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in POPULATION HEALTH RESEARCH
Immunisation in Under Studied and Special Risk Populations:
'Closing the Gap in Knowledge through a Multidisciplinary Approach'

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Complications of Childhood Vaccines

ViM August 2012

Carrington Hotel, Katoomba

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Staff Specialist, Department of Microbiology & Infectious Diseases, CHW

SCIENCE

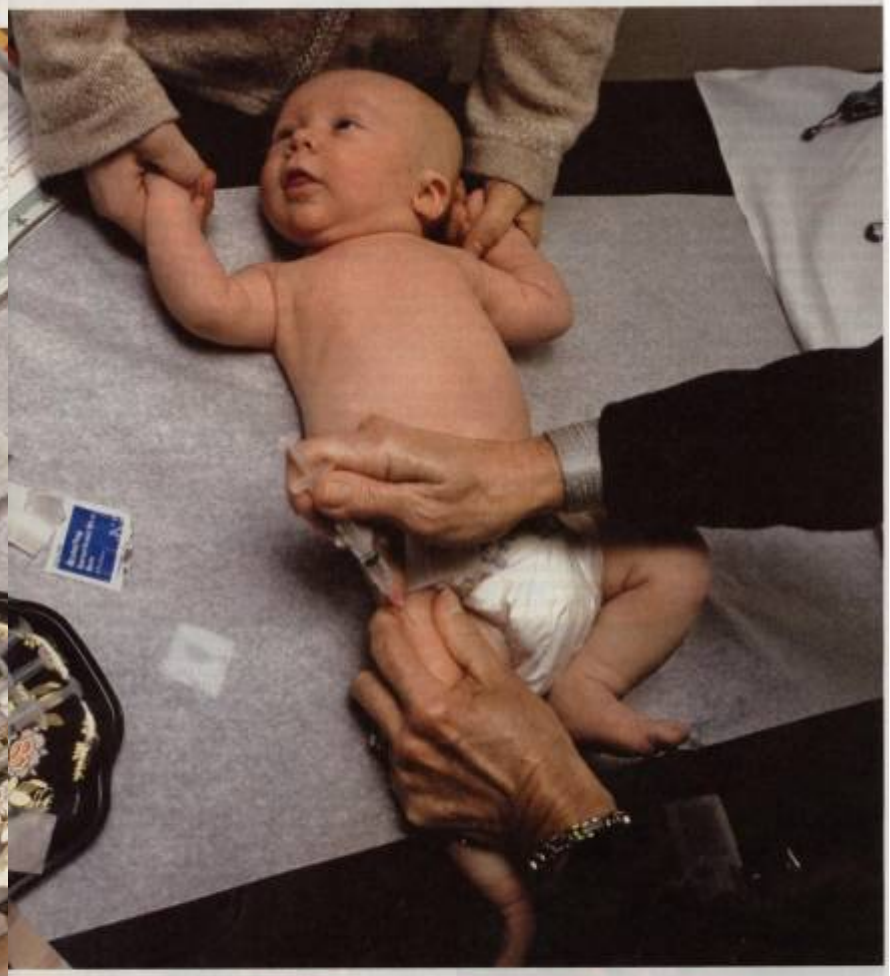
How Safe Are Vaccines?

Parents worried that vaccines trigger autism are increasingly declining the shots for their kids. That's raising fears that long-dormant diseases could return. What the science says about the real risks—and what you should do

BY ALICE PARK

LIFE, IF YOU'RE A BACTERIUM OR virus, boils down to this: finding a pristine human home to provide for your every need, from food and nutrients to shelter against biological storms. As a microbial drifter, you can literally travel the world, hopping from host to host when the opportunity presents itself or when conditions at your temporary residence start heading south. There's no worry about taking along life's necessities either—viruses in particular are adept at traveling light; incapable of reproducing on their own, they think nothing of co-opting the reproductive machinery of their cellular sponsors to help them spawn generation after generation of freeloading progeny.

But ever since Edward Jenner, a country doctor in England, inoculated his son and a handful of other children against smallpox in 1796 by exposing them to cowpox pus, things have been tougher on humans' most unwelcome intruders. In the past century, vaccines against diphtheria, polio, pertussis, measles, mumps and rubella, not to mention the more recent additions of hepatitis B and chicken pox, have wired humans with powerful immune sentries to ward off uninvited invasions. And thanks to state laws requiring vaccinations for youngsters enrolling in kindergarten, the U.S. currently enjoys the highest immunization rate ever; 77% of children embarking on the first day of school are completely up to date on their recommended doses and most of the remaining children are missing just a few shots.



Lying in wait
Six-week old Gavin Hubbard of New Hampshire bravely faces his series of five immunizations in the comforting grasp of Mom

VACCINE TALLY
28
Number of doses of vaccines American children receive by age 2 if they get the complete schedule of immunizations recommended by the Centers for Disease Control and Prevention

STAYING PROTECTED
77%
Percentage of kindergartners in the U.S. who are completely up to date on their vaccinations, in part because schools require it. This is the country's highest rate of immunization ever

OPTING OUT
2%-3%
Percentage of school-age children in the U.S. whose parents have received a religious or philosophical exemption from state vaccination requirements

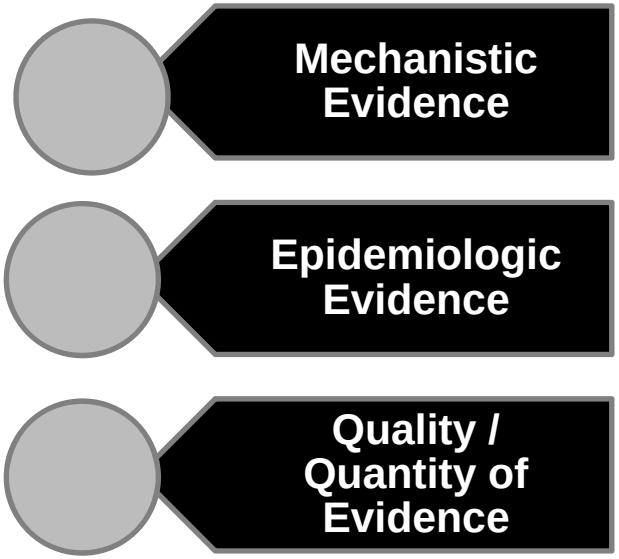
Source: Time Magazine

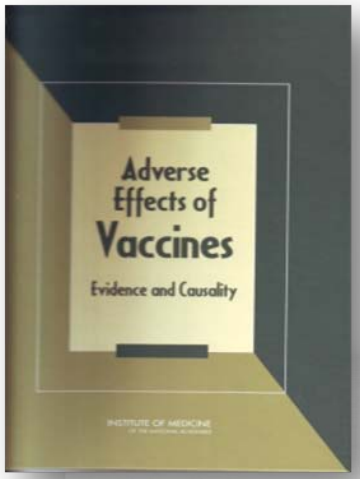
The Cow Pock – Wonderful Effects of the New Inoculation

Outline:

Complications of childhood vaccines

- Assessing safety
- Known complications
- Complications still being explored
- What are not complications





