RV3 Rotavirus Vaccine Program:

A human neonatal rotavirus vaccine to protect against rotavirus disease from birth
Challenges to the success of Rotavirus Vaccines

1. Lower efficacy in developing countries
2. Challenges for implementation
3. Safety concerns
4. Cost
5. Vaccine supply
6. Religious and cultural concerns
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*Ideal time to deliver a rotavirus vaccine is at birth*
Why consider a birth dose?

1. Specific to rotavirus disease
2. Specific for oral rotavirus vaccines
3. Enhance vaccine coverage and impact
Why consider a birth dose?

1. Specific to rotavirus disease
   - First rotavirus infection
     - most severe
     - produces a immune response that limits disease on re-infection
   - Younger age at first infection in developing countries
     - Gap in protection:
       - 6-8 weeks: Peak age of rotavirus hospitalisation in Australia post-rotavirus vaccine introduction = infants <2 months of age
       - Time to complete protection after 2 or 3 doses administered
   - Neonatal rotavirus strains
     - Some asymptomatic but replicate well in newborns
     - associated with protection from subsequent rotavirus disease

2. Specific for rotavirus vaccines
3. Enhance vaccine coverage and impact
Why consider a birth dose?

1. Specific to rotavirus disease

2. Specific for oral rotavirus vaccines
   - Neutral or alkaline gastric environment
   - Intestinal microbiota is not yet established
   - Potential impact of breast milk antibodies is limited if vaccine is delivered at birth before significant breast milk intake
   - Tropical enteropathy not established
   - Intussusception is extremely rare in < 1 month of age

3. Enhance vaccine coverage and impact
Why consider a birth dose?

1. Specific to rotavirus disease

2. Specific for rotavirus vaccines

1. Enhance vaccine coverage and impact
   - Birth is considered an ideal immunization opportunity
     - Mothers and babies contact with healthcare worker
     - Established EPI time-point in many developing countries (OPV, BCG, HepB)
   - To improve the uptake of other vaccines; co-administration
   - To maximize opportunity for administration of a complete 3 dose regiment
     - Coverage of DTP is best for the first dose and declines with each successive dose
   - Non-specific or indirect benefits of a live vaccine
     - “prime” immune response to other vaccines and to non-target infection
Selecting the best vaccine candidate to target birth dose strategy

• Critical elements
  • Safety
  • Effective in neonates
Selecting the best vaccine candidate to target birth dose strategy

• Critical elements
  • Safety
  • Effective in neonates

**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)
What makes neonatal rotavirus strains different from other rotavirus strains?

1. Differences in structural proteins

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

CM Rippenger et al, Virology 2010

2. Differences in integrin recognition

3. Not all neonatal strains are the same
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?

1. Differences in structural proteins

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
What makes neonatal rotavirus strains different from other rotavirus strains?

1. Differences in structural proteins
2. Differences in integrin recognition
3. Not all neonatal strains are the same

- Structural differences
- Integrin dependence:
  - RV3 is integrin independent
  - 116E used integrins α2β1, β2, αVβ3
Is it possible to take advantage of the novel characteristics of a human neonatal vaccine strain to protect babies against rotavirus disease from birth?
What is RV3?

• Human neonatal rotavirus (G3 P6)
• Isolated from healthy newborns in Melbourne
• In the first 3 years of life, natural asymptomatic infection
  • **100%** protective against SEVERE rotavirus gastroenteritis
  • **56%** protective against ANY rotavirus gastroenteritis
• Appears to be naturally attenuated
  ▪ Never identified in
    o Sibling of naturally infected infants
    o In a child admitted to RCH with acute RV gastroenteritis
RV3-BB vaccine

1. Novel vaccine strain; RV3-BB
   - Single human neonatal rotavirus strain
   - Monovalent
   - G3 P[6]

2. Target birth dose administration

3. Potential for significant contribution to global rotavirus vaccine supply
   - Partnership with Bio Farma – *porcine-free vaccine*
   - Target P6 serotypes - Africa
Phase IIa Trial – Safety and Immunogenicity

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.

