Murdoch Childrens Research Institute
Healthier Kids. Healthier Future.

ncirs
NATIONAL CENTRE FOR IMMUNISATION RESEARCH & SURVEILLANCE

Intussusception and rotavirus vaccines in Australia

ACIP meeting June 2013

Peter McIntyre MBBS, PhD on behalf of:

John Carlin[1] PhD, Kristine Macartney[2] MBBS, MD, Kate Lee[1] PhD, Helen Quinn[2] PhD, Jim Buttery[1] MBBS, Julie Bines[1] MD, Ruth Lopert[3] MB BS MPH

1. Murdoch Children's Research Institute, Royal Children's Hospital and University of Melbourne

2. National Centre for Immunisation Research and Surveillance, Children's Hospital at Westmead, Sydney, and University of Sydney

3. Therapeutic Goods Administration, Canberra, Australia

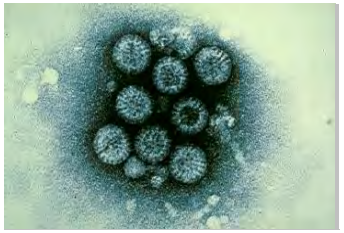
Acknowledgements and Conflicts of Interest

- **Acknowledgements**
  - National study: **John Carlin** (Professor of Biostatistics and study lead); other authors as listed previously
  - National ICD-coded study: Han Wang (Statistician)
  - NSW substudy: Nicholas Wood (Clinical lead), Aditi Dey, Kathryn Cannings, Sarah Moberley#
  - Others: Brynley Hull NCIRS, State/Territory contributors to case finding and chart review, PAEDS investigators (Elizabeth Elliot[1], Helen Marshall[2], Peter Richmond[3])
- **Funding sources and conflicts of interest**
  - Funding: Therapeutic Goods Administration (TGA), Australian Government Department of Health and Ageing, NSW Ministry of Health
  - Peter McIntyre has received in kind support for research conducted at NCIRS from GSK and Merck.

NSW Ministry of Health, ^ Therapeutic Goods Administration
1. University of Sydney, 2. University of Adelaide, 3. University of Western Australia

ncirs
NATIONAL CENTRE FOR IMMUNISATION RESEARCH & SURVEILLANCE

Australia, Rotavirus and Vaccine Timelines



Australian Government
Department of Health and Ageing

Information for Immunisation Providers
February 2011

Rotavirus vaccine and intussusception

- Rotavirus – discovered in Melbourne
- Bishop R et al *Lancet* 1973

RotaShield and intussusception

Rotateq on Vaccines For Children

Rotarix and Rotateq on Australian National Program

- Australian data suggest increased risk of IS post dose 1 for both vaccines
- Mexico study shows risk post dose 1 of Rotarix
- ACIP, WHO SAGE and Australian TGA announce preliminary data - low risk of IS post current vaccines, overwhelming benefits of preventing rotavirus disease

- First published study of association between **both** rotavirus vaccines and IS (dose 1) from Australian PAEDS network: Buttery *et al, Vaccine* 2011 (February)

- Association between Rotarix and IS, predominantly post dose 1 in Mexico: Patel *et al, NEJM* 2011 (June)

- Ecological study from USA (Yen *et al, JID* 2012) finds upward trend in ICD-coded IS in young infants

- Second published study from Australia confirms association
  - **both vaccines**
  - **dose 1 and 2**

- Carlin *et al, Clin Inf Dis* 2013 (in press, July)

