Vaccinology 2017

Hanoi, Vietnam
October 2017

Active surveillance to assess vaccine benefits and risks

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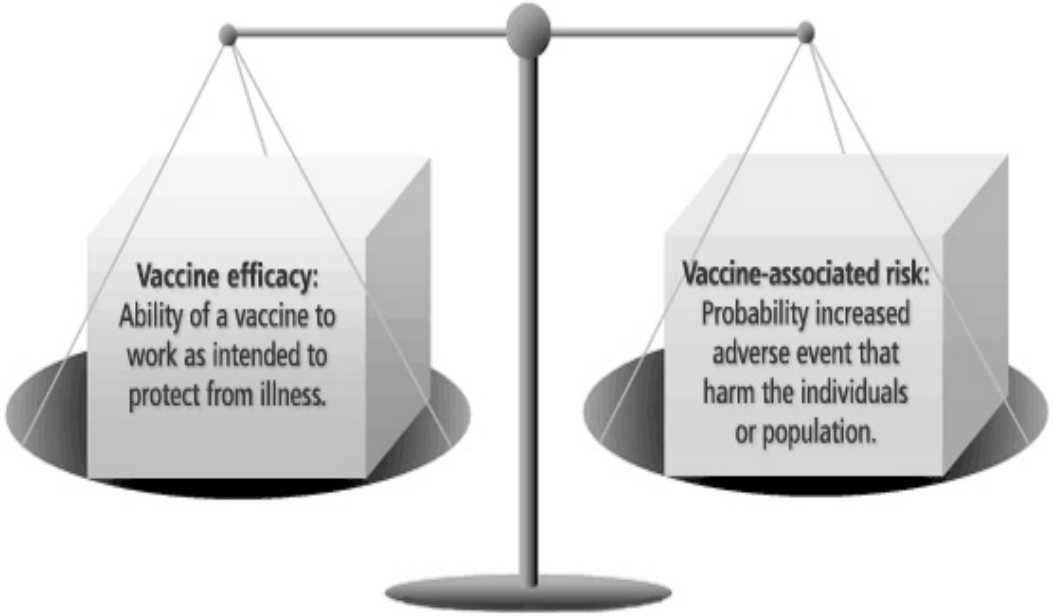
NO CONFLICTS of interest

Active surveillance to assess vaccine benefits and risks

- Overview
- ‘Routine’ surveillance
- Active surveillance network examples – Australia
- Implementation (benefit/risk) research – case studies



WHO's implementation research themes

1	Minimize barriers and improve coverage of vaccines currently in use
2	Conduct impact evaluation of vaccines in use
3	Improve methods for monitoring of immunization programmes

WHO IVIR meeting 2015
http://www.who.int/immunization/sage/meetings/2015/october/Kang_IVIRAC_SAGE_Oct_2015C.pdf?ua=1

Before program

- Anticipated impact and cost effectiveness
  ? Real vaccine preventable incidence
  - ? NNV to prevent 1 case

- Program implementation – need for strong focus

Only part of the picture…..?

Approaches

Available data and surveillance capacity pre-program varies

Coverage

- Doses distributed or administered?
- By region (aggregated) or individual level data ?
- By specific groups (age, sex, location)
- Delays in provision?

Understanding inherent and potential LIMITATIONS of each approach

Existing national databases in Australia

- immunisation register – now all age, child only until 2016
- notifiable diseases – rapid but limited utility for some diseases
- hospitalisation and death databases – de-identified + delays
- primary care - limited data
- Safety – 'passive' AEFI reporting

Limited capacity and lengthy waiting time to link datasets

Active surveillance?
2 network examples

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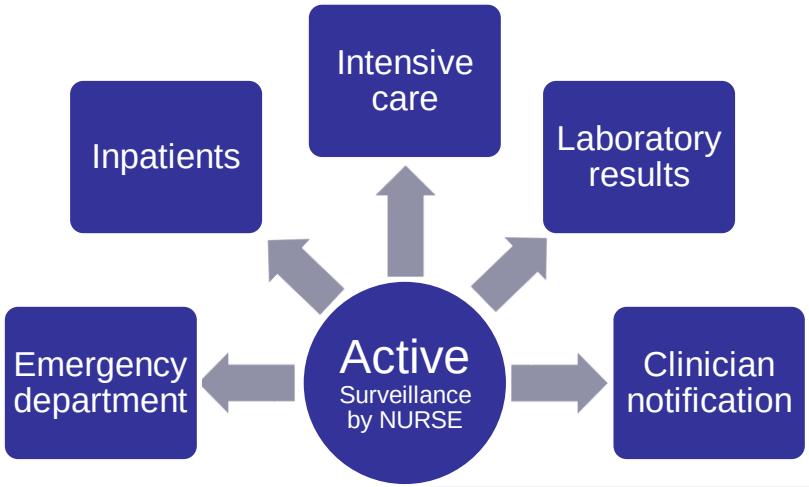
1. Sentinel real-time hospital-based surveillance



Active Sentinel Surveillance
- Pre-specified conditions
- 8 Australian paediatric hospitals

Recruit patients that meet criteria
- Waiver of consent
- Patient data collection
- Collection of specimens

Analyses
- Before – after incidence (RI)
- VE using TND (controls)
- Severity, risk factors

