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ORVAC Stage One

Optimising Rotavirus Vaccine for Aboriginal Children

Bianca Middleton

March 2023

discovery for a healthy tomorrow

Rotavirus in Australia

Pre-Vaccine Era (before 2006)

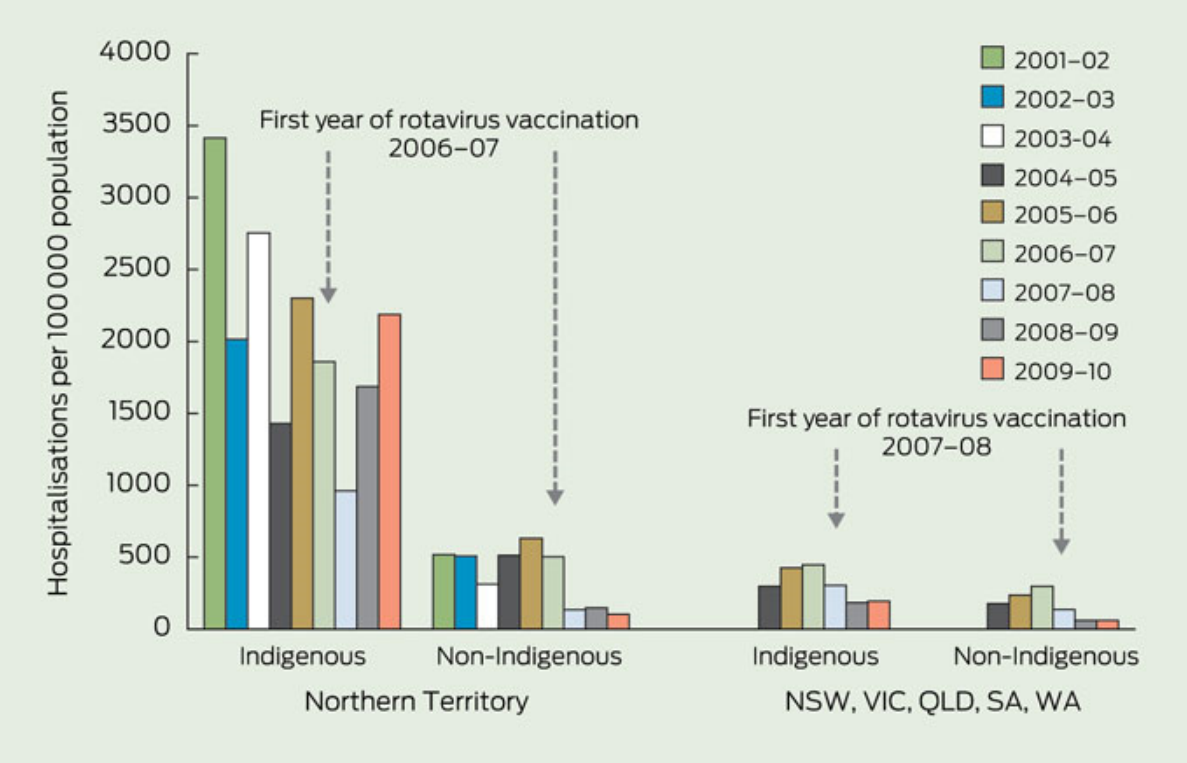
- approx 10 000 hospitalisations/ year
- approx 22,000 ED presentations/ year
- 115,000 visits to primary care/ year

** Aboriginal and Torres Strait Islander children < 12 months old were hospitalised at a rate more than five times higher.

Newall 2006, Schultz 2006

Rotavirus in the Northern Territory

Rotavirus Hospitalisations



Dey 2012

Vaccine Effectiveness

Rotavirus Outbreaks

2007 Rotavirus Outbreak NT

- G9P[8]; **VE 85%** (95%CI: 23 to 97%)

2009 Rotavirus Outbreak NT

- G2P[4]; **VE 19%** (95% CI: -105 to 68%)

2017 Rotavirus Outbreak NT & WA

- G2P[4]; **VE 21%** (95%CI: -66% to 54%)
  - median age 19 months

** waning immunity in second year of life

Snelling 2009, Snelling 2011, Middleton 2020

Additional Dose

Question

- is current 2-dose rotavirus vaccine schedule enough for NT Aboriginal children?