1973 1999 2006 2007 2010 2011 2012 2013

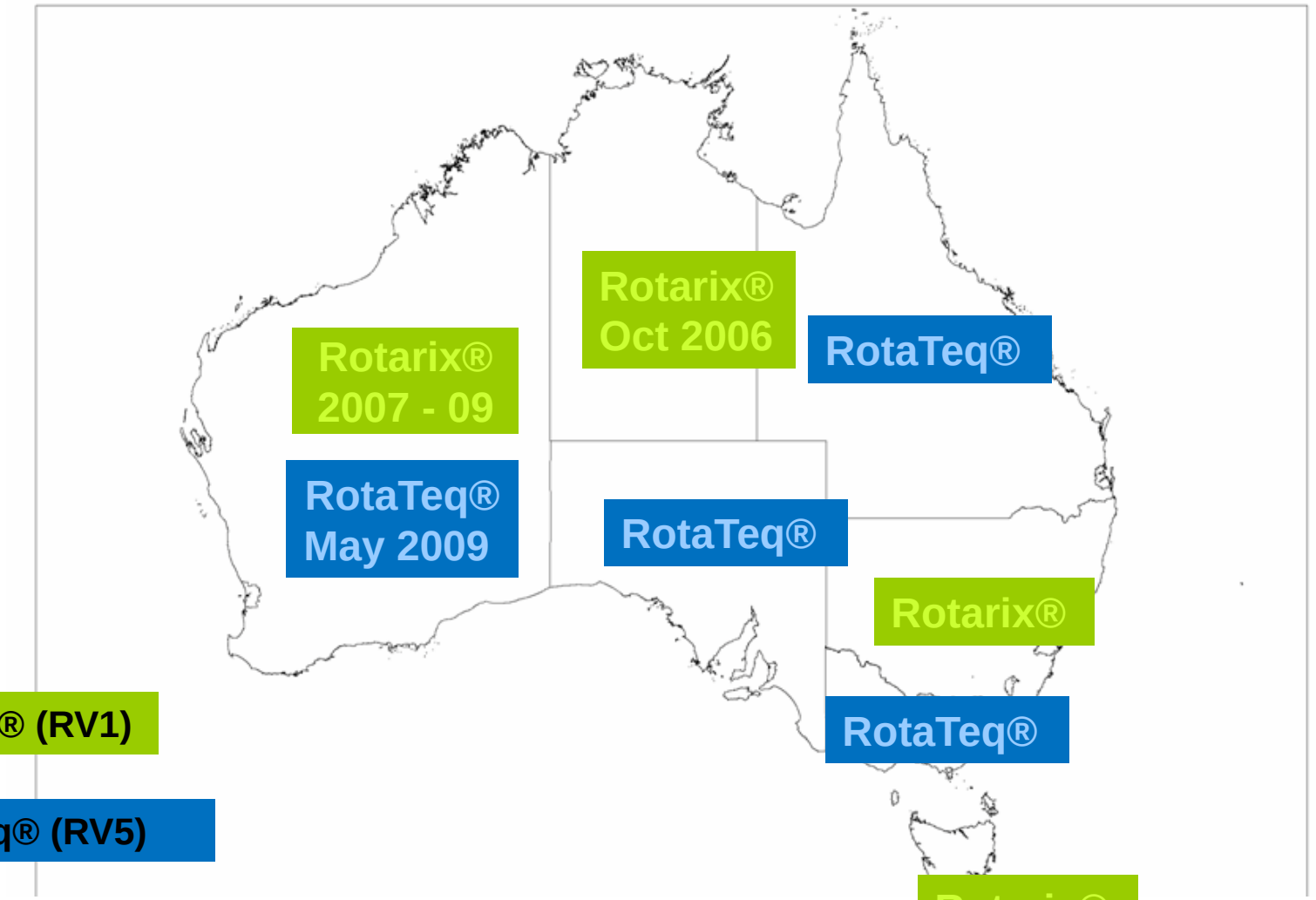
Background

- Annual birth cohort ~ 300,000
  - total population ~ 23 million
- National Immunisation Program (NIP)
  - delivers all included vaccines free of charge
- RotaTeq and Rotarix funded by NIP since July 2007
- Vaccine coverage increased rapidly[1]
  - 85% (2 or 3 doses by age 12 months)
  - Timeliness good (2-3% given later than upper age limits)
- **Intussusception**
  - Australian background rate pre-vaccine of ~ 80 per 100,000 in first year of life [2] double reported from US (38)

1. Hull et al, *Vaccine* 2013; 2. Justice et al *J Pediatr Child Health* 2005

Rotavirus vaccine use in national program

Commenced July 2007 – both vaccines used



Australian studies of intussusception associated with Rotarix and Rotateq vaccines

- First Australian study (92 cases) found cases of IS significantly increased from historical rates

These data led the Australian regulator (Therapeutic Goods Administration, TGA) to commission a larger study led by John Carlin, Professor of Biostatistics, University of Melbourne including IS cases nationwide

Other studies:

- Trends in age-specific incidence – ICD coded cases
- Morbidity in vaccine-proximate versus other cases
  - New South Wales; national in progress
- Vaccine impact – rotavirus-attributable gastroenteritis and intussusception

First published Australian analysis[1] July 2007-Dec 2008 (18 months post introduction)

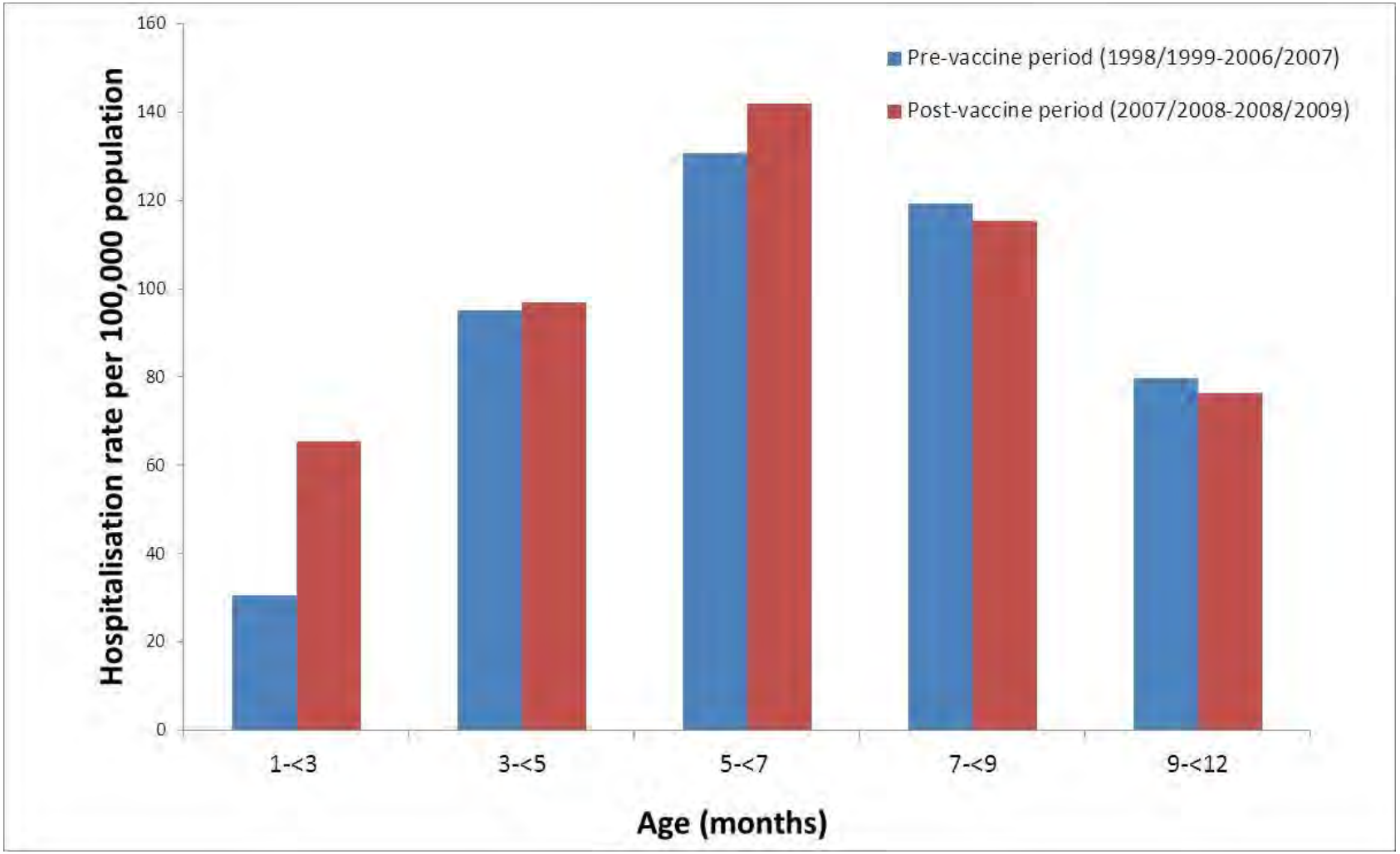
- **Data sources:**
  - **PAEDS** (Paediatric Active Enhanced Disease Surveillance) network = active case ascertainment 4 major paediatric hospitals and
  - **APSU** (Australian Paediatric Surveillance Unit) = paediatrician reporting
- Significant increase in observed vs expected cases (expected = non-confirmed ICD-coded hospitalisations for IS from routine database), infants 1-<3 months
  - **1–7 days post dose 1**
    - RotaTeq RR 5.3 (95% CI 1.1,15.4)
    - Rotarix RR 3.5 (95% CI 0.7,10.1)
  - **1–21 days post dose 1**
    - RotaTeq RR 3.5 (95% CI 1.3, 7.6)
    - Rotarix RR 1.5 (95% CI 0.4, 3.9).
    - No risk difference post dose 2