Reports & publications

Extrapolation to national administrative data sets

PAEDS Paediatric Active Enhanced Disease Surveillance

www.paeds.edu.au

VPDs / Communicable diseases

INFLUENZA

- Influenza
- Pandemic Influenza
- With 15 adult hospital network

PERTUSSIS

- Pertussis
- VE, severity
- Genotypes

VZV

- Varicella and Zoster
- Genotypes
- VE, severity

GP A STREP

- Invasive group A strep
- Genotypes
- severity

MENING

- Invasive meningococcal disease
- Long term f/u

Syndromes

ENCEPHALITIS

- Australian Childhood Encephalitis
- VPDs common – eg influenza

ACUTE FLACCID PARALYSIS

- Acute flaccid paralysis
- Polio elimination

Adverse Events following Immunisation

INTUSSUSCEPTION

- Risk following rotavirus vaccines
- Severity

FEBRILE SEIZURES

- Post MMR, Varicella and MMRV vaccines

GUILLAIN BARRE SYNDROME

- Post Pandemic influenza vaccines

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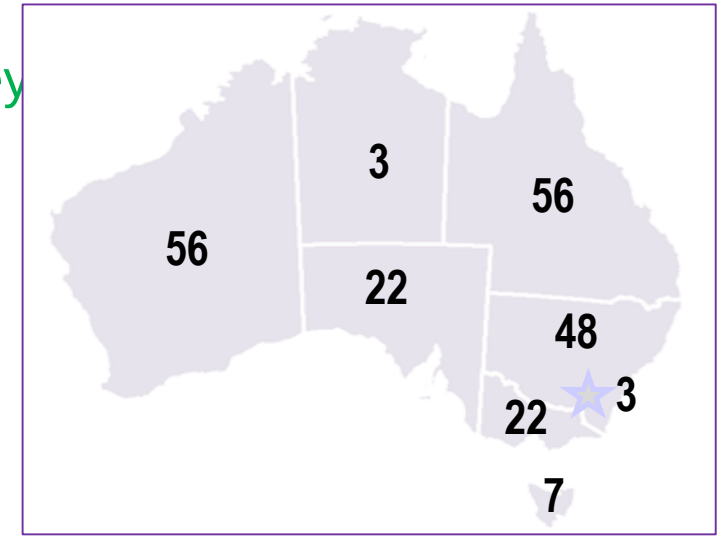
2. Active sentinel vaccine safety surveillance: patient reported outcomes

> 200 immunisation clinics

Patient/parents report AE via simple SMS survey day 3 post vaccination

- All vaccines: automated, opt-out
- Response rates ~ 70%
- Most objective measures
  - ISR
  - Fever
  - Medical attention (proxy - severe AE)
- Follow-up of medically attended cases



Number of state/territory surveillance sites

August 2017

AusVaxSafety SmartVax

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AusVaxSafety

SmartVax

SMS/email to participants-- Any reactions afte vaccination?

Yes?

Was medical attendance sought?

No?

No?

Yes?

Flagged for follow-up

Safety signal detected? Bayesian/FIR CUSUM analyses

Reports to Government & public (weekly/fortnightly/monthly)

Improved vaccine safety monitoring, transparency, public confidence

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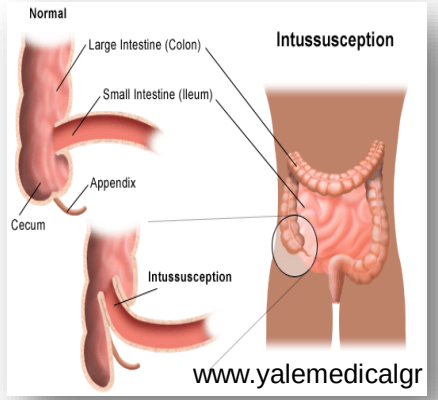
Case study:

ROTAVIRUS

Intussusception (IS) following rotavirus vaccination



2007

rotavirus vaccination on NIP

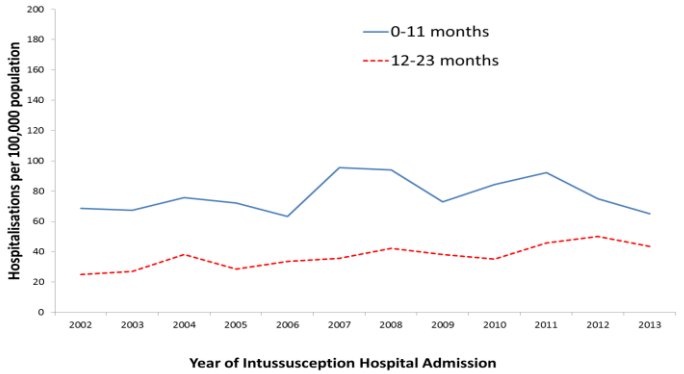
2011 Sentinel surveillance – clinically confirmed cases comparison with historical ICD-coded data

2013 Cases (confirmed) from 2 sources

Self controlled case series – IRR in risk v. non risk periods (0-7;0-21 days post vaccination compared with non risk periods)

2014 No difference in clinical outcomes (vaccine associated/non vaccine associated)

2016 Trends in hospital-coded IS – increase in dose 1 age group (1-3 months only)



	Pre-vaccine period (2002-2006)		Post-vaccine period (2009- 2013)	
Age (months)	Rate	(95% Confidence Interval)	Rate	(95% Confidence Interval)
1-<3	27.3	(20.7-35.3)	46.3	(38.2-55.5)
3-<5	80.1	(68.5-93.0)	80.6	(69.9-92.5)
5-<7	142.7	(127.1-159.7)	103.0	(90.8-116.3)
7-<9	103.1	(89.9-117.7)	105.3	(93.0-118.8)
9-<12	67.8	(59.1-77.5)	82.2	(73.3-91.9)
0-<12	69.4	(64.9-74.1)	77.7	(73.4-82.3)

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Buttery, J, Danchin M et al, Vaccine 2011; Quinn, et al, PIDJ 2012; Carlin JB, Macartney K, Lee KJ, et al. Clinical Infectious Diseases 2013;57:1427-1434; Buttery et al PHAA NIC 2014; Dey, A Rota meeting 2016.

Intussuception in infants in Asia

Country	Incidence: 100,000 infants < 1 year/child years	Reference
Indonesia	18	Dewi et al 2012#
Malaysia	17.8	Giak et al 2008
Uzebekistan	23	Latipov et al 2011
Thailand	19.7-47.8	Khumjul et al 2009
Singapore	26-39.9	Tan et al 2009
Taiwan	68.4	Ho et al 2005
Hong Kong	88.2	Nelson et al 2002
Bangladesh	97	Zaman et al 2009
Japan	180-190	Takeuchi et al 2012
South Korea	236 (<2 yrs)	Jo et al 2009
Vietnam	302	Bines et al 2006

The Children's
Excellence in clinical care, research and education

Slide courtesy of Prof Julie Bines
http://www.sabin.org/sites/sabin.org/files/Julie%20Bines%20Intussusception_web.pdf

Effect of a rotavirus vaccination program, as compared with no rotavirus vaccination program in Australia

Annual Hospitalisations in children < 5 years of age	Without vaccination program
Rotavirus attributable gastroenteritis#	11073
Intussusception using RotaTeq and/or Rotarix*	144

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

Carlin JB, Macartney K, Lee KJ, et al. Clinical Infectious 2013;57:1427-1434.

