ORVAC Protocol

Optimising Rotavirus Vaccine in Aboriginal Children

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Rotavirus Epidemiology

CAUSES OF CHILDHOOD GASTROENTERITIS

- **Rotarix**: 2 months & 4 months
- **RotaTeq**: 2 months, 4 months & 6 months

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**Post-Licensure Studies**

High Income Countries
- **Rotarix**: VE 85 – 96%
- **RotaTeq**: VE 98 – 100%
**Rotavirus Vaccine**

Low & Middle Income Countries

- **Rotarix**: VE 49 – 77%
- **RotaTeq**: VE 43 – 64%

- protection not enduring / complete
  - Bolivia: 2-11mo = 76% > 12mo = 45%
  - Malawi: < 12mo = 70% 12-23mo = 31%
  - Moldova: 6-11mo = 84% 12-23mo = 46%

**Rotavirus in the Northern Territory**

RV Hospitalisations (pre & post vaccine)

- Australian Non-Indigenous children: < 1 per 1000 children
- NT Indigenous children: 22 per 1000 children
Rotavirus in the Northern Territory

Rotavirus Notification Data for G2P[4] Outbreaks: Children < 5 yrs

<table>
<thead>
<tr>
<th></th>
<th>2004 Outbreak</th>
<th>2009 Outbreak</th>
<th>2017 Outbreak</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration (days)</td>
<td>52</td>
<td>56</td>
<td>43</td>
</tr>
<tr>
<td>Number of cases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>71 (59%)</td>
<td>75 (63%)</td>
<td>80 (54%)</td>
</tr>
<tr>
<td>Aboriginal</td>
<td>65 (92%)</td>
<td>66 (88%)</td>
<td>70 (88%)</td>
</tr>
<tr>
<td>Hospitalised</td>
<td>66 (93%)</td>
<td>59 (79%)</td>
<td>66 (83%)</td>
</tr>
<tr>
<td>Length of stay</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>5 (3-7)</td>
<td>4.5 (2-7)</td>
<td>4 (3-5)</td>
</tr>
<tr>
<td>Months of age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>9 (6-16)</td>
<td>12 (5-22)</td>
<td>16.5 (9-22)</td>
</tr>
</tbody>
</table>

Presented by Heather Cook at the 2017 Northern Territory Centre for Disease Control Conference, 13-15 Sept 2017

Indigenous Health Priority

Rotavirus an Indigenous Health Priority

- Round Table meeting of Aboriginal Community-Controlled Health Organisations convened by Centre for Research Excellence in Immunisation in Understudies and Disadvantaged populations (Nov 2013)
- 3rd National Indigenous Immunisation Research Workshop (Nov 2013)
- Aboriginal Health Research Forum, Telethon Kids Institute (May 2016).
Question

• is current two dose Rotarix schedule enough for Northern Territory Aboriginal children?

• would they benefit from a 3rd (booster) dose?

Clinical Trial for Clinical Endpoint

• traditional 3 vs 2 dose trial; would need to randomise (and follow) 1,000 infants for 3 years to have an 80% chance of showing ↓ number episodes of clinical gastroenteritis.

BUT only 1,000 Aboriginal babies born in the NT every year, population dispersed across a very large geographical area, and they are heavily researched.
Clinical Trial for Immunological Endpoint

- vaccine confers most of its effects by stimulating anti-rotavirus antibodies; only need to randomise 250 infants & follow for 1 month to show/exclude antibody response

- IMPORTANT: if 3 doses doesn’t confer an improved antibody response there is unlikely to be enough justification to do a clinical trial of 1000 infants

- BUT successful trial unlikely to change vaccine policy

Traditional Approach

- do an immunogenicity trial with 250 infants

- based on the results make a ‘go/no-go’ decision about starting a field trial with 1,000 infants

- hope for a conclusive result x 2!
Optimising Rotavirus Vaccine in Aboriginal Children

Clinical Trial Objective

To determine if additional dose of oral Rotarix (RV1) given to NT Aboriginal children aged 6 - 11 months confers significantly better protection against gastroenteritis than the current two-dose vaccine schedule.

Study Design

- phase IV clinical trial
- double-blind, randomised, placebo-controlled
- third scheduled dose of Rotarix (or placebo) at 6-11 months
- Northern Territory Aboriginal or Torres Strait Islander infants

Two-Stage Design

- Stage 1: enroll up to 250 infants for immunological outcome
- Stage 2: enroll up to 1000 infants (& follow for 3 years) to review clinical outcome (decreased clinical gastroenteritis)
Co-Primary Outcomes

Immunological Outcome
• increased seroconversion (serum anti-rotavirus IgA > 20 U/ml 28 - 55 days post Rotarix (RV1) / placebo)

Clinical Outcome
• reduced medical attendance with gastroenteritis in the first three years of life (clinic, emergency, hospitalisation)

Secondary Outcomes

Immunological Outcome
• change in anti-rotavirus IgA titre post Rotarix/placebo

Clinical Outcomes
• reduced hospitalisation with all cause diarrhea
• reduced hospitalisation with rotavirus-confirmed diarrhea
• reduced rotavirus notifications
Pragmatic
• very few exclusionary criteria
• infants with contraindication to Rotarix (RV1) vaccine

Setting
• urban, rural & remote Northern Territory

Bayesian Adaptive
• no fixed sample size (max 1000 infants)
• frequent interim analysis (after every 50 participants)
• pre-specified stopping rules (superiority / futility)
• fixed 1:1 enrolment
Interim Analysis

Given the accumulated data:

• what is probability antibody response is better in additional Rotarix group (compared to placebo)?
  – If very high → stop taking bloods & continue for clinical outcome
  – If very low → stop enrolling for futility

• what is predicted probability time-to-clinical gastroenteritis is longer in additional Rotarix dose group (compared to placebo)?
  – If very high → stop enrolling for expected success
  – If very low → stop enrolling for futility
  – otherwise continue to enrol in the study.

Adverse Events

• Rotashield (1990s): increased risk intussusception
• Upper Age Limit Restrictions; Rotarix < 6 months
• Phase III: no increased risk
• Post Licensure: approx 6 cases per 100,000 infants

• Data Safety & Monitoring Board
Advice & Support

- Menzies Child Health Indigenous Reference Group
- Cultural Advisor: Ada Parry
- Indigenous Members of Steering Committee

Strengths

- first clinical trial to evaluate the immunological and clinical response of Rotarix in infants > 6 months
- pragmatic trial design
- innovative bayesian adaptive design

Limitations

- only capture gastro presenting for medical attention
- unable to confirm if all gastroenteritis is rotavirus
Trial Progress

- NHMRC funding
- Central Australia HREC/ Top End HREC approval
- Recruitment March 2018
  - four large remote communities in Top End & urban Darwin
  - additional sites in Top End & Central Australia
- Participants 127
- Second Interim Analysis

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Menzies Child Health Indigenous Reference Group
Thank You