How to assess causality?
US Institute of Medicine Framework

ORIGINAL RESEARCH IN HUMANS

OTHER LITERATURE

Controlled Observational Studies and Randomized Trials

Uncontrolled Clinical Studies and Surveillance Studies

Case Reports

Animal and In Vitro Studies

Reviews of Consequences of the Natural Infection

Excluded studies with very serious limitations from the Epidemiologic Evidence

Excluded studies with very serious limitations from the Epidemiologic Evidence

Included studies with case descriptions that met minimum attribution elements in the Mechanistic Evidence

Excluded reports that did not meet minimum attribution elements for Mechanistic Evidence

Included reports with case descriptions that met minimum attribution elements in the Mechanistic Evidence

Studies Included in the Weight of Epidemiologic Evidence

Studies Included in the Weight of Mechanistic Evidence

High (increased or null/decreased)

Moderate (increased or null/decreased)

Limited

Insufficient

Strong

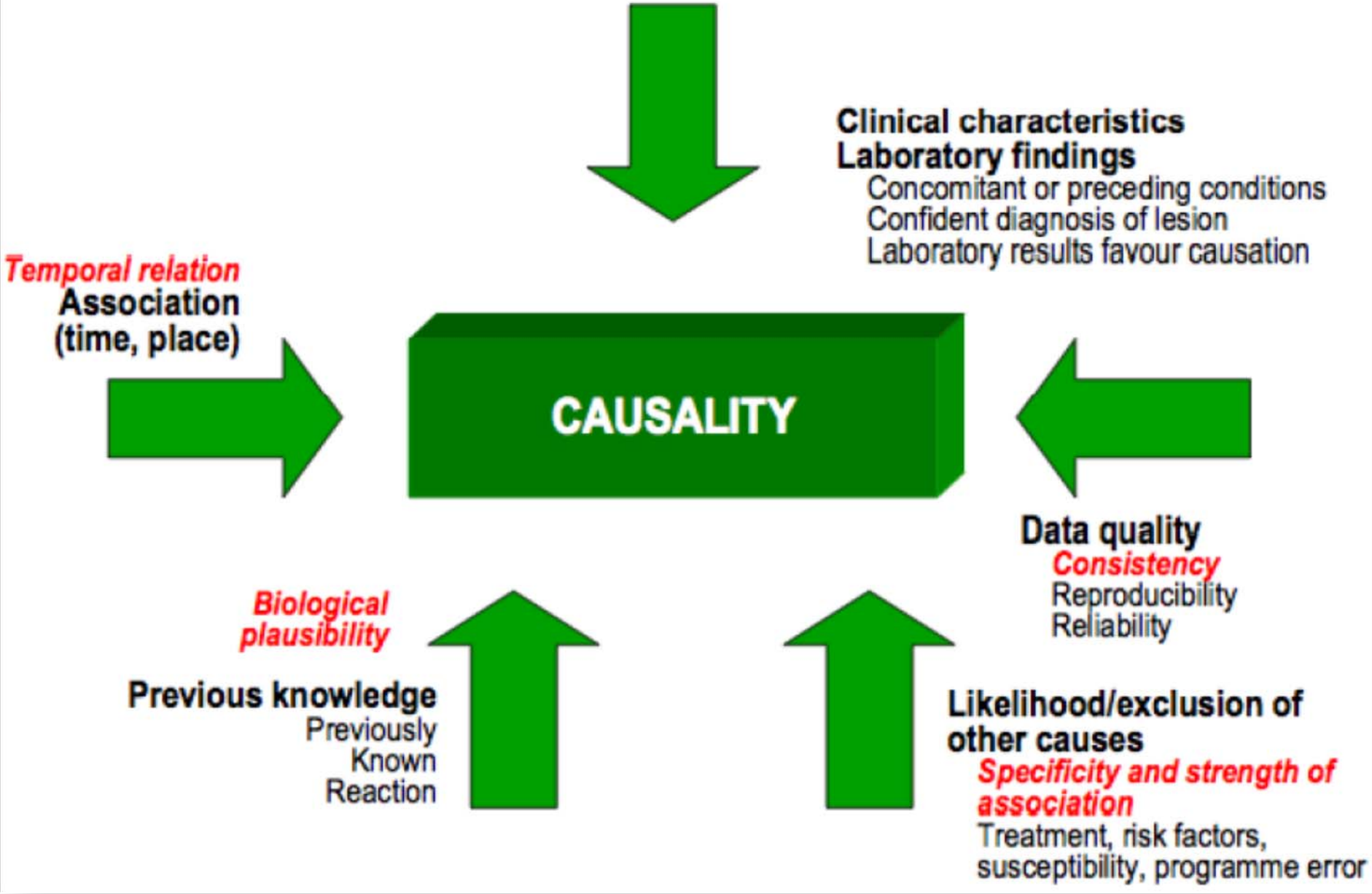
Intermediate

Weak

Lacking

CAUSALITY CONCLUSION

Causality assessment of serious AEFIs



U.S. Food and Drug Administration defines a safe product as:

"one that has acceptable risks, given the magnitude of the benefit expected in a specific population and within the context of alternatives available"

Known complications
Example 1: Injection related event

Injection site reactions

- pain, redness, nodules
- Whole limb swelling (repeated acellular pertussis vaccines, self limited)
- deltoid bursitis (technique !!!)


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

Crawford et al, MJA 2011

- Sometimes it's about the process…….

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

Inappropriate site??

Known complications
Example 1: Whole limb swelling to acellular pertussis

- 5th dose DTPa
- Sometimes includes lymph node involvement
- 24 - 48 hrs post vaccination, last ~ 4 - 5 days
- Also after repeated 23vPPV
- Doesn't usually require antibiotics unless infected (i.e. fever & pain)

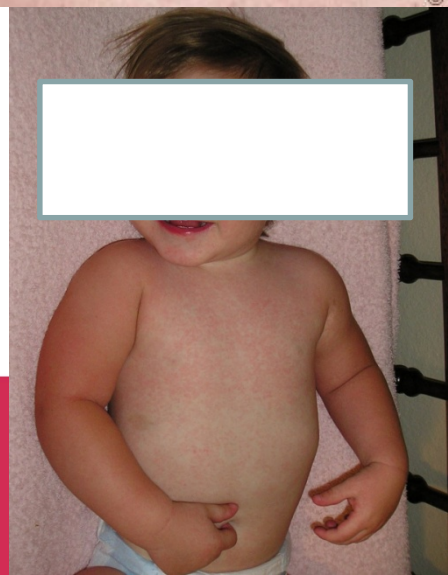
Known complications
Example 2: Anaphylaxis/Hypersensitivity

CASE STUDY

- 6 month old female: urticarial rash around mouth ~ 4 hours post 4 month vaccinations, otherwise well
- Spread to trunk and limbs, lasted 24 hrs

Management

- Skin prick testing to vaccine - negative
- Gave Infanrix-hexa & Prevenar and observed
- No recurrence of symptoms post vaccination
- Proceed with other immunisation at GPs



Courtesy of Dr Nick Wood, Children's Hospital Westmead
Immunisation Adverse Events clinic

Known complications
Example 2: Anaphylaxis/Hypersensitivity

- Rash common post vaccine
- Interpretation
  - Urticarial rash within minutes versus
  - viral type exanthem hrs post
- Ask about other symptoms of anaphylaxis – respiratory, etc
- Anaphylaxis rare
  - 1 in 600,000 doses for hep B vaccine
- Egg allergy with vaccines
  - influenza vaccines: ovalbumin content very low
    - most allergic can be vaccinated

ascia

australasian society of clinical immunology and allergy inc.