Unanticipated benefits of rotavirus vaccines: Reduction in febrile seizures

Study	Seizures outcomes
USA Payne et al CID, 2014	rotavirus vaccination vs no vaccination • first-ever seizures RR = 0.82; 95% CI: 0.73–.91 • all seizures RR = 0.79; 95% CI: 0.71–0.88. • **18-21% protective**
Spain Pardo-Seco et al, PIDJ 2015	rates for *seizures i*n children <5 years pre/post • correlated with coverage (r = −0.673; P = 0.033) and rotavirus admission rates (ρ = 0.506; P = 0.001) • **16.2% (95% CI: 8.3–23.5%) and 34.0% (27.3–40.1%)**
Australia Sheridan et al, J Pediatric Infect Dis Soc. 2016	ED presentation and hospitalization in children • **35.8% and 38.0% effective**, respectively, for febrile seizures up to two years following vaccination.

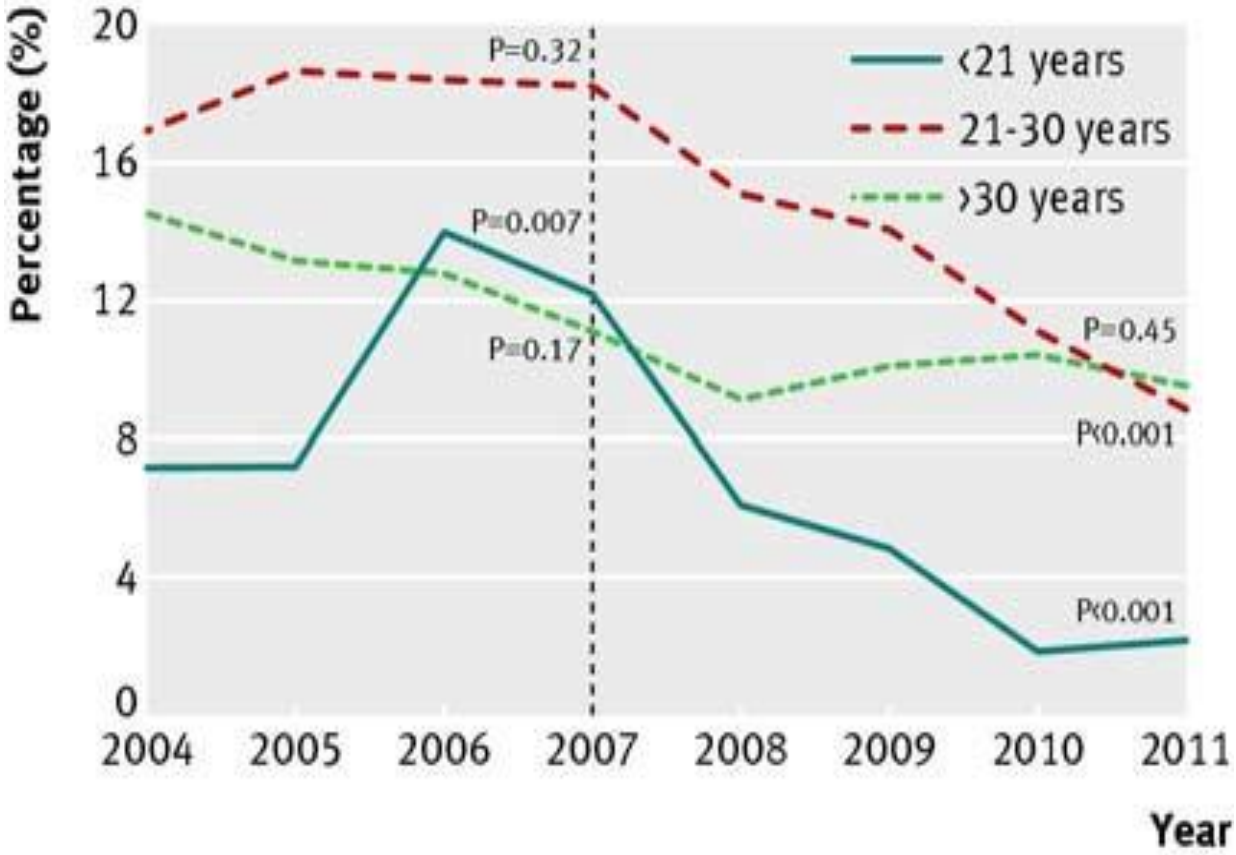
Case study:

HPV

Pre and post program introduction
Declines in genital warts (HPV types 6 and 11)

Ali et al BMJ 2013

- Sentinel surveillance: 8 public sexual health services
- New Australian born patients only 2004-2011- first visit to clinic. N=85,770