1. Buttery et al, *Vaccine* 2011

Age-specific trends in ICD coded hospitalisations

Unpublished data derived from the National Hospital Morbidity Database – Australian Institute of Health and Welfare

Intussusception coded hospitalisation rates in infants, Australia, pre and post rotavirus vaccine introduction, 1998 to 2009[1]



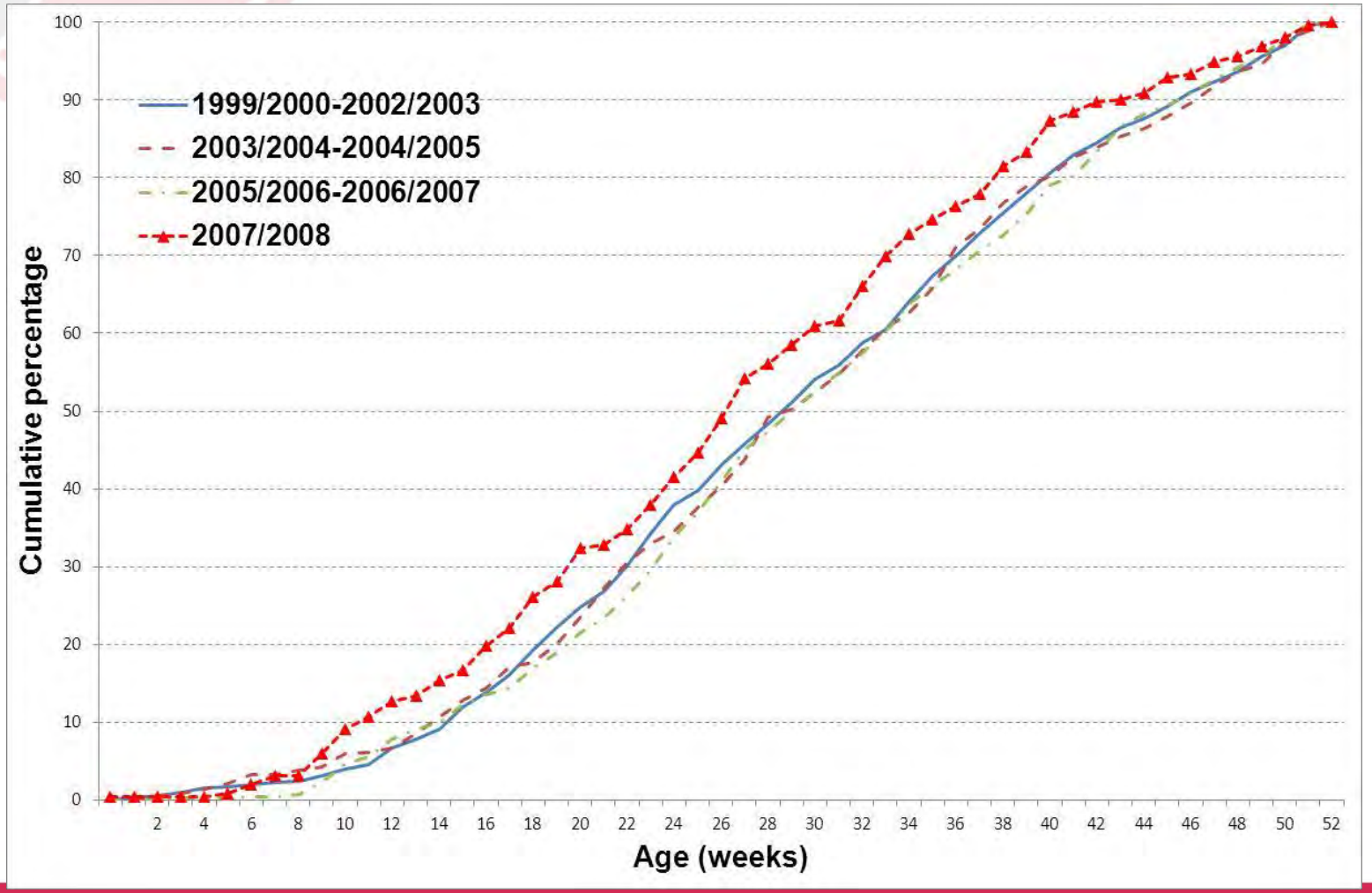
Source: National hospital morbidity database – Australian Institute of Health and Welfare