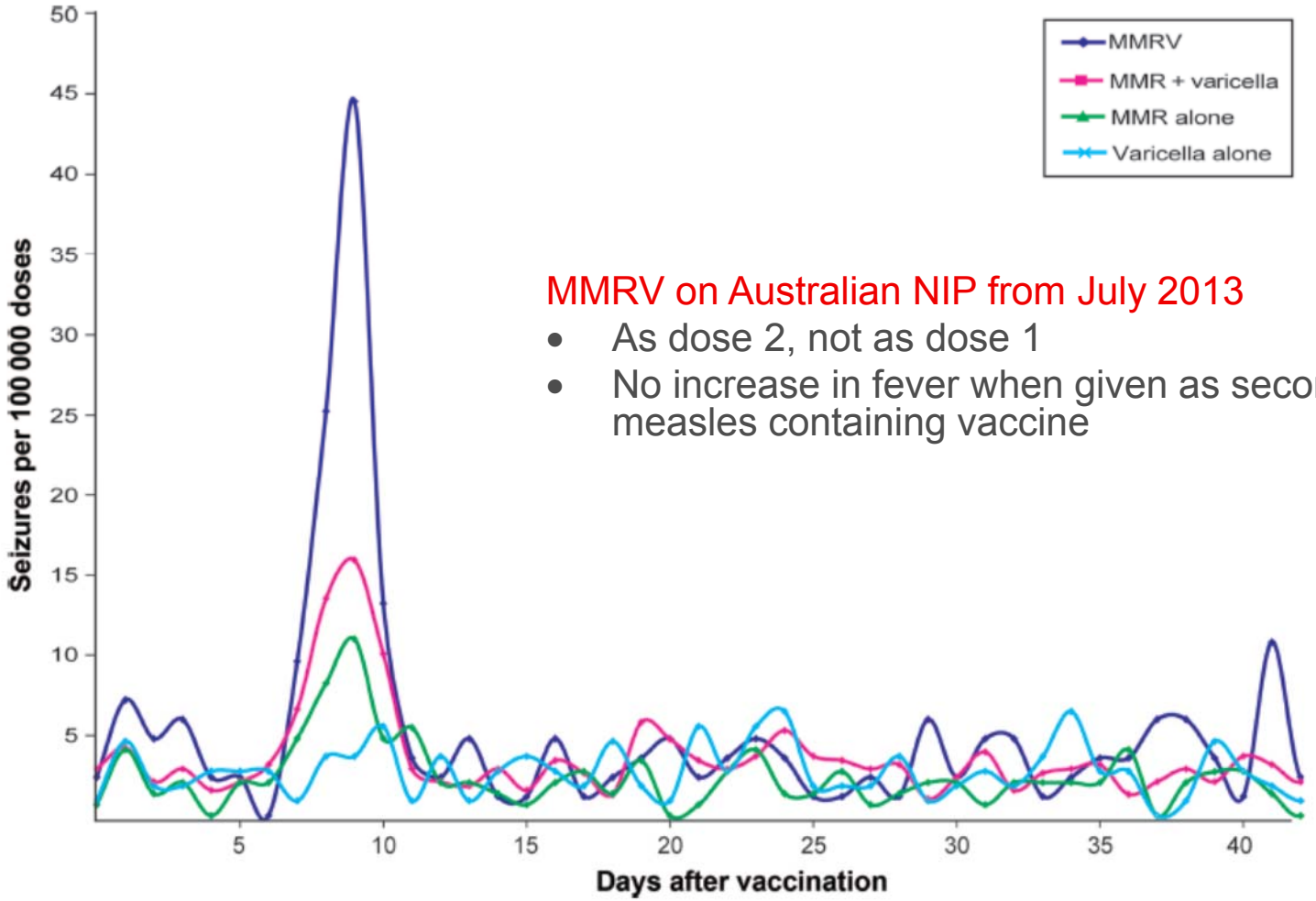
Guidelines for medical practitioners
Influenza vaccination of the egg-allergic individual

September 2010

Known complications example 3: Complications from vaccine virus replication

- Vaccine Associated Paralytic Polio (VAPP)
  - Reversion to neurovirulence during OPV replication
  - 1 in 1 million doses, esp type 2 polio
  - many developed countries switched to IPV (Australia 2005)
- Gastroenteritis/prolonged excretion from oral rotavirus vaccine
  - Severely immunocompromised individuals (eg SCID)
- Disseminated measles/varicella vaccine virus disease
  - Immunocompromised
- Other for measles- containing vaccines
  - Thrombocytopenia
  - Fever and febrile convulsions

MMR and MMRV related seizures



MMRV on Australian NIP from July 2013

- As dose 2, not as dose 1
- No increase in fever when given as second measles containing vaccine

FIGURE 1
Postvaccination seizures among 12- to 23-month-olds according to vaccine received: VSD study population, 2000–2008.

Klein et al. *Pediatrics*. 2010;126:e1-e8

Non febrile seizures in infants and vaccination

De-novo mutations of the sodium channel gene *SCN1A* in alleged vaccine encephalopathy: a retrospective study

Samuel F Berkovic, Louise Harkin, Jacinta M McMahon, James T Pelekanos, Sameer M Zuberi, Elaine C Wirrell, Deepak S Gill, Xenia Iona, John C Mulley, Ingrid E Scheffer

Lancet Neurol 2006; 5: 488-92
Published Online
April 20, 2006
DOI:10.1016/S1474-4422(06)70446-X

Summary

Background Vaccination, particularly for pertussis, has been implicated as a direct cause of an encephalopathy with refractory seizures and intellectual impairment. We postulated that cases of so-called vaccine encephalopathy could have mutations in the neuronal sodium channel α1 subunit gene (*SCN1A*) because of a clinical resemblance to severe myoclonic epilepsy of infancy (SMEI) for which such mutations have been identified.

- 12 / 14 “vaccine encephalopathy” had previously unrecognised Dravet syndrome
    - 11 / 12 had SCN1A mutation

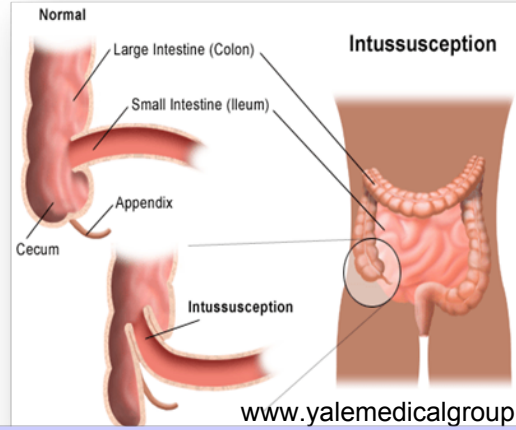
- Did vaccination trigger the onset of Dravet syndrome?
- Did vaccination result in worse neurological outcomes?