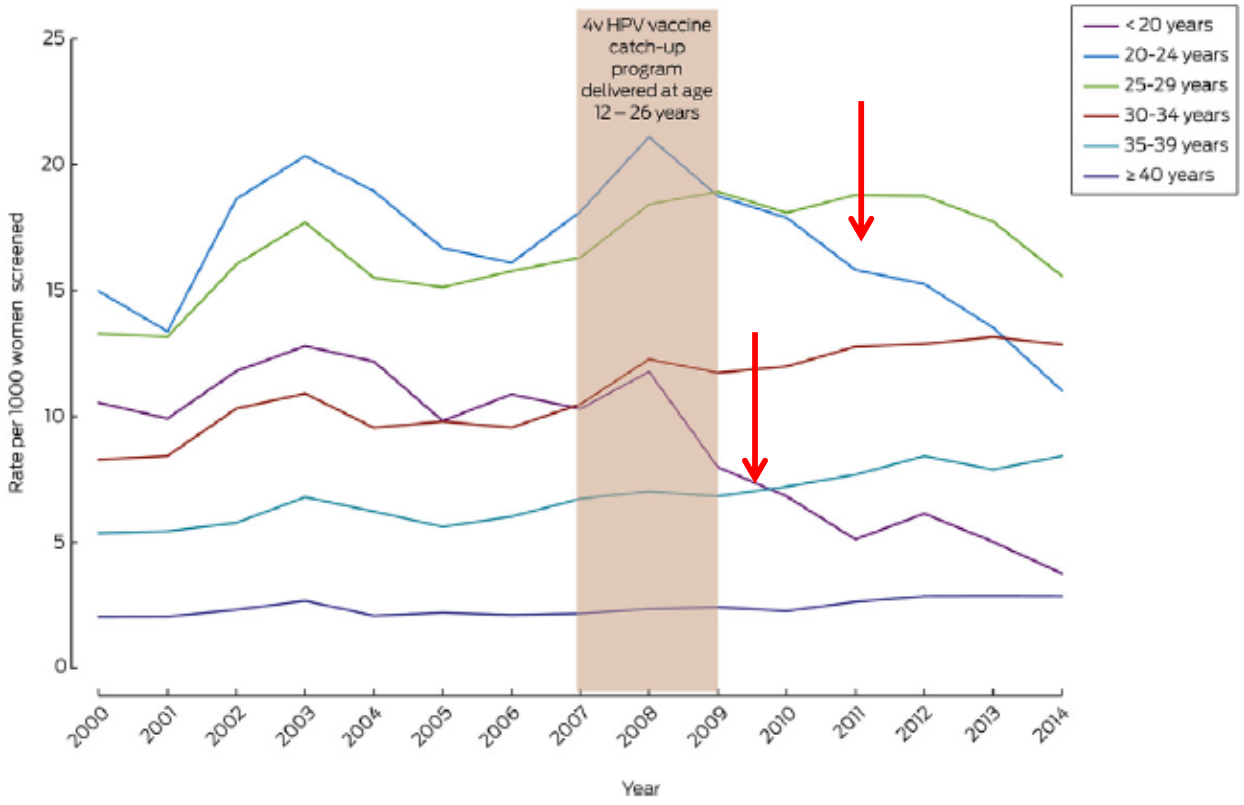


Females <21 years 92.6% decline **Males <21 years** 81.8% decline

Females 21-30 yrs 72.6% decline **Males 21-30 yrs** 51.1% decline post vaccination

Declines in high grade cervical abnormalities

Trends in prevalence rates of high-grade histologically confirmed cervical abnormalities* diagnosed in Victorian women, by age group, 2000–2014



4v HPV = quadrivalent human papillomavirus. * Using Australian Institute of Health and Welfare indicator 4.2, which includes high-grade squamous abnormality, cervical intraepithelial neoplasia (CIN) grade 2, CIN grade 3 or CIN not otherwise specified; high-grade endocervical abnormality, endocervical dysplasia; and high-grade endocervical abnormality, adenocarcinoma in situ (http://www.aihw.gov.au/publication-detail/?id=60129550871). ◆

J Brotherton et al, Medical Journal of Australia, 21 March 2016

Surveillance outcomes

Changes in cervical screening program (2017)

- Reduced age at commencement
- Reduced intervals
- Change from Pap smear to HPV-DNA based

Cost effectiveness modelling (2013)

- Program for males at much reduced vaccine price

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PUBLIC HEALTH

Mass psychogenic response to human papillomavirus vaccination

Jim P Buttery, Simon Madin, Nigel W Crawford, Sonja Elia, Sophie La Vincente, Sarah Hanieh, Lindsay Smith and Bruce Bolam

- 1 month into program commencement - 2007
- One school: 26 girls in sick bay post vaccination, 4 to ED
- no organic cause: prompt thorough response, follow-up, communication

RESEARCH

Syncope and seizures following human papillomavirus vaccination: a retrospective case series

Nigel W Crawford, Hazel J Clothier, Sonja Elia, Teresa Lazzaro, Jenny Royle and Jim P Buttery

Syncope

- HPV and other vaccines, predictable reaction to painful stimulus
- Highest incidence in young adolescents

2013 – male and females
Enhanced surveillance in schools for AEFI, esp syncope

Buttery J et al, MJA 2008; Clements ANZJPH 2007

Countering misinformation

HPV vaccine program setbacks due to unfounded safety concerns

India 2010

- Demonstration project suspended

Japan 2013

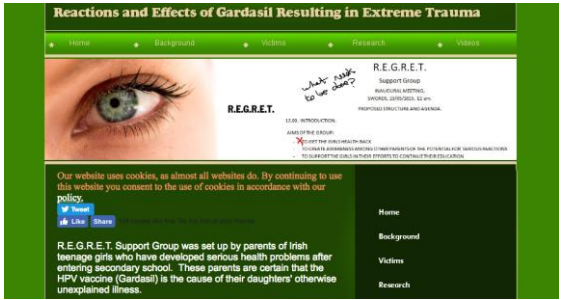
- Public and HCW mistrust, ‘neuro-motor and other conditions’ attributed to vaccine

Denmark 2015

- Vaccine uptake falls due to public mistrust - single clinic attributing POTS to vaccine

