Influenza vaccine safety

Clinical Vaccinology Meeting
Melbourne 5 June 2005

A/Prof Kristine Macartney
Deputy Director
The National Centre for Immunisation Research & Surveillance (NCIRS)
Outline

- Flu vaccine safety issues
- New surveillance systems
- Latest data
- What can I tell my patients now?

Acknowledgments

AusVax Safety
Alexis Pilsbury, Patrick Cashman, Chris Blyth, Alan Leeb, Ian Peters, Annette Reagan, Paul Effler, Peter Richmond, Nigel Crawford, Jim Buttery, Gowrie Selvaraj, Tom Snelling, Peter Jacoby, Nick Wood, Dave Durheim, Stephen Clarke, And many others……...

NCIRS
Jean Li Kim Moy, Robert Booy, Karen Orr
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 freelancing 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 unwanted 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 enrolling 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.

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

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

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
Who has ever hesitated about getting a flu vaccine because you’ve thought about having a reaction?
Vaccine gives me the flu?
- No it doesn’t = INACTIVATED vaccine!
- It can cause short lived aches, myalgia, ? low grade temp
- URI symptoms afterwards - usually coincidental

Egg allergy?
- OK to give flu vaccine
- Ovalbumin content of all brands very low.
- Caveat: If anaphylaxis/severe allergy, refer to clinic for possible graded challenge
Unsafe for my baby?

- NO! Protective for baby!!
- No increased risk of fever or pregnancy/delivery outcomes
- Infants protected from lab-confirmed flu up to age 6 months
Guillain-Barre Syndrome (GBS)?

- Ascending paralysis, infectious diseases trigger (eg campylobactor gastroenteritis)
  • but only 1 in a million risk, at most...
- Influenza infection greater risk of triggering GBS

Narcolepsy?

- Increased risk in children in Europe with adjuvanted pandemic vaccine
- Mechanism unclear, ? Related to pH1N1 antigen conformation
- No narcolepsy increase in Australia, US, China

Crawford MJA, 2013
What’s different about flu vaccine?

- May change composition slightly every year
- Match against circulating strains may vary
- Trivalent inactivated vaccine (TIV) - decades
- Many new vaccine formulations on the horizon
  - QIV (Quadrivalent: 2 A and 2 B strains)
  - Live attenuated intranasal influenza vaccine (LAIV)
    - N Hemisphere > 10 years, ? Australia in 2017

...and in Australia, one brand surprised us in 2010
Adverse Events Surveillance: Definitions

- Passive surveillance = report information spontaneously
- ‘Enhanced’ passive surveillance = encourage reports ++
- Active surveillance = all those vaccinated (and sometimes non-vaccinated) approached for information

Key points

- An association in time doesn’t = causality
- Epidemiologic studies, often with detailed individual assessment, are needed to show a causal relationship
“Passive” Surveillance Systems

**Strengths**
- Large population cover
- Simple to operate/inexpensive
- Signal detection
- Hypothesis generation
- Triggers further investigation

**Weaknesses**
- Reporting biases
  - Under-reporting
  - Stimulated reporting
  - Inconsistent data quality/completeness
- Can’t determine AEFI incidence
- Not designed to assess causality
2010

- Increase in fever and febrile seizures in children
- One astute nurse! (signal in WA and SA)
- From only ONE brand = BioCSL Fluvax
- Program suspended, confidence lost
- But why????
  - Had been used in 2008 and 2009 in large numbers of children in WA
  - 2 strain change in 2010 – new pH1N1 and B strain
  - Root cause analysis took years
  - Poor splitting of vaccine, lipid RNA fragments, manufacturing methods in relation to new strains

Armstrong et al, Markovsky et al,
Cytokine storm related in inadequate splitting of vaccine: immune hyper-stimulation: High fevers, fits…
Vaccines and the benefit-risk balance
Influenza vaccination prevents not only primary syndrome of flu but also complications including febrile convulsions which are much more common than encephalitis...

Five year-old Behnam went from a snuffle and a headache at a birthday party on Saturday to intensive care by Monday morning.....

Swine flu 2009
Children fully immunised TIV

45%

Ministerial Review into the Public Health Response into the Adverse Events to the Seasonal Influenza Vaccine

Final Report to the Minister for Health
July 2010

Review of the management of adverse events associated with Panvax and Fluvax

Professor John Horvath AD MBBS FRACP
Influenza vaccine coverage & parents attitude in WA

Parents attitude: Influenza vaccine is safe
Agree: 60% in 2008-2009 vs. 30% in 2010-2012
Disagree: 3% 2008-2009 vs. 14% in 2010-2012

Blyth C et al. The impact of pandemic A(H1N1)pdm09 influenza and vaccine-associated adverse events on parental attitudes and influenza vaccine uptake in young children. Vaccine, 2014; 32,4075–81
But…..