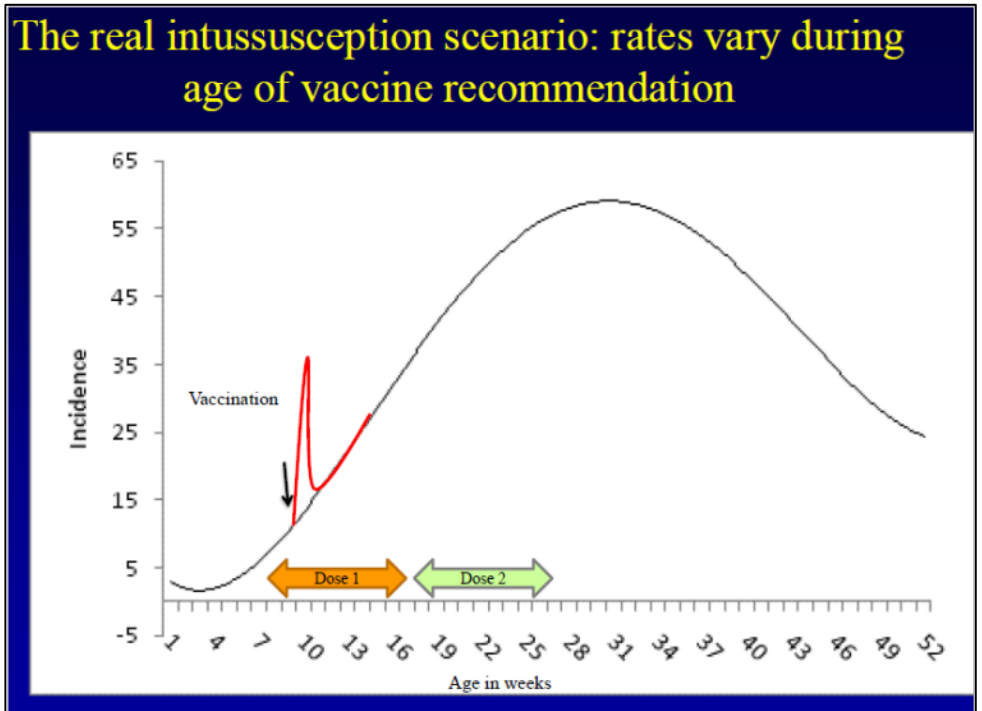
Complications still being explored
Example 1: Hypotonic hyporesponsive episode (HHE)

- Sudden onset reduced muscle tone
- Hyporesponsiveness, Pallor or cyanosis
- Median onset = 3-4 hours after vaccination
- Median duration = 6-30 minutes
- Incidence - 1:20 000 to 1:30 000
- Pathogenesis
  - not known ? glucose, ? pain response ? infant syncope
- No long term sequelae
- Management - subsequent doses not generally contraindicated

Complications still being explored
Example 2: Intussusception and rotavirus vaccines

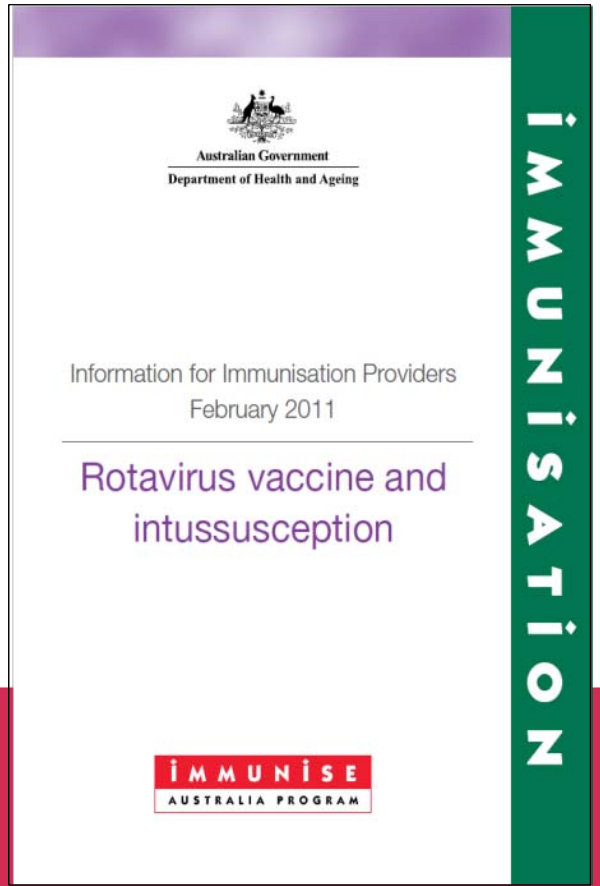
- Usually idiopathic (40% adenovirus infection)
- 80% of cases occur <24 months of age, rare
- Background rate 40 per 100,000 (USA)
- Rotashield (USA 1999) 1 excess case / 5-10,000 doses

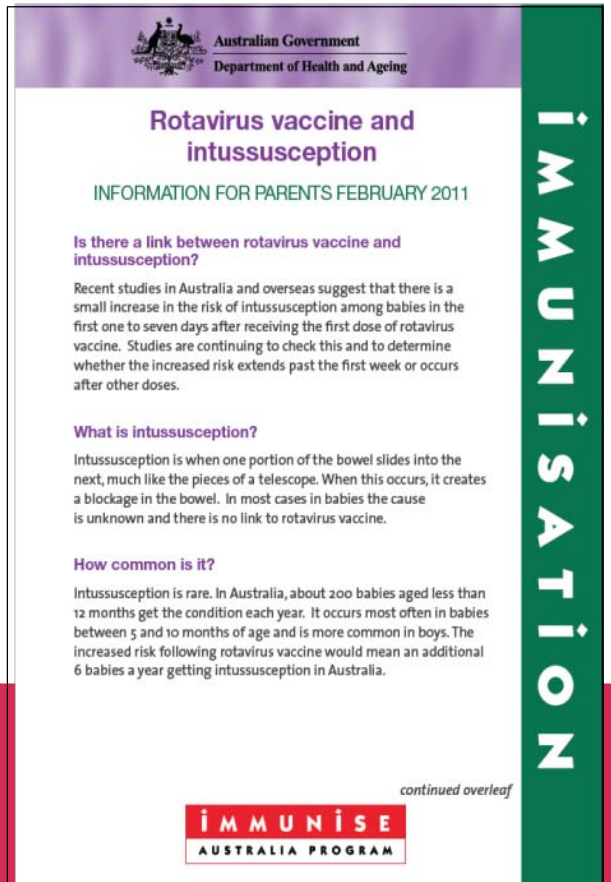




Complications still being explored
Example 2: Intussusception and rotavirus vaccines