Ireland 2016

- Sudden decline in coverage -‘concerned parent’ group object to vaccine



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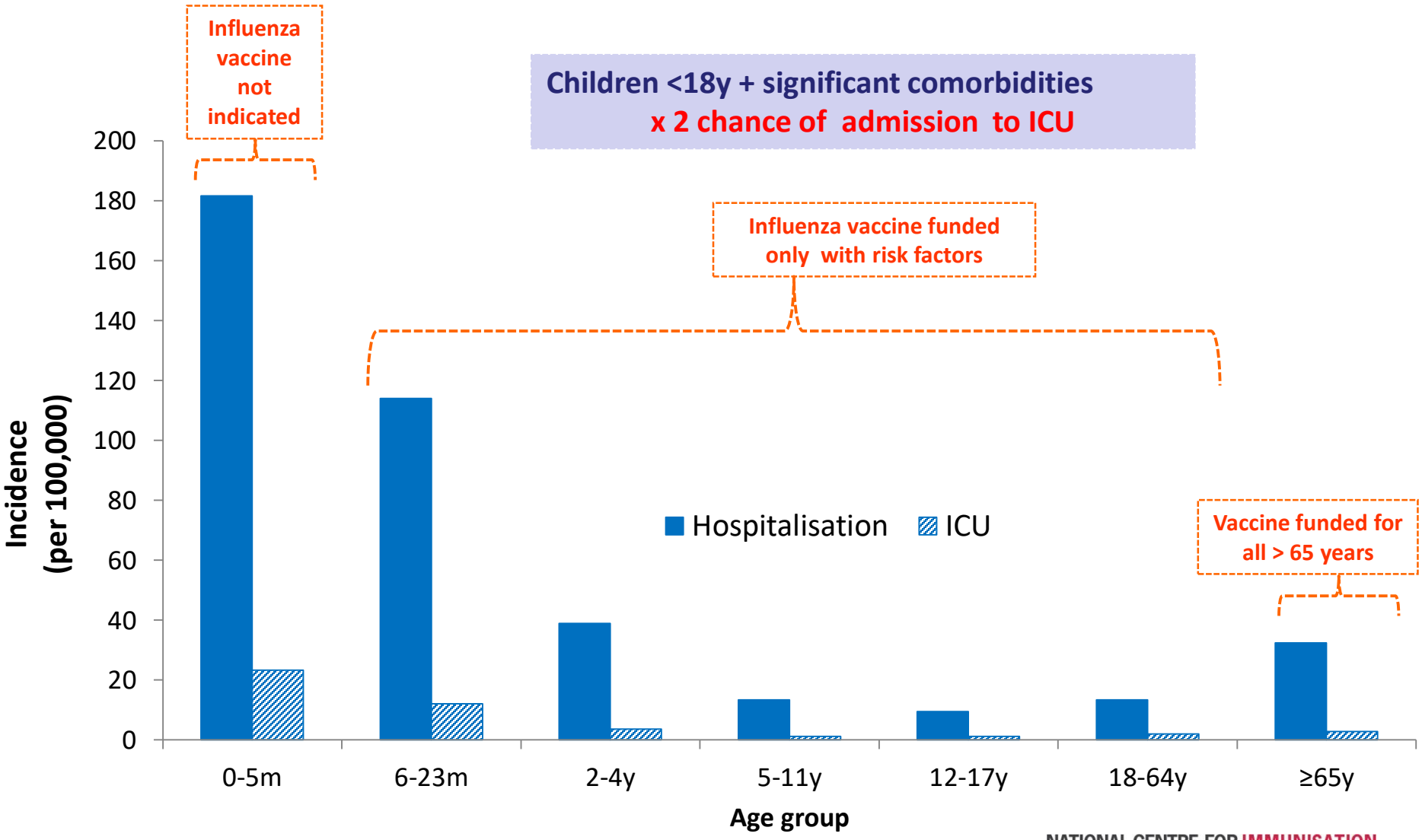
Case study:

INFLUENZA

Background – 2010
Child vaccination suspended due to fever/febrile convulsions from one vaccine brand