Hospitalisation episodes coded as intussusception Australia pre (1998 to 2007) vs post (2007 to 2009) rotavirus vaccine on NIP

	Pre-vaccine period July 1998 to June 2007	Post-vaccine period July 2007 to June 2009	Post-vaccine/ Pre-vaccine period Incidence Rate Ratio (IRR)		
Age (months)	Rate per 100,000	Rate per 100,000	IRR	95% Confidence Interval	
1-<3	**30.4**	**65.3**	**2.15**	**1.58**	**2.91**
3-<5	95.0	97.0	1.02	0.81	1.28
5-<7	130.6	141.9	1.09	0.90	1.31
7-<9	119.2	115.3	0.97	0.79	1.19
9-<12	79.8	76.2	0.95	0.78	1.17
0-<12	83.10	89.3	1.07	0.98	1.18
0-<24	57.13	66.3	1.16	1.07	1.26

Source: AIHW National Hospital Morbidity Database

Intussusception coded hospitalisations by week of age and birth cohorts, Australia, 1999 to 2008 (financial years July-June)



Source: AIHW National Hospital Morbidity Database

Association between confirmed cases of intussusception and Rotateq and Rotarix vaccines – Australia 2007 – 2010[1]

1. Carlin J, Macartney K, Lee et al Increased risk of intussusception associated with both currently licensed rotavirus vaccines in Australia's national immunisation program. *Clinical Infectious Diseases* - in press

National study of Rotavirus vaccines and IS: Methods

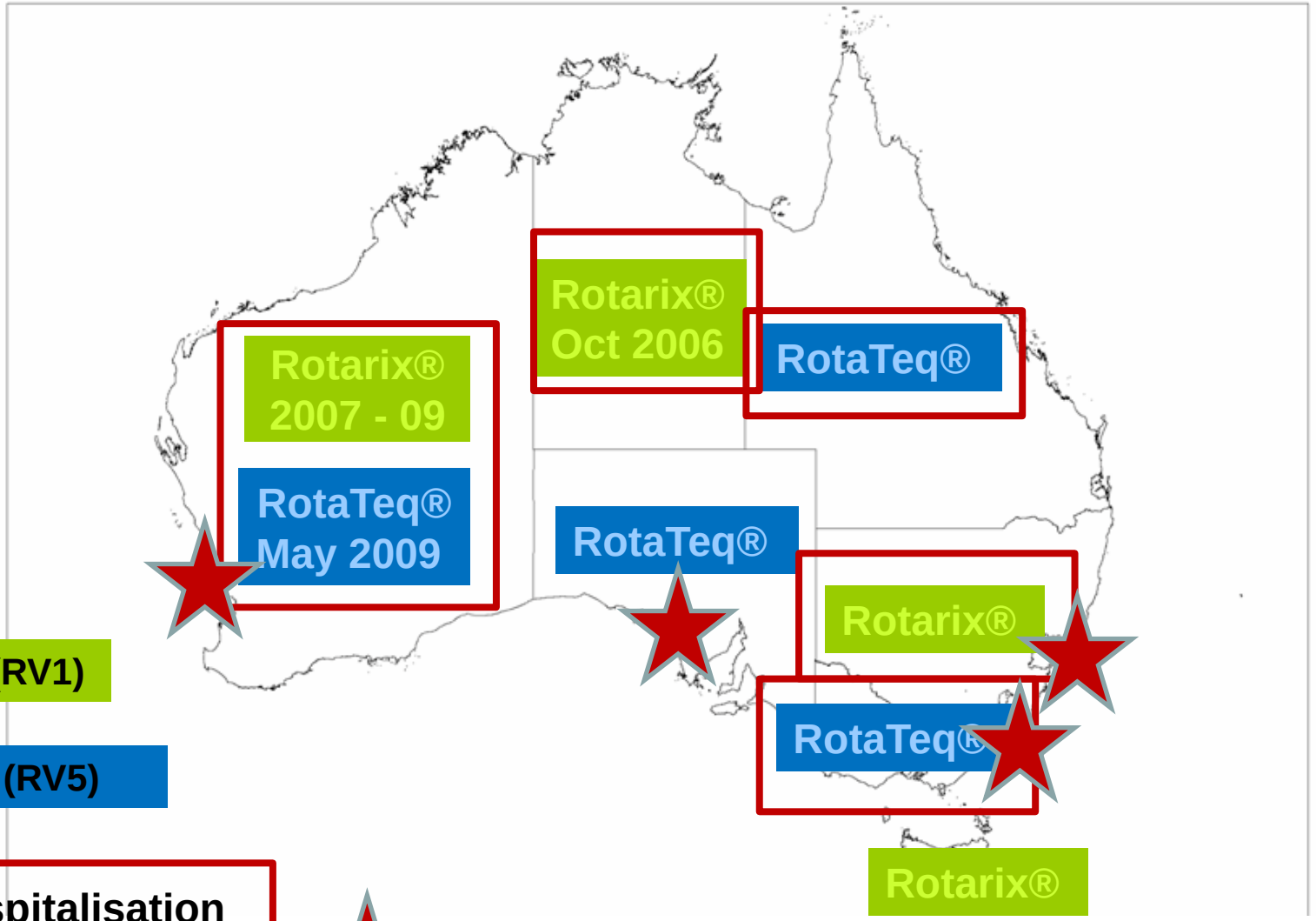
- Case ascertainment (2 sources)
  - IS-coded hospital discharges (ICD-10 code K56.1) hospitalisation databases (5 State/Territories)
  - Prospective active hospital-based surveillance via PAEDS network (4 State paediatric hospitals)
- Age range: infants 1-<12 months
- 3 year observation period: July 2007-June 2010
- All cases chart reviewed – Brighton level 1 only selected (duplicates removed where overlap from 2 sources)
- Vaccination history verified from Australian Childhood Immunisation Register (ACIR)