- NEW VACCINES (from 2007: Rotarix and RotaTeq)
- Post licensure surveillance – Australia (Buttery et al, *Vaccine* 2011)
- Additional 2 cases per 100,000 infants vaccinated
    - 4 fold increase 1-7 days post dose 1 (1-2 excess/100,000 infants)





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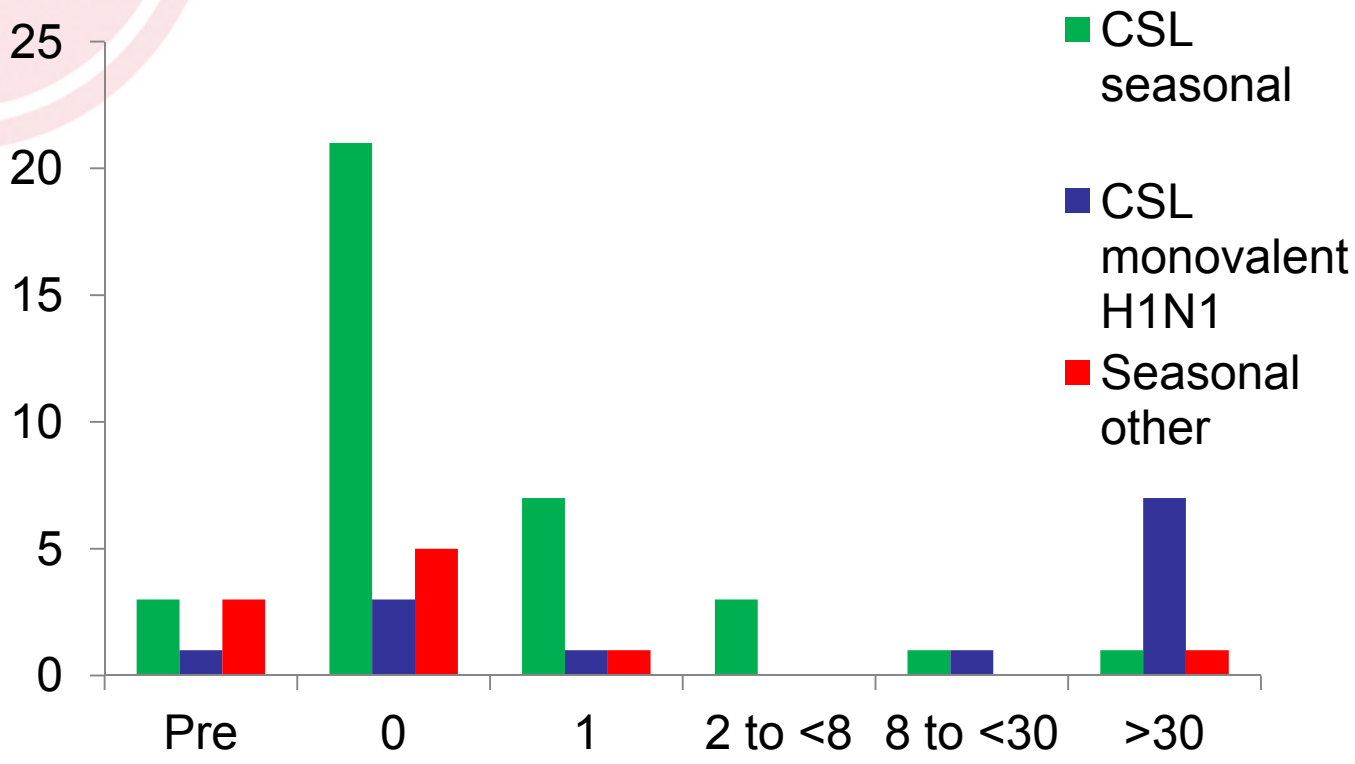
Complications still being explored
Example 3: Febrile convulsions and CSL Fluvax 2010



- Detected due to widespread use in < 5 year program in WA – all suspended
- High fever, cytokine stimulation, typical febrile convulsions
- Manufacturing issue/splitting/new strain combination…….
- CSL brand (*Fluvax*) not for use in children < 10 years
- Other influenza vaccine brands – good safety profile

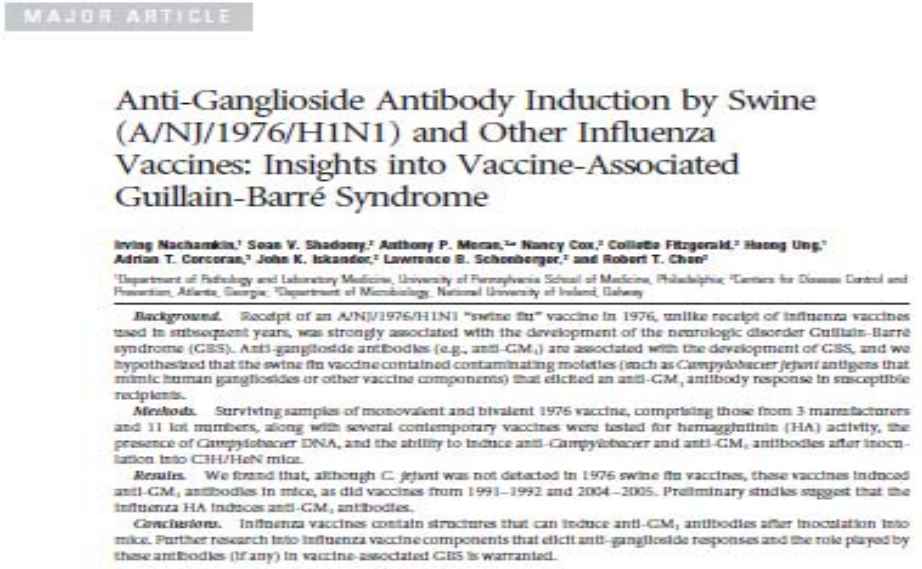
? RARE Complication still being explored
Example 3: Guillain-Barre Syndrome (GBS) and influenza vaccines

- Acute onset of muscle weakness +/- paralysis
- Cause remains unclear - *Campylobacter jejuni* infection linked 40%
- Link with 1976 Swine flu vaccine, USA

Since that time…

- Not convincing association since (? 1 in 1 million, some years)
- >4 epidemiologic studies of GBS post pandemic influenza vaccines
  - No risk
  - or
  - 1-2 excess per 1 million doses

Greene eta l, Wise et al, Nelson et al
Am J Epidemiology 2012



MAJOR ARTICLE

Anti-Ganglioside Antibody Induction by Swine (A/NJ/1976/H1N1) and Other Influenza Vaccines: Insights into Vaccine-Associated Guillain-Barré Syndrome

Irving Nachamkin,[1] Sean V. Shadomy,[2] Anthony P. Moran,[1,a] Nancy Cox,[2] Colletta Fitzgerald,[2] Huong Ung,[1] Adrian T. Corcoran,[3] John K. Iskander,[2] Lawrence B. Schonberger,[2] and Robert T. Chen[2]

[1]Department of Pathology and Laboratory Medicine, University of Pennsylvania School of Medicine, Philadelphia; [2]Centers for Disease Control and Prevention, Atlanta, Georgia; [3]Department of Microbiology, National University of Ireland, Galway

Background. Receipt of an A/NJ/1976/H1N1 "swine flu" vaccine in 1976, unlike receipt of influenza vaccines used in subsequent years, was strongly associated with the development of the neurologic disorder Guillain-Barré syndrome (GBS). Anti-ganglioside antibodies (e.g., anti-GM_1) are associated with the development of GBS, and we hypothesized that the swine flu vaccine contained contaminating moieties (such as *Campylobacter jejuni* antigens that mimic human gangliosides or other vaccine components) that elicited an anti-GM_1 antibody response in susceptible recipients.