Influenza-coded hospitalisation rates, Australia 2002–2013



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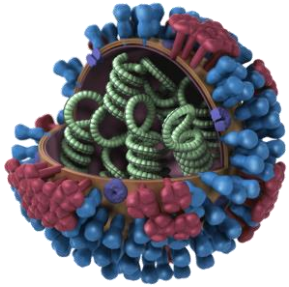
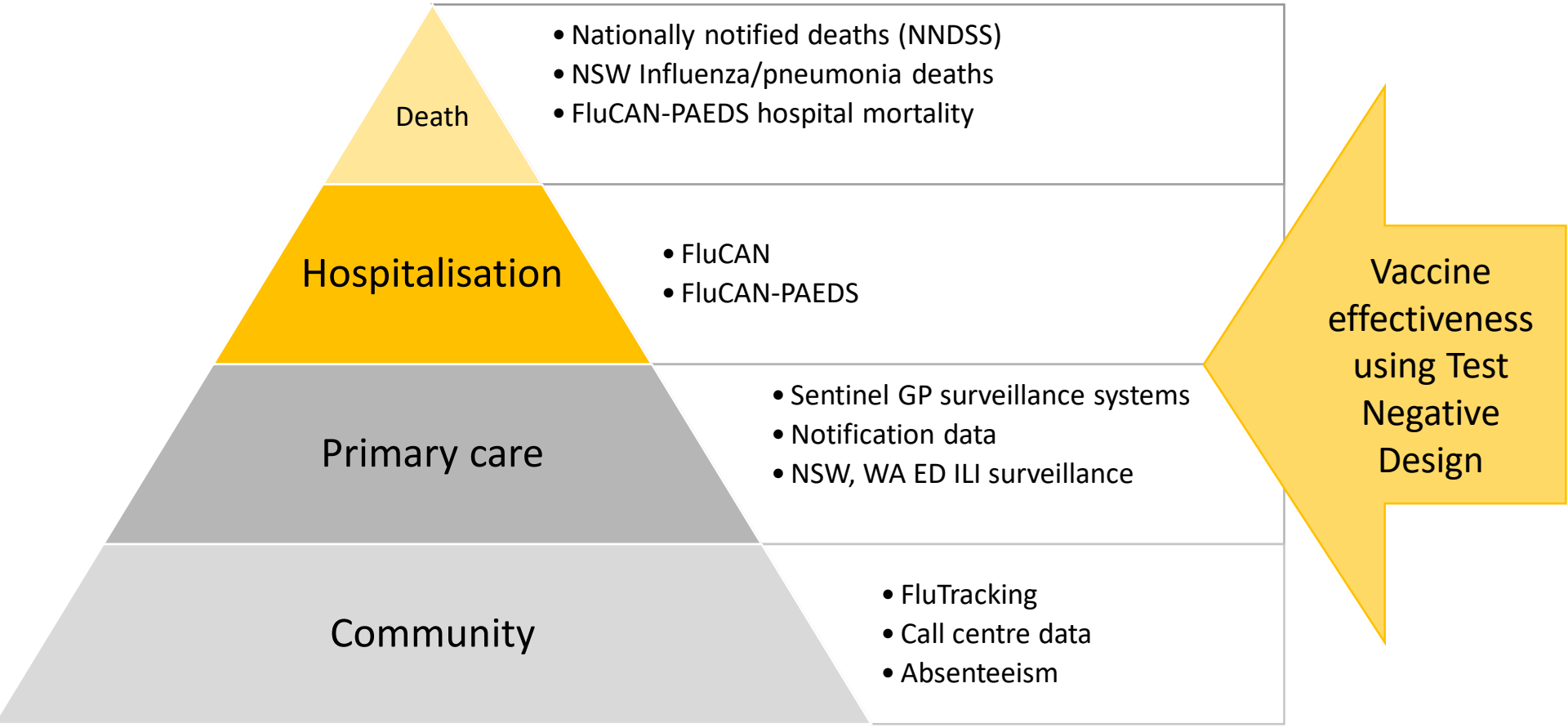
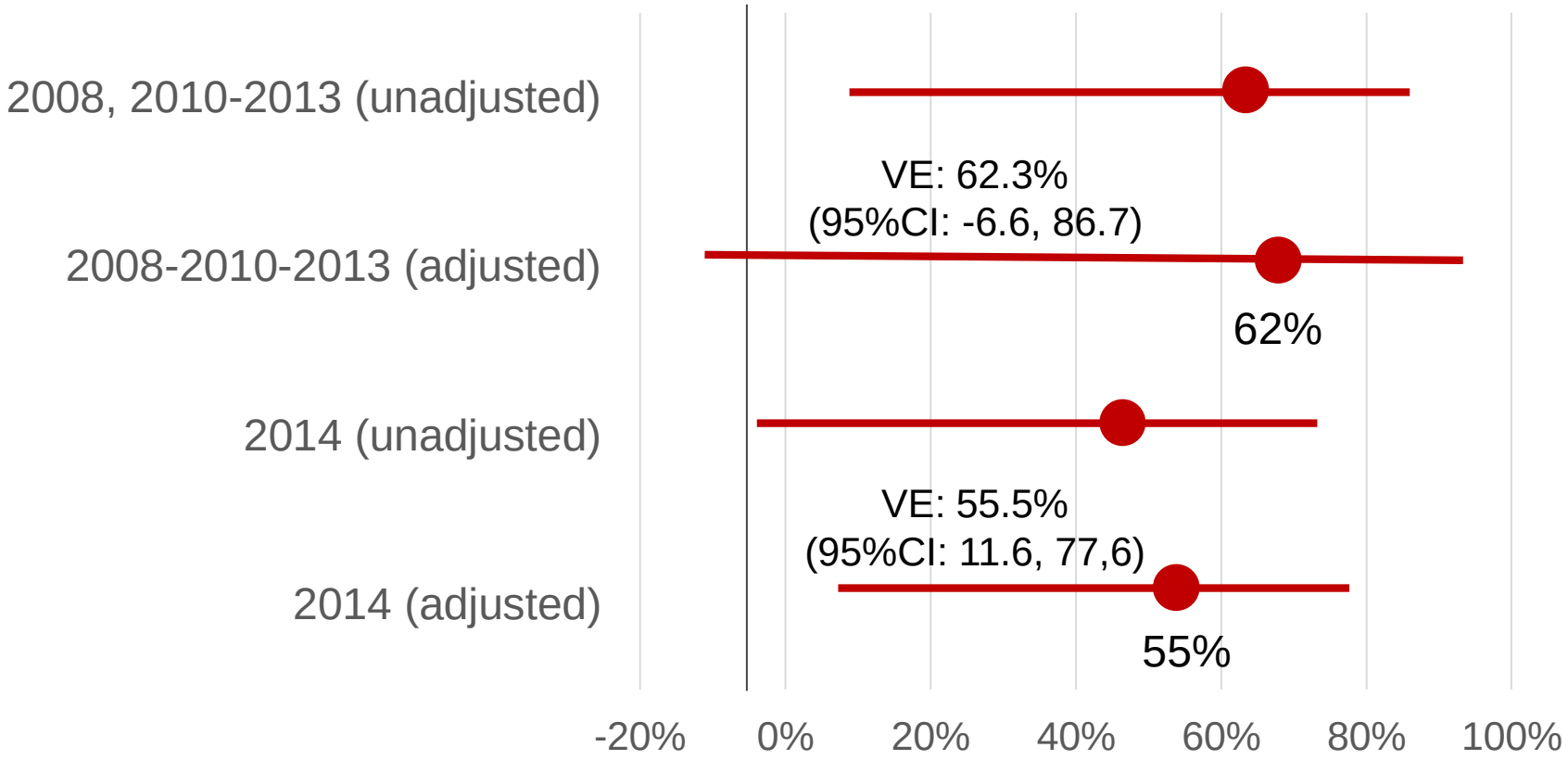
Influenza Surveillance - Australia





Do influenza vaccines work in children?

Hospitalisation



- Case control studies using test negative design
- Controls = children hospitalised with RTI with no or ORV