National study: analysis methods

- Self controlled case-series
  - Multiple sensitivity analyses
- Case-control method
  - ACIR used to identify age-matched controls (within 1 day of birth): 10 randomly selected
  - Limited demographics on register – matching on gender, State
- Risk defined for pre-specified periods post-vaccination
  - 1-7 days, 8-21 days
- Vaccine-attributable IS was compared with estimated reductions in gastroenteritis hospitalisations
  - using RI from SCCS (midpoint of estimates from the two vaccines)

Rotavirus vaccines and IS national study

Case ascertainment July 2007-June 2010



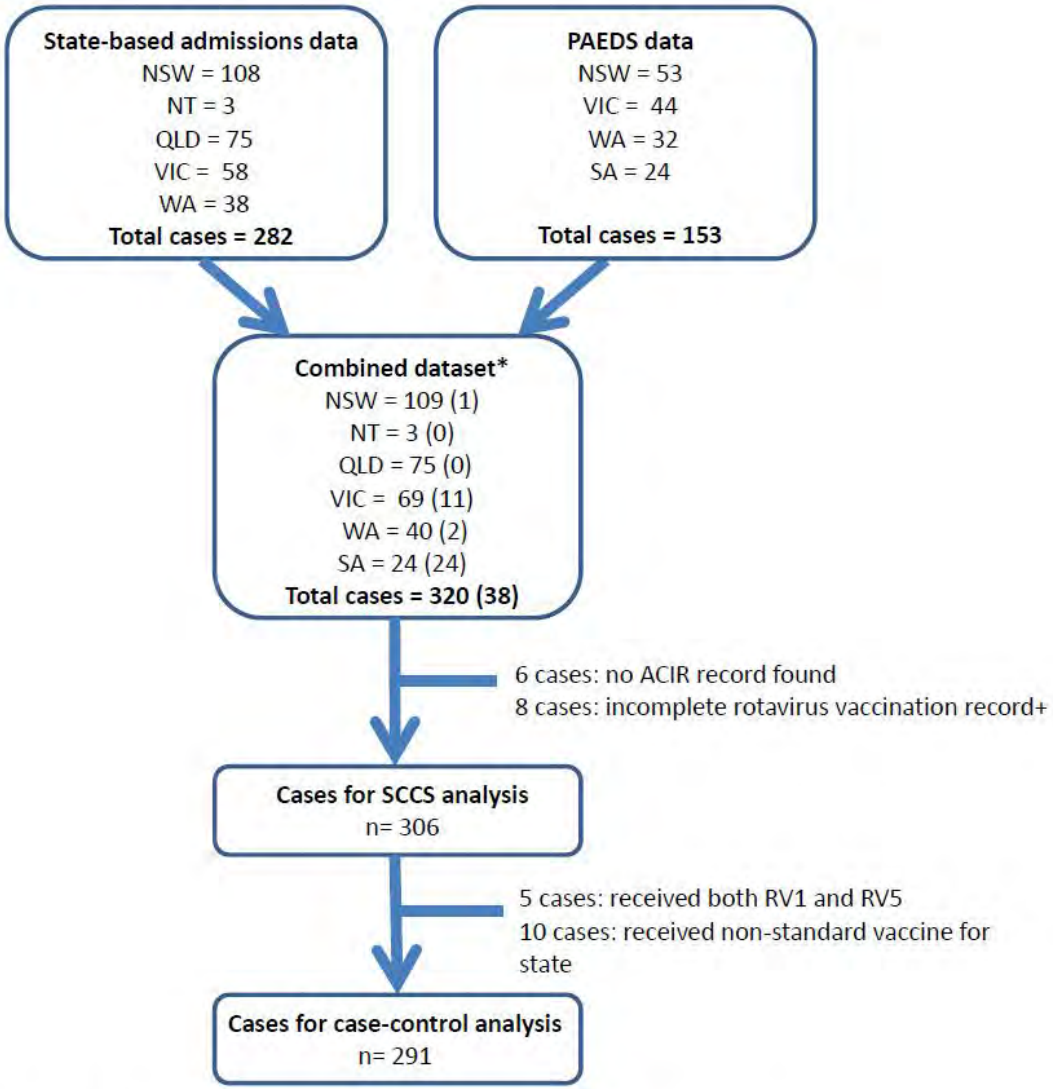
Rotarix® (RV1)

RotaTeq® (RV5)