Methods. Surviving samples of monovalent and bivalent 1976 vaccine, comprising those from 3 manufacturers and 11 lot numbers, along with several contemporary vaccines were tested for hemagglutinin (HA) activity, the presence of *Campylobacter* DNA, and the ability to induce anti-*Campylobacter* and anti-GM_1 antibodies after inoculation into C3H/HeN mice.

Results. We found that, although *C. jejuni* was not detected in 1976 swine flu vaccines, these vaccines induced anti-GM_1 antibodies in mice, as did vaccines from 1991–1992 and 2004–2005. Preliminary studies suggest that the influenza HA induces anti-GM_1 antibodies.

Conclusions. Influenza vaccines contain structures that can induce anti-GM_1 antibodies after inoculation into mice. Further research into influenza vaccine components that elicit anti-ganglioside responses and the role played by these antibodies (if any) in vaccine-associated GBS is warranted.

What are not complications

- Not true adverse reactions
- Linked because of timing (AEFI)

?

temporal vs causal

What are not complications

- SIDS
- Autism and MMR vaccine
- Inflammatory bowel disease and MMR vaccine
- MS and Hep B vaccine/HPV vaccine
- Diabetes and HIB vaccine
- Asthma
- Others…..

Sunday Times 28 Jun p. 7

Simon Burt

Legal claim: Mary Robinson and her five autistic children

Vaccine panel's drug firm links

ONE third of the members of a government committee that has advised that the MMR vaccine against measles, mumps and rubella is safe have financial interests in drug companies that make the treatment, *writes Rosie Waterhouse.*

Twelve of the 36 members of the Committee on Safety of Med
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Campaigners against the MMR vaccine, who fear it causes autism or bowel disease in children, claim the financial links between drug watchdogs and the pharmaceutical industry could lead to a conflict of interest.

One lobby group, Jabs, is to write to ministers, asking for an inquiry. Last week Mary

Dr Andrew Wakefield,
Gastroenterologist
Royal Free Hospital
UK

Guardian Weekly February 28–March 6 2002 9

Parents favour single jabs for their children

Guardian Weekly November 6–12 2003

UK News

Doctors' row reignites debate over MMR vaccine

Researcher warns of measles epidemic and says no link between jab and autism

Sarah Boseley

The long-running controversy over the MMR vaccination last week turned unexpectedly into a public battle of words between two doctors responsible for the research paper that began the scare five years ago.

Andrew Wakefield and Simon Murch, both gastroenterologists at the Royal Free medical school in London, have taken very different paths since their paper was published in the Lancet in February 1998. Dr Wakefield's hypothesis that the MMR triple jab against measles, mumps and rubella could be responsible for rising rates of autism among children has made him a hero to many parents

dence of a link and warning of the likelihood of a measles epidemic because of the low rate of vaccination, which is down to 61% in parts of London.

Dr Wakefield responded by alleging that Dr Murch had acted only because he was under pressure from his medical bosses. "I have been there, I have done it," said Dr Wakefield in a BBC interview. "His laboratory is under threat. He has failed to gain due promotion. He has been strongly advised to withdraw from scientific publications that involve any mention of my name or association with MMR and bowel disease.

"If that is not an infringement of academic freedom and certainly an implied threat, then I don't know

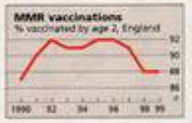
A girl being given the MMR vaccination Photograph: Science Photo Library

well advised to give children the jab separately. Although the paper states that it "did not prove an association between measles, mumps, and rubella vaccine and the syndrome described", the scientific uncertainty got lost in the panic.

Dr Murch and his team have continued to research the links between bowel disease and autism, and have established a connection. One of his reasons for speaking out is that he felt his results were being distorted by the anti-MMR camp to make them look as though they bolstered the case for the jab causing autism. They do not, he said.

In his letter Dr Murch says that although there is now more evidence of the association between inflammation of the gut and autism, the link to the MMR jab has never been proven. "By any rational standards of risk benefit calculation, it is an illogical and potentially dangerous mistak

Britain's MMR scare



Public-health authorities owe citizens unspun information and a measure of respect. Official propaganda scorns both

BRITAIN is in a renewed state of alarm over the combined MMR vaccine, routinely given to children to guard them

two ways. First, move as close to compulsory vaccination as public opinion will allow. In Britain this takes the form of se-
he alternative course of
ve) single vaccines. Par-
g. Second, wage a pro-
truth, never qualifying
ver it takes to get them
ity at large.
proach has drawbacks.
ts—not that this would
. Also, more serious ac-
Quasi-compulsion plus
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outcome—well, that is

THE ECONOMIST JANUARY 27TH 2001

Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive devel...
A J Wakefield; S H Murch; A Anthony; J Linnell; et al
The Lancet; Feb 28, 1998; 351, 9103; Health Module
pg. 637

EARLY REPORT

Early report

Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children

A J Wakefield, S H Murch, A Anthony, J Linnell, D M Casson, M Malik, M Berelowitz, A P Dhillon, M A Thomson, P Harvey, A Valentine, S E Davies, J A Walker-Smith

Neurogenic diagnosis in 12 children referred to paediatric gastroenterology unit. Wakefield et al Lancet 1998; 351

Child	Behavioural diagnosis	Exposure identified by parents or doctor	Interval from exposure to first behavioural symptom	Features associated with exposure	Age at onset of first symptom		
					Behaviour	Bowel	
1	Autism	MMR	1 week	Fever/delirium	12 months	Not known	←
2	Autism	MMR	2 weeks	Self injury	13 months	20 months	←
3	Autism	MMR	48 h	Rash and fever	14 months	Not known	←
4	Autism? Disintegrative disorder?	MMR	Measles vaccine at 15 months followed by slowing in development. Dramatic deterioration in behaviour immediately after MMR at 4-5 years	Repetitive behaviour, self injury, loss of self help	4-5 years	18 months	←
5	Autism	None—MMR at 16 months	Self-injurious behaviour started at 18 months		4 years		
6	Autism	MMR	1 week	Rash & convulsion; gaze avoidance & self injury	15 months	18 months	←
7	Autism	MMR	24 h	Convulsion, gaze avoidance	21 months	2 years	←
8	Post-vaccinial encephalitis?	MMR	2 weeks	Fever, convulsion, rash & diarrhoea	19 months	19 months	
9	Autistic spectrum disorder	Recurrent otitis media	1 week (MMR 2 months previously)	Disinterest; lack of play	18 months	2-5 years	←
10	Post-viral encephalitis?	Measles (previously vaccinated with MMR)	24 h	Fever, rash & vomiting	15 months	Not known	←
11	Autism	MMR	1 week	Recurrent "viral pneumonia" for 8 weeks following MMR	15 months	Not known	←
12	Autism	None—MMR at 15 months	Loss of speech development and deterioration in language skills noted at 16 months			Not known	←

MMR=measles, mumps, and rubella vaccine.