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

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Optimising Rotavirus Vaccine in Aboriginal Children

Clinical Trial Objective

To determine if administration of an additional (booster) dose of oral Rotarix rotavirus vaccine to Northern Territory Aboriginal children 6 to 11 months old confers significantly better protection against gastroenteritis than the current 2-dose vaccine schedule

ORVAC Clinical Trial

Study Design:

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

Pragmatic: very few exclusionary criteria

- infants with contraindication to Rotarix vaccine only

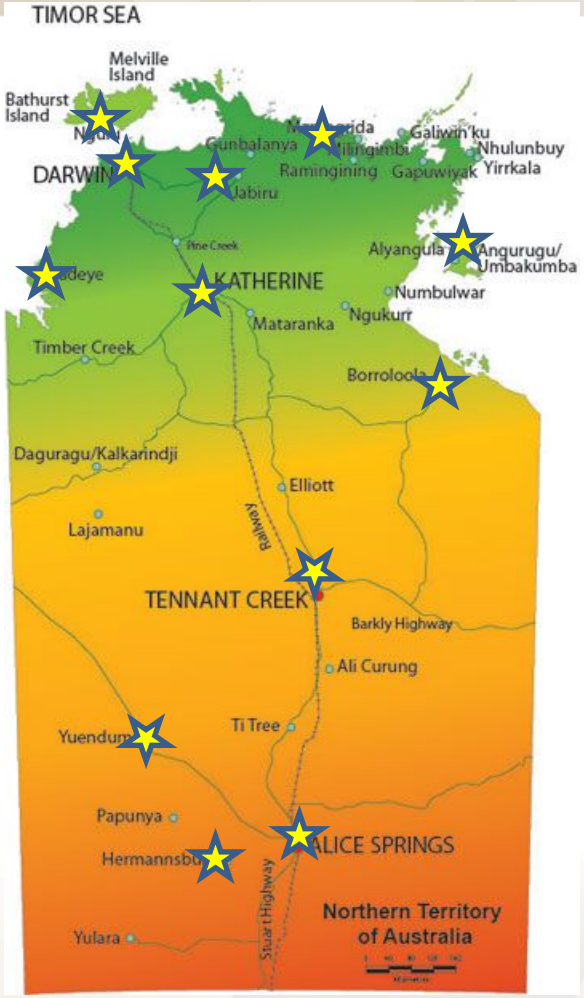
ORVAC Clinical Trial

Setting: urban, rural & remote Northern Territory

Northern Territory

- 1.35 million square kilometres
- population: 247,000 people
- Aboriginal and Torres Strait Islander - 30%

- 84 remote Aboriginal communities
- 500 homelands



ORVAC Clinical Trial

ORVAC Study

Immunological Outcome

- Primary Outcome: increased seroconversion
  - serum anti-rotavirus IgA > 20 U/ml 28 - 55 days post Rotarix / placebo

Clinical Outcome

- Primary Outcome: reduced medical attendance with gastroenteritis in the first three years of life (clinic, emergency department, hospitalisations)

ORVAC Clinical Trial

ORVAC Study

ORVAC Stage One: Immunological Outcome

- Primary Outcome: increased vaccine seroresponse
  - serum anti-rotavirus IgA > 20 U/ml 28 - 55 days post Rotarix / placebo

ORVAC Stage Two: Clinical Outcome

- Primary Outcome: reduced medical attendance with gastroenteritis in the first three years of life (clinic, emergency department, hospitalisations)

ORVAC Clinical Trial

Methods:

Baseline Visit

- serum: baseline anti-rotavirus IgA
- randomise: vaccine or placebo

Follow-Up Visit (Day 28 – 55)

- serum: follow-up anti-rotavirus IgA

Safety Check:

- Day 7: phone-call
- Day 28: medical record review

ORVAC Clinical Trial

Results:

- 253 Children
- March 2018 – Aug 2020
- median age: 8 months
- residence
  - regional urban 42%
  - remote 58%
- 2x prior Rotarix doses: 95%

Table 1. Baseline Demographic Characteristics, Prior Vaccine Doses, and Seropositivity for the Randomized Population

Characteristic	Infants by Vaccine Group, No. (%)[a]	
	Rotarix (n = 128)	Placebo (n = 125)
Male sex	64 (50.0)	67 (53.6)
Age, median (IQR), mo	8.5 (6.9–10.3)	8.7 (7.3–10.3)
Indigenous status		
Aboriginal	123 (96.1)	121 (96.8)
Torres Strait Islander	5 (3.9)	2 (1.6)
Aboriginal and Torres Strait Islander	0 (0)	2 (1.6)
Usual location		
Regional urban	31 (24.2)	33 (26.4)
Remote	97 (75.8)	92 (73.6)
Breastfed		
Exclusively	10 (7.8)	8 (6.4)
Partially	89 (69.5)	97 (77.6)
Not breastfed	29 (22.7)	20 (16.0)
Weight, median (IQR), k	8.5 (7.7–9.4)	8.5 (7.8–9.1)
MUAC, median (IQR), mm	145 (140–155)	144 (140–155)
Preenrollment Rotarix doses		
1st Dose	128 (100)	125 (100)
Age at 1st dose, median (IQR), wk	6.6 (6.2–7.1)	6.7 (6.3–7.6)
2nd Dose	119 (93.0)	122 (97.6)
Age at 2nd dose, median (IQR), wk	17.9 (17.3–18.8)	17.7 (17.4–18.4)
Seroresponse at baseline(IgA ≥20 AU/mL)		
Yes	83 (64.8)	92 (73.6)
No	37 (28.9)	29 (23.2)
Missing	8 (6.2)	4 (3.2)
IgA concentration at baseline, median (IQR), AU/mL	59.6 (17.8–151.0)	93.1 (21.2–164.0)