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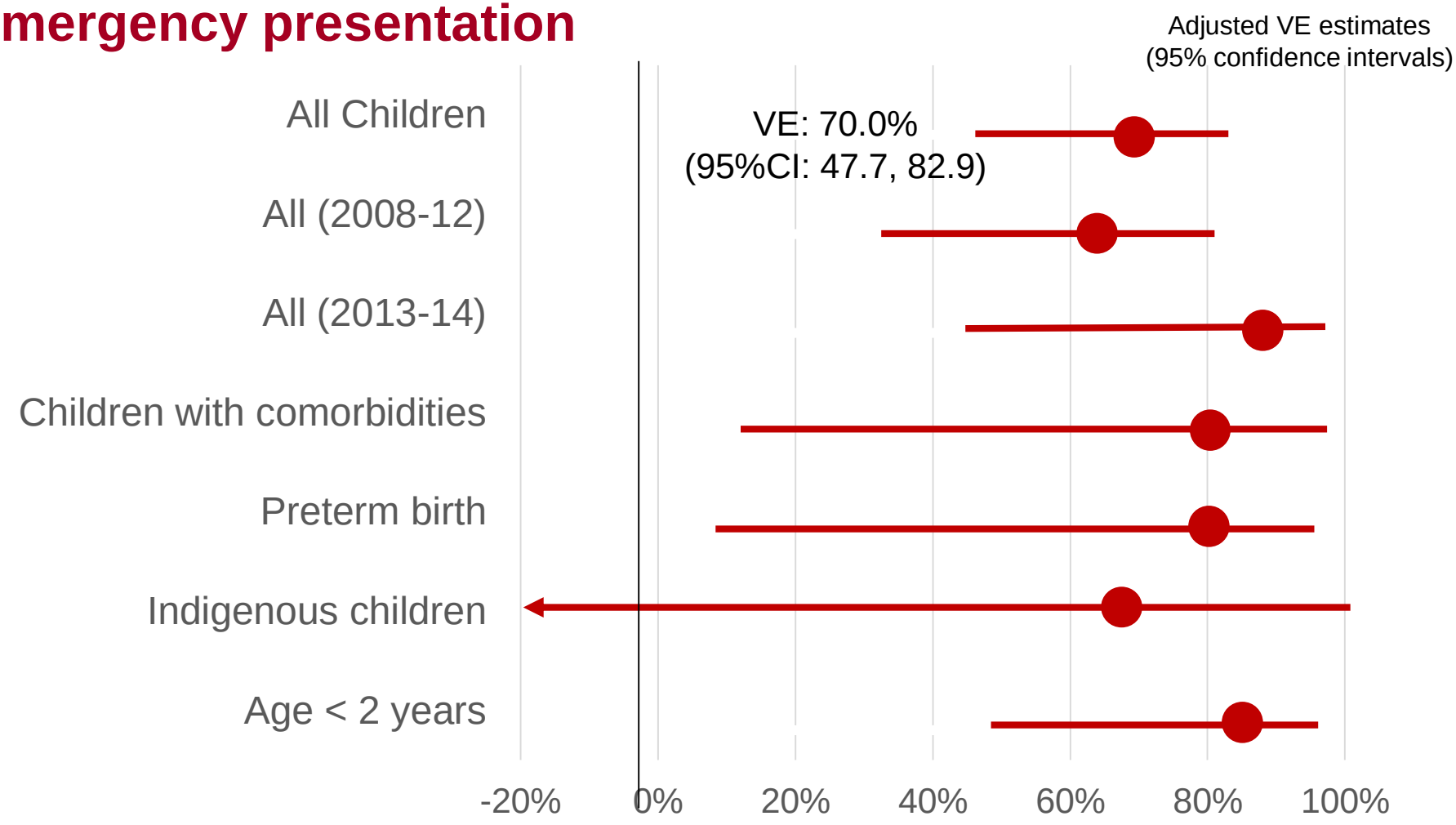
Blyth CC et al, Vaccine 2015; Blyth CC et al; Eurosurveillance 2016

Do influenza vaccines work in children?

Emergency presentation



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Data from WA WAIVE study, courtesy of Chris Blyth

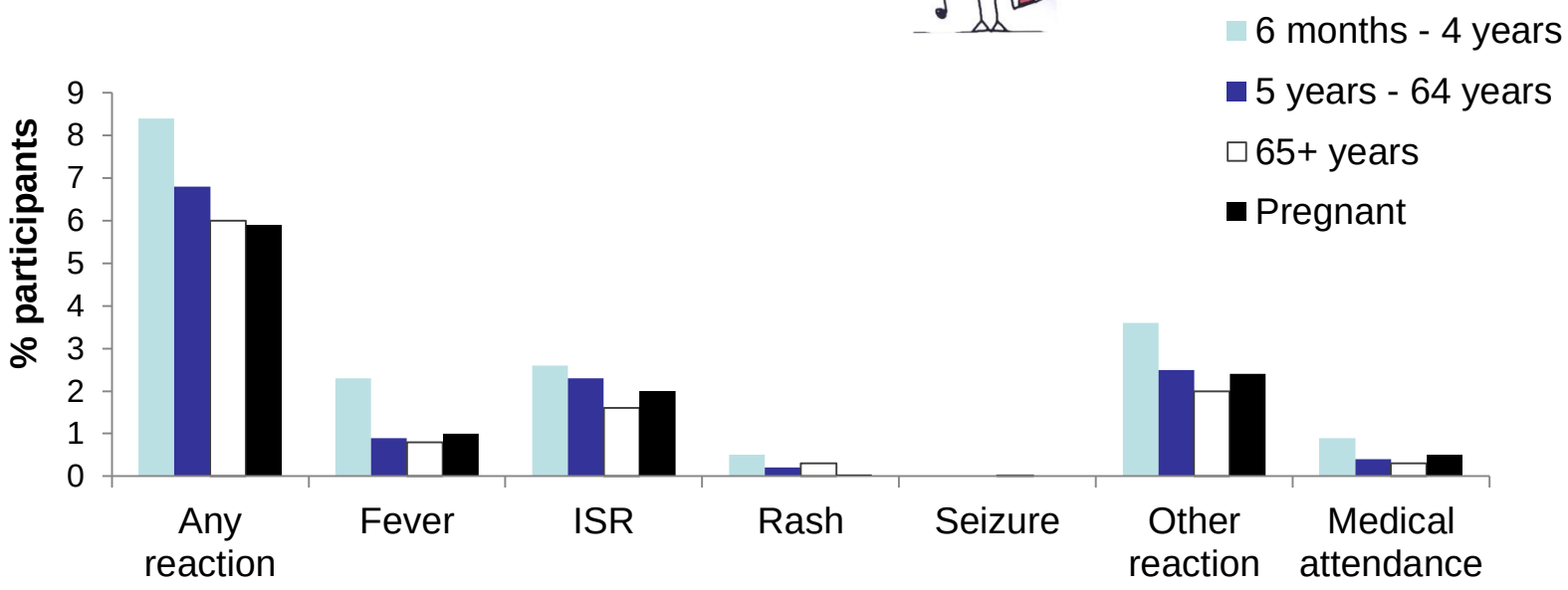
Blyth CC et al, Pediatrics 2014; Blyth CC et al, PIDJ 2016