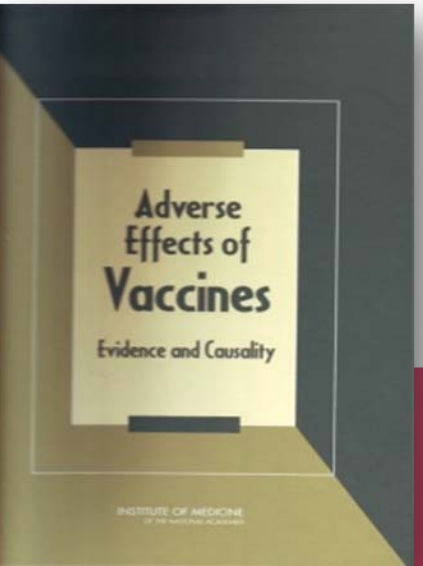
← IBD symptoms preceded diagnosis of autism

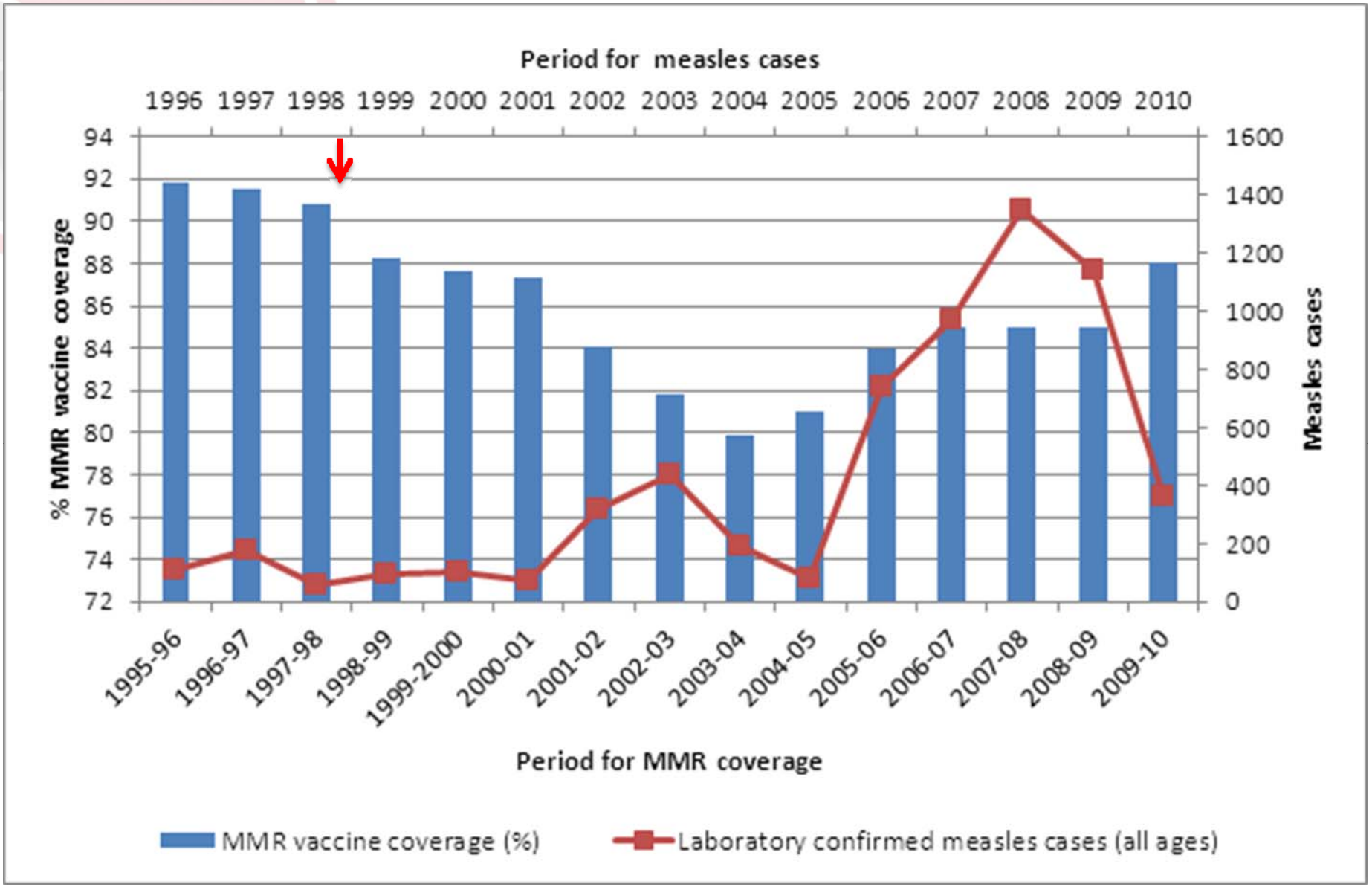
← Autism preceded IBD

← Onset of IBD symptoms unknown

"The committee has a high degree of confidence in the epidemiologic evidence based on four studies with validity and precision to assess an association between MMR vaccine and autism; these studies consistently report a null association."

Institute of Medicine, 2011. *Adverse Effects of Vaccines: Evidence and Causality.* Washington, DC: The National Academies Press.





MMR coverage at 24 months in the UK and laboratory confirmed measles for all ages (England and Wales), 1995-2010.

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Likelihood of an event (vaccination) being considered a trigger of a disease

Increases if:

- Event is perceived to be
  - aggressive (needle, compulsory immunisation)
  - Complex (immune stimulation)
  - Has long lasting effects (induction of immunity)
- Disease is only partly characterised
- New vaccines meet all of these criteria for severe “outcomes”

Temporal association

- rises when high coverage attained rapidly for new vaccines
- baseline incidence of many diseases in adolescent/young adult populations not well known