Study completion 30 May 2014

Vaccine take
Serum immune response: 3-fold increase in serum anti-rotavirus IgA or serum neutralising antibody (SNA) from baseline at day 28 post-dose; or RV3-BB virus excretion in stool day 3-5 post-dose by RT-PCR

Safety and Tolerability Assessment
Solicited GIT and systemic symptoms (7 day diary card)
Unsolicited symptoms (28 day diary card)
Blood: FBC, LFT, U&E/Cr, urine
Cumulative Vaccine take – *Intention To Treat Analysis*

Neonatal schedule

Infant schedule
Components of Vaccine Take

Neonatal Schedule

- slgA
- Stool Excretion
- Vaccine Take

Infant Schedule
Key Conclusions: Phase 2a

Administered in a neonatal or infant schedule

- RV3-BB was well tolerated
- RV3-BB was strongly Immunogenic ≥ 90%

Two doses of RV3-BB in an infant schedule

- vaccine take in 93% vs placebo 13%

Neonatal schedule

- post dose 1 vaccine take 20% vs placebo 0%
- Post dose 3 vaccine take 90% (ITT), 96% (PP)
RV3 Phase IIb Clinical Trial
Safety, Immunogenicity & Efficacy Trial

Double blind randomized placebo controlled trial
3432 participants
Yogyakarta, Central Java
Phase II b 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
To assess the efficacy 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
Study Design

**NEONATAL SCHEDULE**

- **Immediately post delivery:**
  - **0–5 days of age**
    - **Dose 1:**
      - RV3-BB Vaccine

- **8–10 weeks of age**
  - **Dose 2:**
    - RV3-BB Vaccine

- **14–16 weeks of age**
  - **Dose 3:**
    - RV3-BB Vaccine

- **28 days post dose 3:**
  - Blood sample

- **18–20 weeks of age**
  - **Dose 4:**
    - Placebo

- **28 days post dose 4:**
  - Blood sample

**PLACEBO**

- **Immediately post delivery:**
  - Cord blood sample

- **8–10 weeks of age**
  - Placebo

- **14–16 weeks of age**
  - Placebo

- **28 days post dose 3:**
  - Blood sample

- **18–20 weeks of age**
  - Placebo

- **28 days post dose 4:**
  - Blood sample

**INFANT SCHEDULE**

- **Immediately post delivery:**
  - Cord blood sample

- **8–10 weeks of age**
  - RV3-BB Vaccine

- **14–16 weeks of age**
  - Placebo

- **28 days post dose 3:**
  - Blood sample

- **18–20 weeks of age**
  - RV3-BB Vaccine

- **28 days post dose 4:**
  - Blood sample
Status Update

• Initial cohort n=1649: completed 16 January 2015
• A total of 5,989 doses administered at 2 Feb 2015

Diagram:

- Target n = 1647
- Randomised n = 1649
  - Discontinued from Treatment n = 15 (0.9%)
  - Active participation n = 1595 (96.7%)
  - Withdrawn n = 39* (2.4%) * includes 8 deaths

Graph:

- Y-axis: 0 to 1649
- X-axis: 13-Jan to 16-Jan
- 2013-2015
Progress of efficacy assessment

Age of participants at 2 Feb 2015

- 11% completed @18 months
- 74% < 12 months of age

Diarrhea Capture

- 676 diarrhea episodes (of any severity); 1809 samples collected
- 72 severe (vesikari score ≥11)
Status Update

- Expanded cohort commencing 1 May 2015:
  - Total n=3432
  - Ethics Committee approval January 2015
  - BPOM approval pending
- Additional 4 sites: total 25
- Timelines:
  - full recruitment complete April 2016
  - Final report December 2017
RV3-BB Vaccine Development
BioFarma Indonesia

• Target Product Profile
  • Liquid 1ml
  • Manufactured using bovine trypsin
  • 3 dose regiment, birth dose strategy
  • Currently at -20oC
  • Formulation under development to achieve 2-8oC

• Regulatory strategy:
  • Indonesia BPOM licensure  2018/9
  • WHO Prequalification
  • Global implementation
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