Complications of Childhood Vaccines

ViM August 2012
Carrington Hotel, Katoomba

A/Prof Kristine Macartney
Deputy Director of Government Programs, NCIRS
Associate Professor, Paediatrics and Child Health, University of Sydney
Staff Specialist, Department of Microbiology & Infectious Diseases, CHW
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 host is pivotal for your every need, from food and nutrients to shelter against biological stress. As a microbial drifter, you can literally travel the world, hopping from host to host when the opportunity presents itself or when conditions of your temporary residence start heating up. There’s no worry about taking along life’s necessities either—viruses in particular are adept at transferring genetic material or explicit instructions to their cellular parasites to help them spawn generation after generation of transmitting 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 pustules, things have been tougher on humans who must welcome intruders. In the past century, vaccines against diphtheria, polio, pertussis, measles, mumps, and rubella, for instance, are the most recent addition of household names to chicken pox, have offered humans with powerful immune systems to ward off unwanted invaders. And thanks to state laws requiring vaccinations for youngsters enrolling in kindergarten, the U.S. currently enjoys the highest immunization rates ever. Only 15% of children embarking on the first day of school are completely up to date on their recommended doses and more than half of remaining children are missing just a few shots.

Schlingin want
Six-week-old Gunn Hudson of New Seabury, Mass., will never have to worry about catching chicken pox. The child, inoculated at birth, will most likely never know what a chicken pox pustule feels like. And the experts who advise parents that vaccines are safe and effective say they won’t stop there. They’re-agendas are as far-reaching as the vaccines are potent.

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.

STATE PROTECTED

77%
Percentage of school-aged children 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.
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
Causality assessment of serious AEFIs

Clinical characteristics
- Concomitant or preceding conditions
- Confident diagnosis of lesion
- Laboratory results favour causation

Temporal relation
Association (time, place)

Data quality
- Consistency
- Reproducibility
- Reliability

Biological plausibility
- Previous knowledge
  - Previously known reaction

Likelihood/exclusion of other causes
- Specificity and strength of association
  - Treatment, risk factors, susceptibility, programme error
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 !!!)

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............

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

Buttery MJA 2008
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
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
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

Non febrile seizures in infants and vaccination

- 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

The real intussusception scenario: rates vary during age of vaccine recommendation
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)
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
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 et al, Wise et al, Nelson et al
*Am J Epidemiology* 2012
What are **not** complications

- Not true adverse reactions
- Linked because of timing (AEFI)
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…..
Vaccine panel's drug firm links

ONE third of the members of a government committee that advises on the MMR vaccine against measles, mumps and rubella is claimed to have financial interests in drug companies that make the treatment, writes Richard Warnock.

Twelve of the 36 members of the Committee on Safety of Medicines links to drug companies, including those responsible for the mumps vaccine, own shares in companies that stand to benefit from its sale.

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 Donaldson, director of the Department of Health, asked a panel of experts to consider the evidence.

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

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

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

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

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.”

MMR coverage at 24 months in the UK and laboratory confirmed measles for all ages (England and Wales), 1995-2010.
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
For children <5 years:

71% \downarrow in rotavirus admissions

\sim 7,700 admissions averted per year

Dey et al 2012, MJA in press.
Diphtheria

Emergency tracheostomy, RAHC
Acknowledgements

Kath Cannings
Nick Wood
Julie Leask
Campbell King (illustrations)