Seigrist CMAJ, 2007

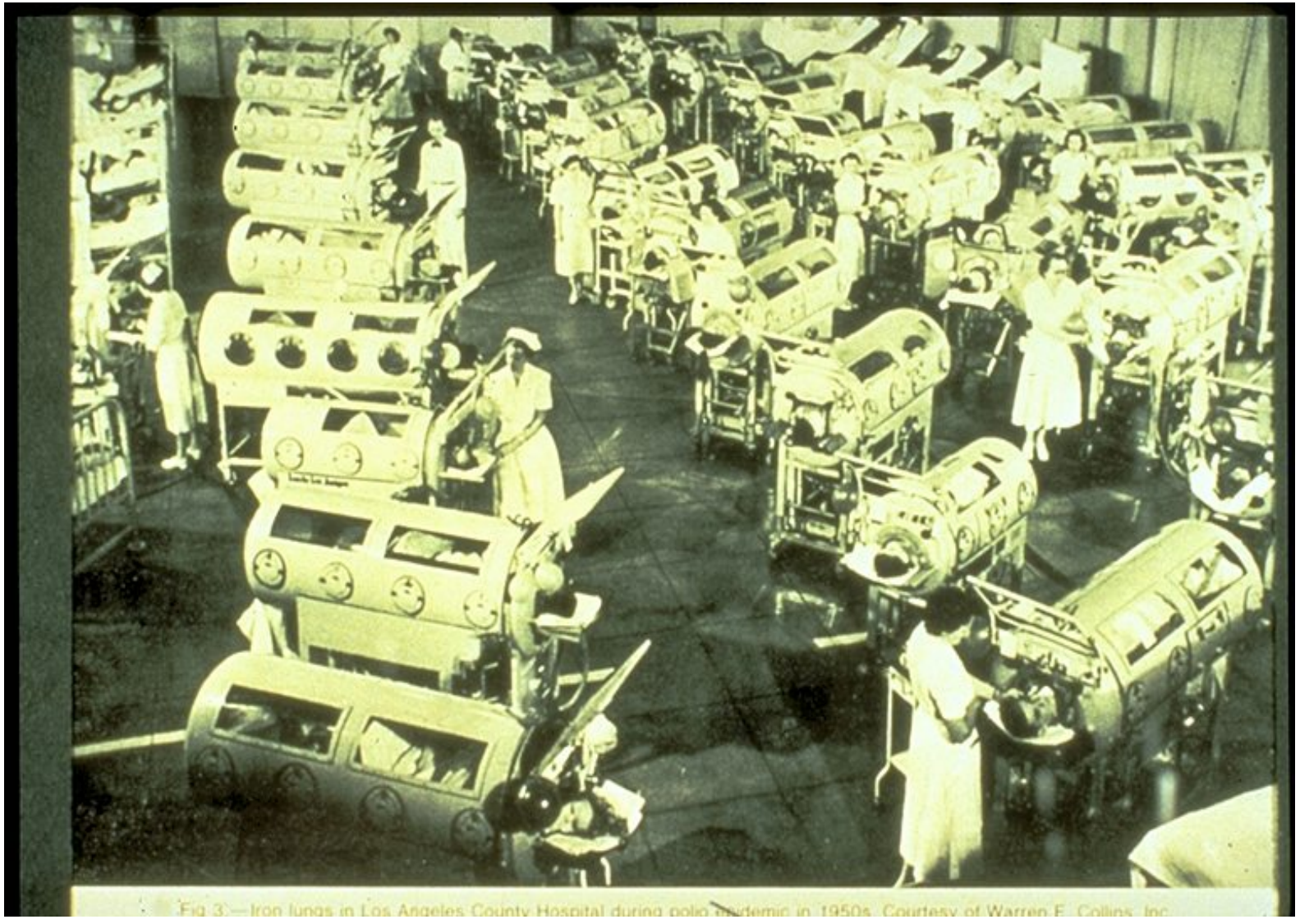
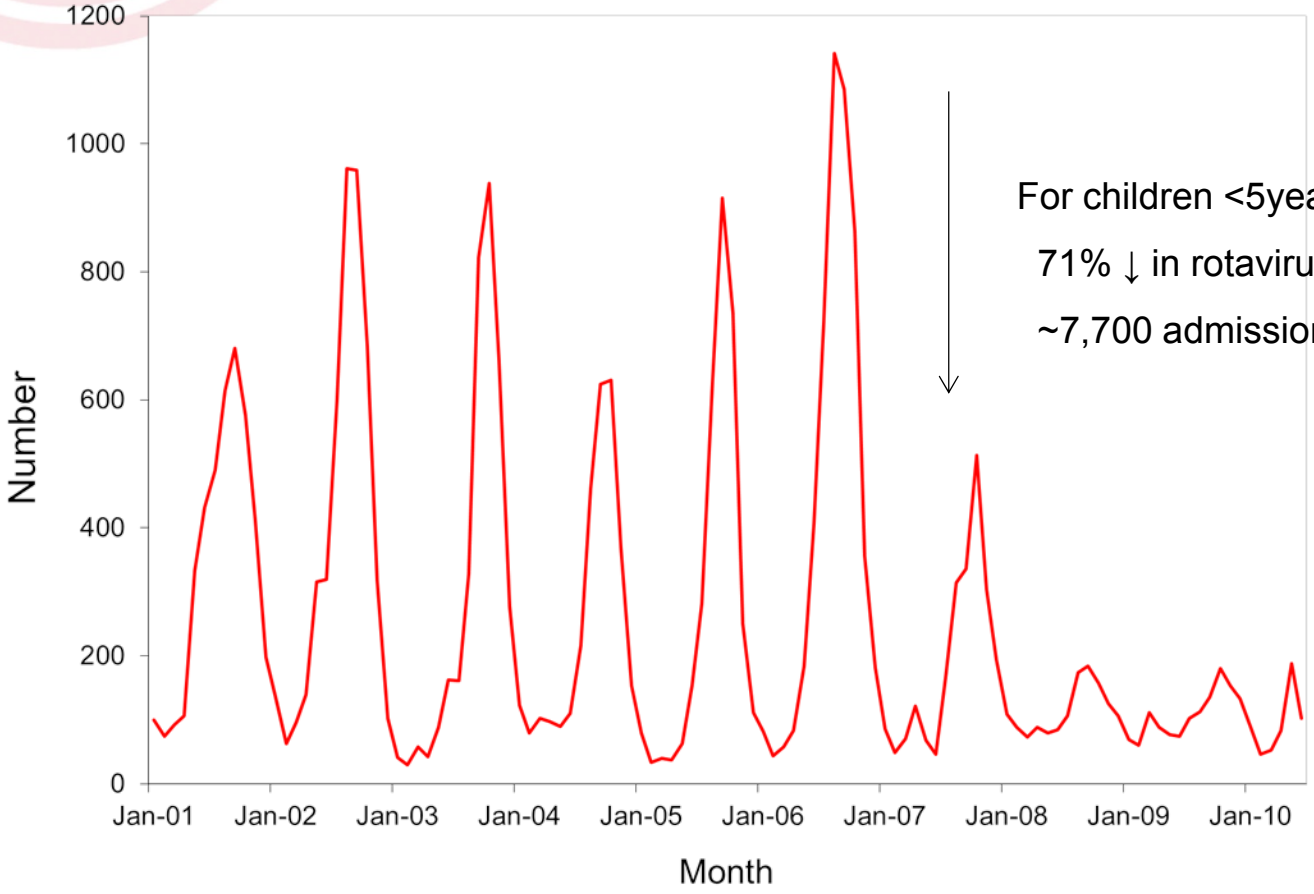


Fig 3.—Iron lungs in Los Angeles County Hospital during polio epidemic in 1950s. Courtesy of Warren E. Collins, Inc.

Rotavirus hospitalisations, Australia



For children <5years:

71% ↓ in rotavirus admissions

~7,700 admissions averted per year

Dey *et al* 2012, MJA *in press*.

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Diphtheria

Emergency tracheostomy, RAHC

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Julie Leask
Campbell King (illustrations)

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