3-BB vaccine

- Exclusively human single neonatal rotavirus strain
- Stable, naturally attenuated and adapted to the infant gut
- Natural infection is asymptomatic and protective
- Protection is heterotypic
- Ideal candidate for administration at birth
- Phase I clinical trials – well tolerated, 8/9 infants had evidence of vaccine take after a single dose
- Phase II trials – New Zealand and Indonesia underway
- Great team that is passionate and committed
  - MCRI, Gadjah Mada University, Bio Farma
  - University of Otago
  - Expert Advisory Committee
RV3 Rotavirus Vaccine Program

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Carl Kirkwood
Jim Buttery
Margie Danchin
Ruth Bishop
Graeme Barnes
Emma Watts
Jane Standish
Will Siero
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Kate Lee
Daniel Crowley
Fran Justice
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Jim Ackland: Global Solutions]

Gadjha Mada University
Yati Soenarto
Jarir Atthobari
Cahya Dewi Satria
The team at PRO and Sites

University of Otago, NZ
Pam Jackson
Amanda Mulch
The team at Dunedin Hospital

BioFarma
Dr Iskandar
Novila Bachtiar
Ismu Prastywati
Mahrani
Latri
All the team at Bio Farma
Acknowledgements

- National Health and Medical Research Council, Australia
- Bill and Melinda Gates Foundation
- New Zealand Health Research Council
- Bio Farma, Indonesia
- AusAID
- PATH
- Murdoch Childrens Research Institute
- University of Melbourne
- Royal Children’s Hospital Foundation