Hospitalisation DATABASE review

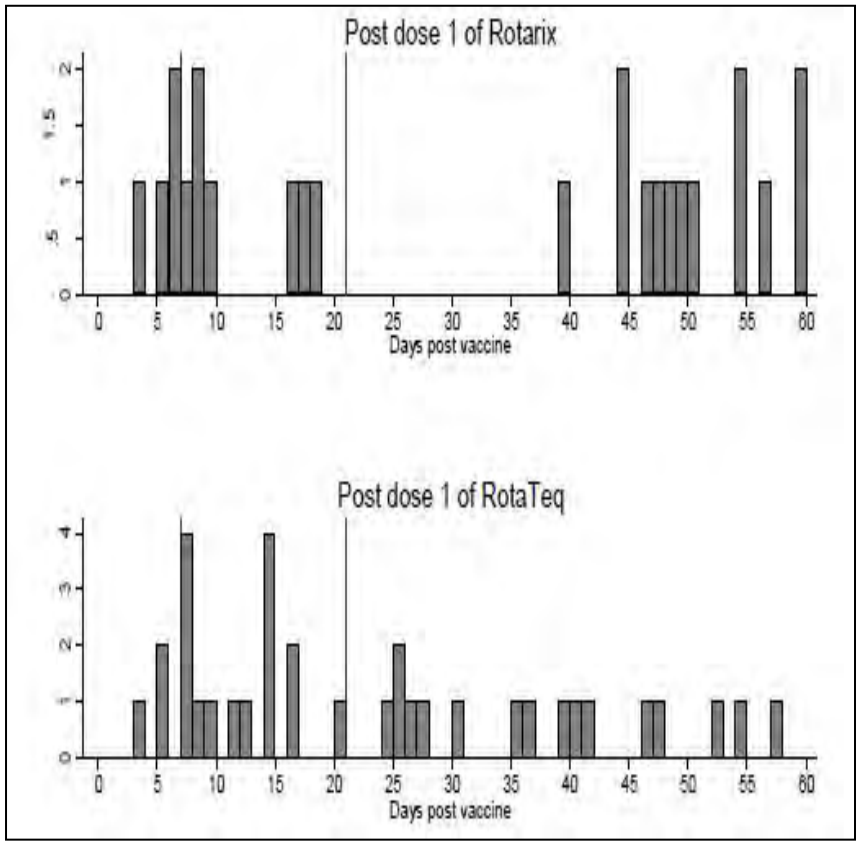
PAEDS Site

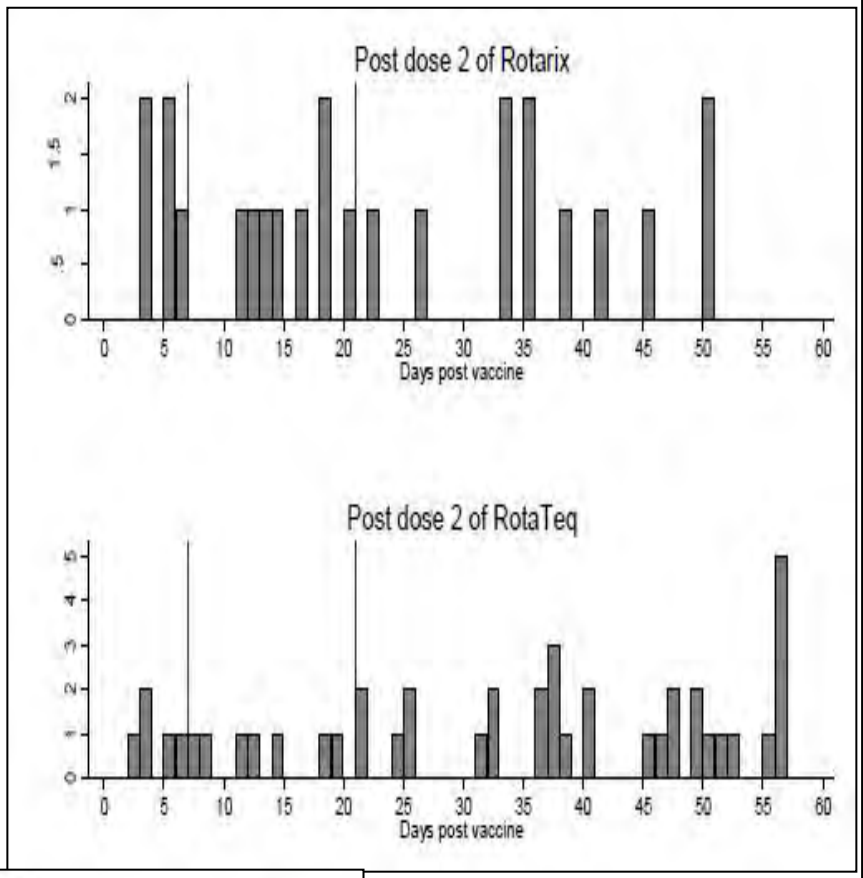
Summary of national cases for SCCS and CC analysis

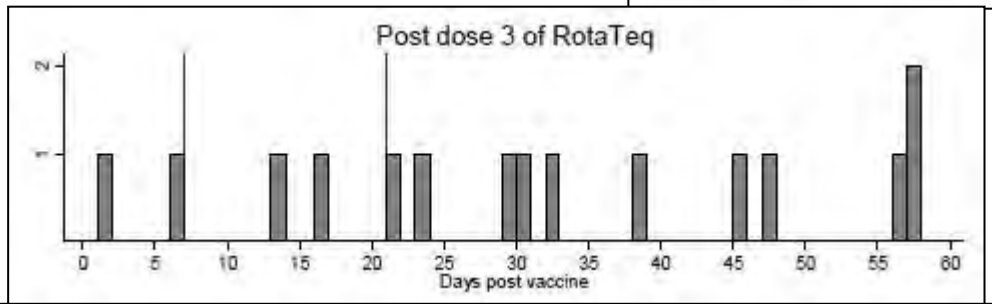


Note: these figures are restricted to Brighton Level one primary cases only.
*Includes all 282 cases from the state-based admissions data plus an additional 38 cases captured by PAEDS. Numbers in brackets correspond to the additional cases identified through PAEDS.
+ ACIR record indicated receipt of a second (or third) dose of rotavirus vaccine but had missing data for earlier dose/s.