Active influenza vaccine safety surveillance – SMS based

1 April 2017 – 3 September 2017

✓*No safety signals identified*

- 73,560 participants responded
- 6.6% event rate
- 0.4% medical attendance rate



Case study:

MMRV VACCINE

MMRV vaccine introduction

Research

JAMA Pediatrics | Original Investigation

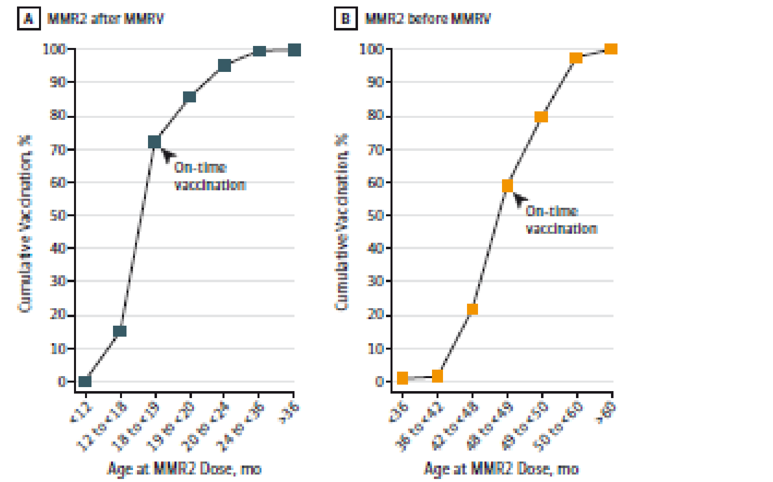
Evaluation of Combination Measles-Mumps-Rubella-Varicella Vaccine Introduction in Australia

Kristine Macartney, MD; Heather F. Gidding, PhD; Lieu Trinh, PhD; Han Wang, MStats; Aditi Dey, PhD; Brynley Hull, MPH; Karen Orr, RN; Jocelynne McRae, MPH; Peter Richmond, MBBS; Michael Gold, MB, CHB; Nigel Crawford, PhD; Jennifer A. Kynaston, MBBS; Peter McIntyre, PhD; Nicholas Wood, PhD; for the Paediatric Active Enhanced Disease Surveillance Network

Table 1. Australian NIP Schedule Before and After Introduction of MMRV From July 1, 2013

Age	Before July 1, 2013	After July 1, 2013
12 mo	MMR	MMR
18 mo	Monovalent varicella[a]	MMRV[b]
48 mo	MMR[b]	NA

Figure. Proportion of Children With On-Time Vaccination for Dose 2 of Measles-Containing Vaccine Before and After Measles-Mumps-Rubella-Varicella (MMRV) Vaccine Introduction



On-time vaccination was defined as vaccine receipt within 30 days of the recommended age. MMR indicates measles-mumps-rubella; MMR2, dose 2 of MMR-containing vaccine in cohort born between July 1 and December 31, 2012 (A), and cohort born between January 1 and June 30, 2009 (B).

- Varicella uptake improved at age 2 years by 4% (from 85.9 to 89.9%)
- On time vaccination for measles-containing vaccine dose 2 increased by 13.5%
- No increased risk of febrile seizures post MMRV vaccine (used as dose 2 at age 18 months)

Table 3. FS Risk Following Dose 1 of MMR and a Subsequent Dose of MMRV in Young Children

Analysis	Method for Age Control	FS Episode	Vaccine	RI −1 to −13 Days, (95% CI)	P Value	RI 5 to 12 Days, (95% CI)	P Value	RI 13 to 30 Days, (95% CI)	P Value
Primary	11-14, 15-18, and 19-23 mo	Unique[a]	MMR	0.41 (0.18-0.94)	.04	2.71 (1.71-4.29)	<.001	0.89 (0.54-1.48)	.66
		Unique[a]	MMRV	1.26 (0.77-2.07)	.36	1.08 (0.55-2.13)	.82	1.08 (0.67-1.74)	.74
Secondary	1-mo intervals	Unique[a]	MMR	0.42 (0.18-0.97)	.04	2.57 (1.56-4.23)	<.001	0.83 (0.49-1.40)	.48
		Unique[a]	MMRV	1.25 (0.74-2.14)	.40	1.17 (0.57-2.40)	.67	1.10 (0.66-1.83)	.72
Secondary	11-14, 15-18, and 19-23 mo	First	MMR	0.37 (0.15-0.92)	.03	2.85 (1.78-4.56)	<.001	0.82 (0.47-1.43)	.48
		First	MMRV	1.37 (0.81-2.33)	.24	1.06 (0.49-2.27)	.89	1.21 (0.73-2.01)	.73

Abbreviations, FS, febrile seizure; MMR, measles-mumps-rubella; MMRV, measles-mumps-rubella-varicella; RI, relative incidence.

[a] First FS episode or multiple FS episodes, with the episodes separated by at least 7 days.

EDITORIAL

Using Disease Epidemiology to Optimize Immunization Schedules

Cindy M. Weinbaum, MD, MPH; Walter A. Orenstein, MD

Macartney et al[1] report in this issue of *JAMA Pediatrics* on the safety of using combination measles-mumps-rubella-varicella (MMRV) vaccine as the second dose of measles-mumps-rubella (MMR) vaccine and sole dose of varicella vaccine in Australia, and the effect of this policy on national vaccine coverage. They

Related article

dence declined 84.6%, with the largest declines reported in children aged 5 to 9 years (89.3%) and 10 to 14 years (84.8%).[6]

In 2005, a combined live, attenuated MMRV vaccine (ProQuad; Merck & Co Inc) was licensed for use in children aged 12 months to 12 years. The use of combination vaccines is a practical way to reduce the number of injections a child receives and can improve timely vaccination coverage; combi-

Acknowledgements

Chris Blyth