- Adults, including pregnant women, didn’t get fever and thus similar AEs
- Issue in children
  - have more robust immunologic response
- bioCSL Fluvax
  - No longer registered for use in children
  - Multiple approaches to risk reduction

But…..could this happen in children again?
An adult flu shot did this to my boy

The Telegraph
Sunday November 10, 2013

Fluvax brand administered despite widespread education/change in packaging etc
Systematic Review of fever, febrile convulsion and serious adverse events following inactivated Trivalent Influenza Vaccines (TIV) in Children

_Eurosurveillance in press 2015_

Jean Li-Kim-Moy, PhD student
Jiehui Kevin Yin, Harunor Rashid, Gulam Khandaker, Catherine King, Kristine Macartney, Robert Booy
<table>
<thead>
<tr>
<th>Age</th>
<th>Dose 1</th>
<th>Dose 2</th>
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<td>6-35 months</td>
<td>558</td>
<td>548</td>
<td>162</td>
<td>18</td>
<td>854</td>
<td>766</td>
<td>1022</td>
<td>781</td>
<td>398</td>
<td>548</td>
<td>18</td>
<td>854</td>
<td>766</td>
<td>1022</td>
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<tr>
<td>≥3 years</td>
<td>162</td>
<td>18</td>
<td>18</td>
<td>18</td>
<td>1022</td>
<td>781</td>
<td>398</td>
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<td>398</td>
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<td>6m – 17 years</td>
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Fever rate (%) 95%CI

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<tr>
<td>6-35 months</td>
<td>5.1</td>
<td>4.3</td>
<td>4.4</td>
<td>0</td>
<td>26.4</td>
<td>19.4</td>
<td>18.8</td>
<td>9.7</td>
<td>5.0</td>
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<tr>
<td>≥3 years</td>
<td>4.4</td>
<td>4.4</td>
<td>4.4</td>
<td>0</td>
<td>4.7</td>
<td>4.7</td>
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<td></td>
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<tr>
<td>6m – 17 years</td>
<td>4.7</td>
<td>4.7</td>
<td>4.7</td>
<td>0</td>
<td>4.7</td>
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**Sanofi**

- **Age**: 6-35 months
- **Dose 1**: 558 children, Fever rate: 5.1 (2.8-8.1)%
- **Dose 2**: 548 children, Fever rate: 4.3 (2.8-6.2)%
- **≥3 years**: 162 children, Fever rate: 4.4 (1.2-9.2)%
- **Dose 2**: 18 children, Fever rate: 0 (0-18.5)%

**GSK**

- **Age**: 6m – 17 years
- **Dose 1**: 2151 children, Fever rate: 4.7 (0.9-11.1)%

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**CSL**

- **Age**: 6-35 months
- **Dose 1**: 854 children, Fever rate: 26.4 (21.0-32.3)%
- **Dose 2**: 766 children, Fever rate: 19.4 (15.3-23.9)%
- **3-8 years**: 1022 children, Fever rate: 18.8 (15.9-21.9)%
- **Dose 2**: 781 children, Fever rate: 9.7 (7.7-11.9)%
- **9-17 years**: 398 children, Fever rate: 5.0 (3.3-7.7)%

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*aInsufficient studies for I² calculation*
Recently published RCT of CSL (Afluria = Fluvax) versus Sanofi (Fluzone) - same CSL product licensed by FDA

- Brady et al. *Vaccine 2014* Conducted Sept 2009 – May 2010
- RR fever: ~ 2.5

<table>
<thead>
<tr>
<th>Age</th>
<th>Fever</th>
<th>Afluria (CSL) %</th>
<th>Fluzone (Sanofi) %</th>
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<tbody>
<tr>
<td>6-35 months</td>
<td>Dose 1</td>
<td><strong>37.1 (30.8 – 43.7)</strong></td>
<td>13.6 (9.4 – 18.7)</td>
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<tr>
<td></td>
<td>Dose 2</td>
<td>14.6 (8.2 – 23.3)</td>
<td>13.6 (7.8 – 21.5)</td>
</tr>
<tr>
<td>3-8y</td>
<td>Dose 1</td>
<td><strong>21.8 (16.9 – 27.4)</strong></td>
<td>9.4 (6.1 – 13.7)</td>
</tr>
<tr>
<td></td>
<td>Dose 2</td>
<td>5.9 (1.6 – 14.4)</td>
<td>6.4 (2.1 – 14.3)</td>
</tr>
<tr>
<td>9-17y</td>
<td>Dose 1</td>
<td><strong>6.3 (3.6 – 10.0)</strong></td>
<td>4.0 (1.9 – 7.2)</td>
</tr>
</tbody>
</table>
The safety of seasonal influenza vaccines in Australian children in 2013