Timing of IS cases in Australia (n=306) with respect to doses 1,2 and 3 of rotavirus vaccines (Rotarix and RotaTeq)







Self-controlled case series analysis based on 306 cases of intussusception (infants aged 1– <12 months, 3 year period)

		RI	(95% CI)		P
RV1	Dose 1, 1-7 days	6.76	(2.40,	19.01)	<0.001
	Dose 1, 8-21 days	3.45	(1.33,	8.94)	0.011
	Dose 2, 1-7 days	2.84	(1.10,	7.34)	0.031
	Dose 2, 8-21 days	2.11	(0.97,	4.62)	0.061
RV5	Dose 1, 1-7 days	9.89	(3.70,	26.42)	<0.001
	Dose 1, 8-21 days	6.32	(2.78,	14.37)	<0.001
	Dose 2, 1-7 days	2.81	(1.16,	6.80)	0.022
	Dose 2, 8-21 days	1.77	(0.81,	3.88)	0.155
	Dose 3, 1-7 days	0.75	(0.18,	3.11)	0.688
	Dose 3, 8-21 days	0.56	(0.17,	1.82)	0.333

Case-control analysis of association between IS and: (a) RV1 vaccination and (b) RV5 vaccination

a) RV1 vaccine

	OR	(95% CI)		P
Dose 1, 1-7 days	15.61	(3.36,	72.57)	<0.001
Dose 1, 8-21 days	6.48	(1.74,	24.16)	0.005
Dose 2, 1-7 days	2.44	(0.80,	7.47)	0.118
Dose 2, 8-21 days	1.35	(0.50,	3.63)	0.557

b) RV5 vaccine

	OR	(95% CI)		P
Dose 1, 1-7 days	11.74	(3.18,	43.37)	<0.001
Dose 1, 8-21 days	4.65	(1.80,	12.00)	0.001
Dose 2, 1-7 days	2.53	(0.89,	7.20)	0.081
Dose 2, 8-21 days	1.38	(0.53,	3.62)	0.506
Dose 3, 1-7 days	1.06	(0.23,	4.84)	0.935
Dose 3, 8-21 days	0.80	(0.18,	3.64)	0.773

Multiple sensitivity analyses – SCCS and CC

SCCS

1. Smooth curve (fractional polynomial) for age adjustment using monthly and weekly age categorisation
2. Data for each vaccine analysed separately, with both IS risk fitted by month of age category and using a fractional polynomial
3. Allowing for a change in the likelihood of being vaccinated immediately after an IS event ('healthy vaccinee effect')

   → all minimal impact on relative incidence
4. Removal of cases who received a dose of vaccine outside of the recommended age range for that vaccine dose → weakening of dose-1 association for RV1

Case-control analysis

1. Restricted, to cases and matched controls who received their final dose of vaccine before the recommended upper age limit

   →a similar weakening of dose-1 association for RV1 was observed as when late vaccinated cases removed from SCCS analysis

Limitations

- Near complete case ascertainment
  - Included jurisdictions have >95% of all population
  - Missed cases from non-included jurisdictions/non-reviewed cases unlikely to bias estimates due to uniformity of vaccine coverage
- Lack of ability to control for clinical factors in CC analysis due to limited data available from ACIR
- Small numbers, despite near complete capture
- Generalizability to other settings

