Results from the Phase I trial of RV3-BB Rotavirus Vaccine

A human neonatal rotavirus vaccine

The aim of the program is to:

- To develop a low cost oral rotavirus vaccine to protect infants from birth, particularly in developing countries
- Use a birth dose vaccination strategy
  - Protect infants earlier in settings where rotavirus infections endemic and occur less than 3 months
  - Neonatal administration provides an excellent opportunity for attendant health care workers to access the infant and mother
- Low intussusception risk
RV3-BB Rotavirus Vaccine Program
– protection of infants from birth against Rotavirus

• The vaccine candidate
  • Oral 1ml (~8.3 x 10^6 FFU/ml) in WHO prequalified vero cells under GMP at Meridian Life Sciences, Memphis
• Second generation vaccine
• Culmination of almost four decades of research in Australia by Murdoch Childrens Research Institute, the Royal Children’s Hospital Melbourne and the University of Melbourne
• Follows the discovery of rotavirus by a team of staff led by Professor Ruth Bishop in 1973.
What is RV3?

- Rotavirus isolated from healthy newborns from Obstetric Hospitals in Melbourne in 1975
- Human rotavirus G3 P6
- In the first 3 years of life, natural asymptomatic infection:
  - 100% protective against SEVERE rotavirus gastroenteritis
  - 75% protective against MODERATE rotavirus gastroenteritis
  - 56% protective against ANY rotavirus gastroenteritis
  - NOT protective against rotavirus infection
Strengths of RV3-BB vaccine

- Exclusively human neonatal rotavirus strain
- Stable, naturally attenuated and adapted to the infant gut
- Natural infection is asymptomatic and protective
- Protection is heterotypic
- Replicates in the presence of high titres of maternal antibody and breast-feeding
- Ideal candidate for administration at birth
- Phase I and II trials of low titre RV3 vaccine demonstrated it was well tolerated in infants
- Developed in collaboration with a developing country vaccine manufacturer, Bio Farma Indonesia
Methods – Phase I trial

Single centre double-blind randomised placebo control trial conducted at Royal Childrens Hospital and Murdoch Childrens Research Institute, Melbourne

Assess safety, tolerability and immunogenicity
Randomised (1:1), placebo controlled
Single oral 1 ml dose vaccine (8.3 x 10^6 FFU/ml) or placebo
Methods – Phase I trial

60 participants across three age groups:
- 20 adults, 20 children and 20 infants
  • 10 vaccine and 10 placebo in each group
  • Progression to next age cohort only after DSMB review and demonstration of safety
Methods – Phase I trial

Recruitment:

- Vaccine and Immunisation Research Group (VIRGo) at Murdoch Childrens Research Institute – family database
- HREC approved advertisements – University of Melbourne, parenting magazines
- Maternal and Child Health Centres and antenatal clinics (public hospital)
- Post natal wards (private hospitals) and 6-week baby checks (private obstetricians)
- All infants received 3 doses of Rotateq at completion of the study (within recommended age windows)
- Commenced Feb 2010 and completed in March 2011
Methods

Screening visit:
Blood, urine and stool

Visit 2:
IP plus Mylanta
Breast feeding withheld 30mins before and after IP

Visit 3:
7 day diary card – solicited GIT and systemic symptoms
Blood, Urine, stool – daily day 0-6

Visit 4:
28 day diary card
Blood, Urine, stool
SAE's Day 28
Methods – Phase I trial

(1) 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

(2) Immunogenicity assessment
- IgA/IgG/SNA
- stool

Definition of vaccine take:
3-fold increase in serum anti-rotavirus IgA or serum neutralising antibody (SNA) from baseline at day 28 post-dose
and/or
evidence of RV3-BB viral shedding/replication in the faeces by RT-PCR analysis/ELISA between day 3-6 post vaccination
Final phase I participant
Results

A single dose of RV3-BB vaccine well tolerated in adults, children and infants.

No adverse events were considered to have a definite or probable relationship to the study vaccine.

Serious adverse events (n=1): hospitalization for an episode of pneumonia - assessed by independent pediatrician as unrelated to vaccine (infant cohort).

Unsolicited and solicited adverse events - No relationship identified to treatment assignment.
### Results: Safety

**Serious adverse events:**

6 unrelated; 1 possibly related – elevated ALT (infant cohort)

<table>
<thead>
<tr>
<th>Severe AEs</th>
<th>Cohort 1 (adults)</th>
<th>Cohort 2 (children)</th>
<th>Cohort 3 (infants)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nausea (P)</td>
<td>Croup (V)</td>
<td>Increased ALT (V)*</td>
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<tr>
<td></td>
<td>Neck pain (P)</td>
<td>Sleep terrors (V)</td>
<td>Pneumonia (SAE)(V)</td>
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<td>Vomiting (P)</td>
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</table>

* Child with intercurrent viral infection and receiving prolonged high dose chloramphenicol eye drops
Results: Safety

Solicited GIT adverse events - infants
Results: Safety

Solicited systemic adverse events - infants
## Results: Immunogenicity - infants

<table>
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<tr>
<th></th>
<th>VACCINE TAKE (combined serological response and faeces replication following a single dose of RV3-BB)</th>
<th>SEROLOGICAL RESPONSE (≥3X increase in serum IgA and/or Neutralising Ab at day 28)</th>
<th>RV3-BB IN STOOL (day 3-6 post vaccination)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vaccine</strong></td>
<td>8/9 (89%)</td>
<td>5/9 (56%)</td>
<td>7/9 (78%)</td>
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<tr>
<td><strong>Placebo</strong></td>
<td>2/10 (20%)*</td>
<td>2/8 (25%)</td>
<td>0/10 (0%)</td>
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</tbody>
</table>

* Wild-type rotavirus detected
Results: Immunogenicity

RV3-BB replication/shedding

• No placebo recipients
• No participants at screening
• All infants receiving RV3-BB vaccine had RV3-BB detected in the faeces at least once from day 0
• 7/9 infants receiving RV3-BB vaccine had RV3-BB detected in the faeces at least once from day 3 to 6 suggesting viral replication
Conclusion

RV3-BB is being developed with the aim to provide a low cost neonatal vaccine to prevent rotavirus disease from birth.

In this Phase I study of the RV3-BB rotavirus vaccine in adults, children and infants, a single dose of the vaccine was:

- Well tolerated in adults, children and infants
- Immunogenic with a vaccine take identified in 8/9 (89%) of infants
Conclusion

Administration of a rotavirus vaccine at birth has a number of potential advantages:

• provides the earliest opportunity for protection from rotavirus disease
• a time when mothers and their newborns are most likely to be in direct contact with health services and is an established EPI time-point in many developing countries
• Lower risk of intussusception as intussusception exceptionally rare in newborns
Conclusion

Phase II trials to assess the immunogenicity and efficacy of the RV3-BB rotavirus vaccine with the first dose delivered either at birth or at 6-8 weeks of age are now underway.
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