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ADAPTIVE HEALTH INTELLIGENCE
EVIDENCE IN ACTION

WESFARMERS CENTRE OF VACCINES & INFECTIOUS DISEASES

ORVAC Protocol

Optimising Rotavirus Vaccine in Aboriginal Children

Bianca Middleton, October 2019

discovery for a healthy tomorrow

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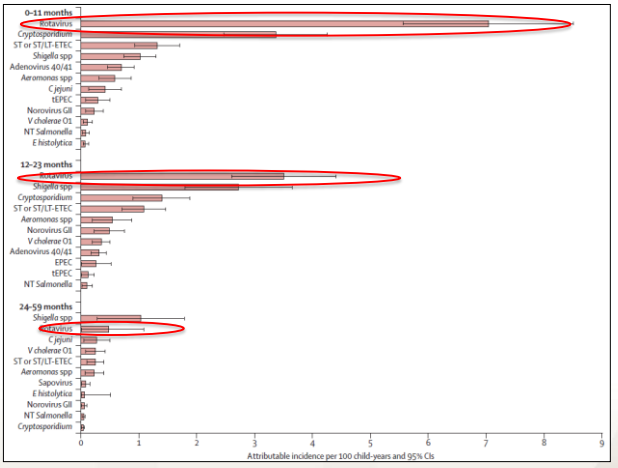
Rotavirus Epidemiology

CAUSES OF CHILDHOOD GASTROENTERITIS

0 – 11 months

12 – 23 months

24 – 59 months



Kotloff KL *et al*. Global Enteric Multicenter Study. Lancet 2013

Rotavirus Vaccines 2006

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

Rotavirus Vaccine

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%**

ROTA Council 2019, Kirkwood 2016

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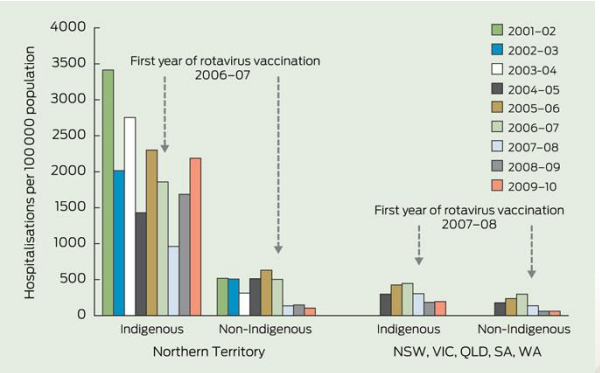
Rotavirus in the Northern Territory

RV Hospitalisations (pre & post vaccine)

- Australian Non-Indigenous children: < 1 per 1000 children
- NT Indigenous children: 22 per 1000 children



Dey 2012

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Rotavirus in the Northern Territory

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

	2004 Outbreak	2009 Outbreak	2017 Outbreak
Duration (days)	52	56	43
Number of cases	71	75	80
Males	42 (59%)	47(63%)	43 (54%)
Aboriginal	65 (92%)	66 (88%)	70(88%)
Hospitalised	66 (93%)	59 (79%)	66 (83%)
Length of stay Median (IQR)	5 (3-7)	4.5 (2-7)	4 (3-5)
Months of age Median (IQR)	9 (6-16)	12 (5-22)	16.5 (9-22)

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

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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).
- Menzies Child Health Indigenous Reference Group (Nov 2013).

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Additional Dose

Question

- is current two dose Rotarix schedule enough for Northern Territory Aboriginal children?
- would they benefit from a 3rd (booster) dose?

Additional 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.

Additional Dose

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

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Additional Dose

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!

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RVAC

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

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RVAC

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)

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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)

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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

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Pragmatic

- very few exclusionary criteria
- infants with contraindication to Rotarix (RV1) vaccine

Setting

- urban, rural & remote Northern Territory

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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

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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..

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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

Carlin 2013

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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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Indigenous Advisors

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Menzies Child Health Indigenous Reference Group

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Thank You