NATIONAL CENTRE FOR IMMUNISATION RESEARCH & SURVEILLANCE

Severity in vaccine-proximate cases

Substudy in State of New South Wales

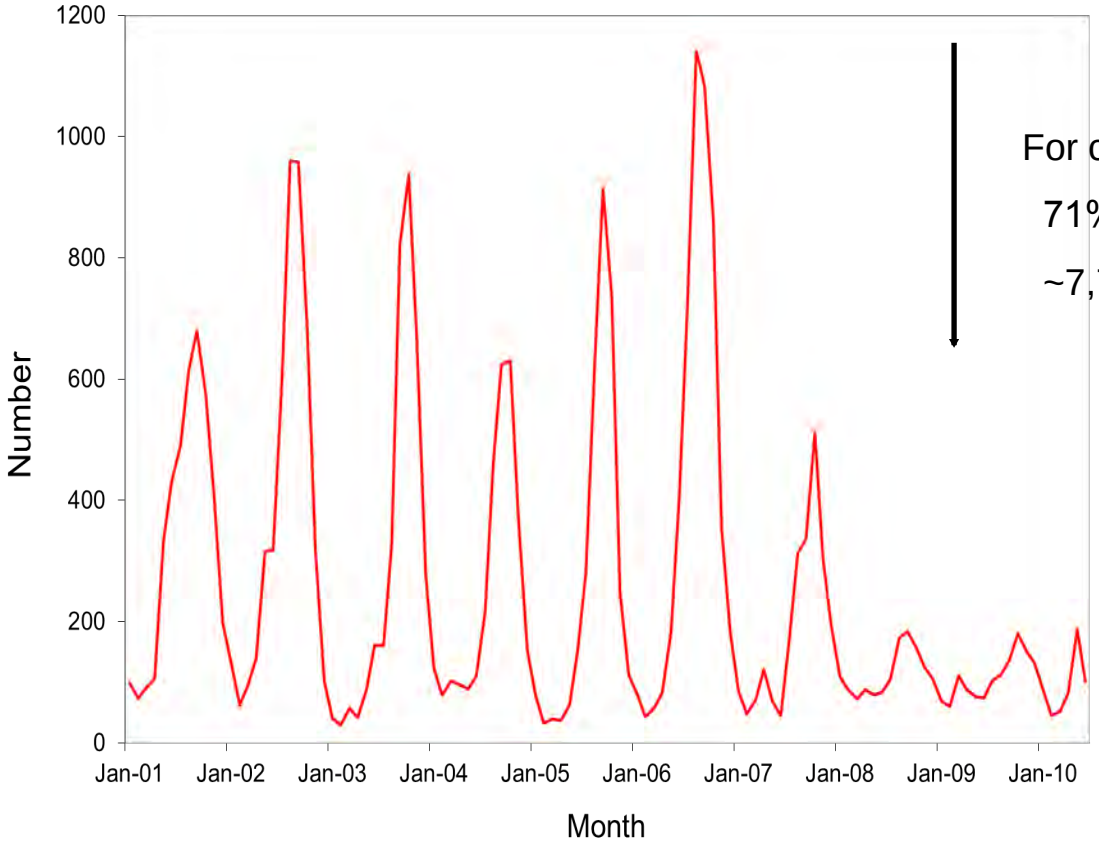
NSW sub-study: Methods and Findings

- Most populous state: 7 million (Birth Cohort: 95,000), use RV1
- 183 episodes coded as IS (hospitalised and ED) in infants < 12 months
- All clinically reviewed (duplicates/transfers removed from 227 coded)
- 113 cases (60%) confirmed as Brighton level 1
  - Most non-confirmed were transfers from small hospitals where clinical features or initial u/sound were suggestive of IS
- SCCS analysis for RV1 IS risk consistent with results of national study
- Vaccine proximate and non-proximate cases same clinical profile
  - ~ one third of confirmed cases required surgery
  - 1 ICU admission
  - No deaths

Overall impact of rotavirus vaccines on morbidity

Australian national data to end 2010

Rotavirus hospitalisations, Australia



For children <5years:

71% ↓ in rotavirus admissions

~7,700 admissions averted per year

Effect of a rotavirus vaccination program, as compared with no rotavirus vaccination program, on hospitalisations for rotavirus attributable gastroenteritis and IS in Australia

Annual Hospitalisations in children < 5 years of age	Without vaccination program	With vaccination program	Number of events averted or caused
Rotavirus attributable gastroenteritis#	11073	4545	- 6528
Intussusception using RotaTeq and/or Rotarix*	240	Up to 258	Up to 18

Methods: Estimates based on method of Patel, et al, NEJM 2011

#: annual number of ICD-coded hospitalisations (data from the Australian Institute of Health and Welfare) for rotavirus AGE and estimated for rotavirus-attributable AGE (derived from Dey et al, MJA 2012 and Jayasinghe et al, Vaccine 2013). Vaccine effectiveness estimates applied by dose (see appendix).

- derived from using ICD-coded hospitalisations (data from the Australian Institute of Health and Welfare) for IS with adjustment for cases confirmed as IS, vaccine coverage, age.

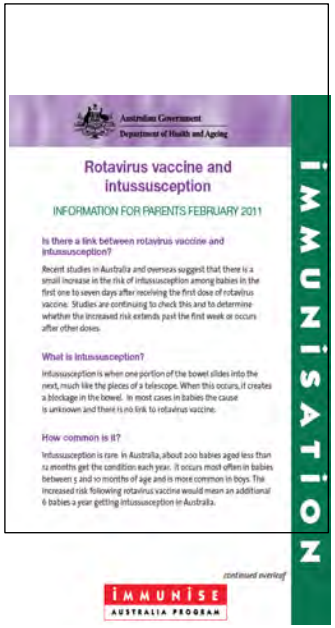
Deaths, hospitalisation and surgery in Australia for IS compared with rotavirus vaccines, with or without a rotavirus immunisation program

	Intussusception (with and without vaccination)	**Rotavirus (with and without vaccination)**
Deaths	None or Rare (<1 per decade)[1,2,3] No deaths in national review (2007-2010)	1 death every 1-2 years pre-vaccination (10 childhood deaths in 12 years)[4]
Hospitalisations	~240 without vaccination (< 12mo) annually[1] up to 18 vaccine-related (additional) / year	~10,000 annually pre-vaccination (<5yrs)[5] ~7,000 prevented annually (6,528[7]-7,700[6])
Surgery	34% (<12 months of age) [1]	0 (presumed)
ICU admission	4% (<12 months of age) [1]	Not known

1. Quinn et al Risk of Intussusception among NSW infants given Rotarix, manuscript in preparation
2. Professor Julie Bines (personal communication);
3. Justice F, Carlin J, Bines J. Changing epidemiology of intussusception in Australia. *Journal of Paediatrics and Child Health.* 2005;41(9-10):475-8.
4. Newall AT, MacIntyre R, Wang H, et al. Burden of severe rotavirus disease in Australia. *Journal of Paediatrics and Child Health*. 2006;42(9):521-7.
5. Galati JC, Harsley S, Richmond P, et al. The burden of rotavirus-related illness among young children on the Australian health care system. *Australian and New Zealand Journal of Public Health*. 2006;30:416-21.
6. Dey et al, MJA 2012
7. Carlin, Macartney, Lee et al, Increased risk of intussusception associated with both currently licensed rotavirus vaccines in Australia's national immunisation program. Submitted for publication

Policy/Practice Implications

- Initial risk estimate (6 excess cases annually) acceptable to providers and parents
- Ongoing Benefit- Risk viewed as favorable by all key Australian advisory committees (ATAGI, ACSOM – TGA)
- New estimates published in 10th Edition Australian Immunisation Handbook, published March 2013
- Advice to parents/providers to be updated
- Changes to vaccine product information via TGA



Summary

- Risk estimates and risk window similar for Rotarix and Rotateq
- Most robust for first dose with at least doubling of risk
- Maximum vaccine-attributable risk of IS increases if using longer time window (to 21 days vs first 7 days) and dose 2:
  - 1-21 days post dose 1 + 1-7 days post dose 2 :

  = 5.0 (95% CI 1.9-10.7) per 100,000 infants vaccinated for **RV1** and

  = 6.9 (95% CI 3.1-13.6) per 100,000 for **RV5**.
- Overall estimate of attributable risk:
  - ~ 6 additional cases of IS per 100,000 vaccinated infants

  = 18 cases annually in Australian birth cohort (11 dose 1, 7 dose 2)
- No increase in case severity identified among vaccine-associated cases
- Risk benefit continues to be judged highly favorable by Australian policy-makers