[a]Abbreviations: AU, arbitrary units; IgA, immunoglobulin A; IQR, interquartile range; MUAC, mid-upper arm circumference.

Data represent no. (%) of infants unless otherwise specified.

ORVAC Clinical Trial

Results:

Analysable Results: 178 children (70%)

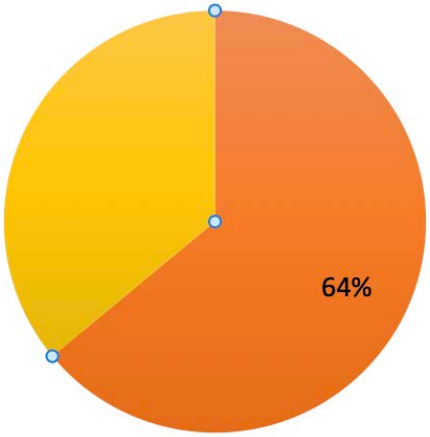
Proportion with vaccine response:

- Booster Dose Rotarix (3-doses): 85%
- No Booster Dose (2-doses): 72%

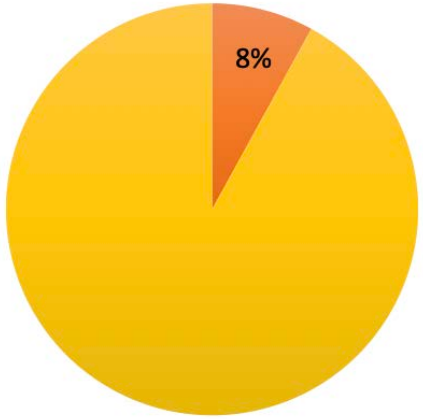
ORVAC Clinical Trial

Results:

sero-conversion among those seronegative at baseline



Booster Dose



Placebo

ORVAC Clinical Trial

Results:

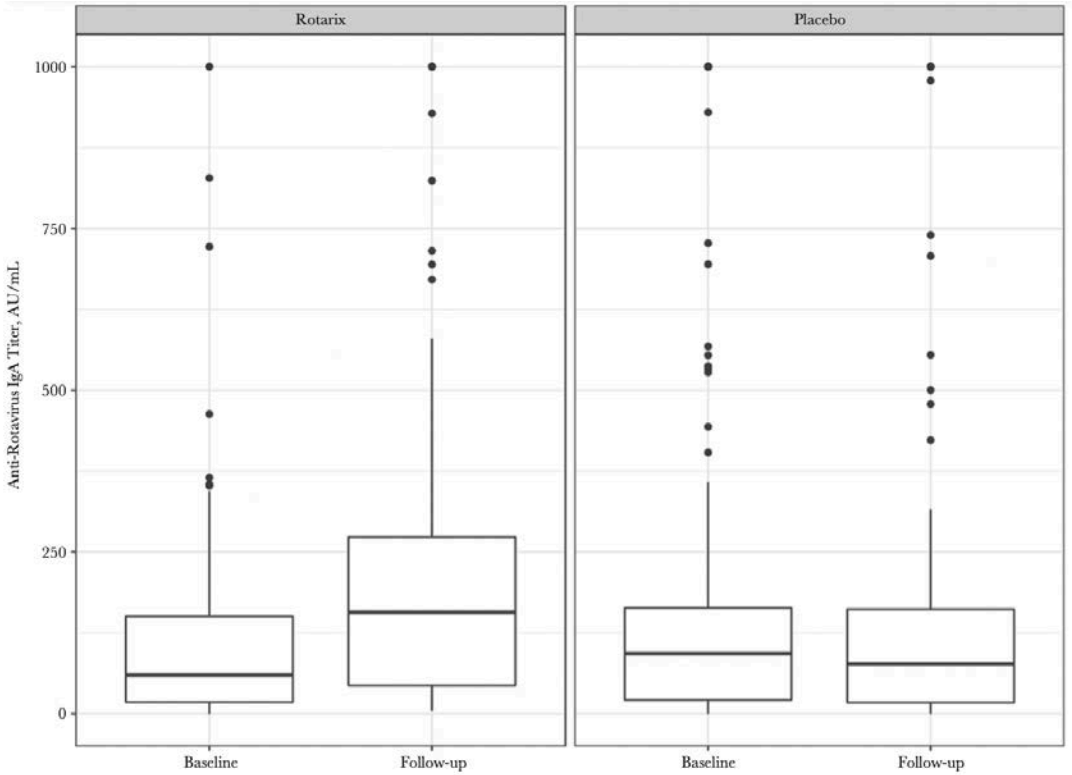


Figure 2. Change in anti-rotavirus immunoglobulin A (IgA) titer from baseline to 28–56 days after the additional dose of Rotarix or placebo. Abbreviation: AU, arbitrary units.

ORVAC Clinical Trial

Safety:

Data and Safety Monitoring Committee (DSMC)

- no cases of intussusception observed
- Baseline Risk for Intussusception for NT Aboriginal children:
  - low (16 vs 92/ 100,000)

Webby 2006

Next Steps

ORVAC Stage Two

- NHMRC funding
- Up to 1000 participants

- Clinical Outcome: reduced medical attendance with gastroenteritis in the first three years of life (primary care, ED, hospitalisations)

- Currently 580 participants

Acknowledgements

ORVAC Investigators

Tom Snelling, Margie Danchin, Mark Jones, Carl Kirkwood, Nigel Cunliffe, Amanda Leach, Jonathan Carapetis, Ross Andrews, Julie Marsh, Claire Waddington,

ORVAC Team

Sarah Gallagher, Jane Nelson, Sarah Royans, Gregoriana Parker, Alex Hinchliff, Gloria Baliva, Lorraine Gilbert, Megan Petery, Alina Iser

ORVAC Community Partners

Ada Parry, Dr Olivia O'Donoghue, Dr Simone Raye, Dr Dennis Bonney, Australian First Nations Reference Group for Child Health at the Menzies School of Health Research, Kalunga Aboriginal Research Development Unit Telethon Kids Institute, Local Community Authority Councils, Aboriginal Controlled Community Health Centres, NT Health

ORVAC Laboratory Partners

Monica McNeal – Cincinnati Children's Hospital, USA; Lea-Ann Kirkham & Caitlyn Granland – Telethon Kids Institute, Australia

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Acknowledgements

References

The Journal of Infectious Diseases

MAJOR ARTICLE

Immunogenicity of a Third Scheduled Dose of Rotarix in Australian Indigenous Infants: A Phase IV, Double-blind, Randomized, Placebo-Controlled Clinical Trial

Bianca F. Middleton,[1] Margie Danchin,[2,3,4] Mark A. Jones,[5,13] Amanda J. Leach,[6] Nigel Cunliffe,[7] Carl D. Kirkwood,[8] Jonathan Carapetis,[5,9] Sarah Gallagher,[1] Lea-Ann Kirkham,[5,9] Caitlyn Granland,[5] Monica McNeal,[10,11] Julie A. Marsh,[5] Claire S. Waddington,[12] and Thomas L. Snelling[5,13,14]

Open access Protocol

BMJ Open The ORVAC trial protocol: a phase IV, double-blind, randomised, placebo-controlled clinical trial of a third scheduled dose of Rotarix rotavirus vaccine in Australian Indigenous infants to improve protection against gastroenteritis

Bianca Fleur Middleton,[1] Mark A Jones,[2] Claire S Waddington,[2,3] Margaret Danchin,[4,5] Carly McCallum,[2] Sarah Gallagher,[1] Amanda Jane Leach,[6] Ross Andrews,[7] Carl Kirkwood,[8] Nigel Cunliffe,[9] Jonathan Carapetis,[2,10] Julie A Marsh,[2] Tom Snelling[2]

Jones et al. Trials (2020) 21:741 https://doi.org/10.1186/s13063-020-04602-w

Trials

UPDATE Open Access

The ORVAC trial: a phase IV, double-blind, randomised, placebo-controlled clinical trial of a third scheduled dose of Rotarix rotavirus vaccine in Australian Indigenous infants to improve protection against gastroenteritis: a statistical analysis plan

Mark A Jones[1*], Todd Graves[4], Bianca Middleton[5], James Totterdell[1], Thomas L Snelling[1,2,3,5] and Julie A Marsh[1]

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Thank You
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Suksma