Fever and febrile convulsions in young Australian children were widely reported after vaccination with one brand of influenza vaccine (Fluvax and Fluvax Junior; bioCSL) in 2010. This unexpected increase in risk (estimated incidence

Abstract
Objective: To examine influenza vaccine safety in Australian children aged under 10 years in 2013.
Design, participants and setting: Active prospective surveillance study conducted with parents or carers of children who received influenza vaccine in outpatient clinics at six tertiary paediatric hospitals or from selected primary health care providers between 18 March and 19 July 2013.

Using automated text messages to monitor adverse events following immunisation in general practice

After the surge in adverse events following immunisation (AEFI) among children receiving seasonal influenza vaccine in April 2010, the limitations of existing systems for monitoring adverse events following immunisation (AEFI) became apparent. A prototype system that monitors adverse events following immunisation (AEFI) and provides automated feedback to parents and health-care professionals was developed. A field test of the system was conducted in a general practice in the Hunter New England region of NSW, Australia. Parents of children aged 0 to 12 years were consented to participate in the study. After immunisation, parents were sent an automated SMS message asking them to report any adverse events they had noticed. The messages were sent 1 day before and 1 day after each scheduled appointment. Health-care professionals received an SMS message asking for consent for the system if the child did not return for their scheduled appointment.

Abstract
Objective: To assess the performance of SmartVax, a prototype active monitoring system for adverse events following immunisation (AEFI) using short message service (SMS) text messages and clinical data extracted from commercially available medical practice management software.

Wood et al MJA 2014; Leeb et al, MJA 2014; Cashman et al, Vaccine
AusVaxSafety
Active influenza vaccine safety surveillance

- **Automated SMS/email follow-up** with parents
  - Children aged < 5 years, 3 days post vax
  - Reply via SMS, web survey – phone call f/u if serious AE
  - Survey response re AEs (fever, medical advice, other)

- Sentinel sites (hospitals/GPs/clinics)
  - 2013 – 600 children
  - 2014: ~ 800 children, all 4 vaccine brands
  - 2015: 4 states participating… 2000 + children……
Installed into GP software
Fully automated SMS send and data receipt
GPs/nurse call back pts with any serious AEFI

ALL VACCINES  !!!!!!
Vaxtracker

- Online survey
- Nurse/admin staff enter patient details into web portal
- SMS send/receive and data collation automatic
- Influenza vaccines, MMRV, other vaccines with GP research project (STARRS, in WA and Vic)
- Fully automated from GP software from late 2015
AusVaxSafety data by state

- NSW
- Vic
- WA
- Linear (WA)

Number

Week

2 3 4 5 6

63%

Slide courtesy of Dr Alan Leeb, WA
2026 surveys completed in 5 weeks (through 31 May 2015)

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Number (%)</th>
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<tbody>
<tr>
<td>Any adverse event</td>
<td>232 (11.5%)</td>
</tr>
<tr>
<td>Fever</td>
<td>87 (4.3%)</td>
</tr>
<tr>
<td>Seizure</td>
<td>3 (0.2%)</td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>45 (2.2%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>29 (1.4%)</td>
</tr>
<tr>
<td>Rash</td>
<td>20 (1.0%)</td>
</tr>
<tr>
<td>Chills/shakes</td>
<td>18 (1.0%)</td>
</tr>
<tr>
<td>Medical advice sought</td>
<td>19 (0.2%)</td>
</tr>
<tr>
<td>ED or hospitalisation</td>
<td>3 (0.2%)</td>
</tr>
</tbody>
</table>
## AusVaxSafety surveillance

<table>
<thead>
<tr>
<th>Vaccine brand</th>
<th>Number (%)</th>
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<tbody>
<tr>
<td>Agrippal</td>
<td>3 (0.2%)</td>
</tr>
<tr>
<td>Fluarix</td>
<td>59 (2.9%)</td>
</tr>
<tr>
<td>Fluarix Tetra</td>
<td>3 (0.2%)</td>
</tr>
<tr>
<td>FluQuadri</td>
<td>4 (0.2%)</td>
</tr>
<tr>
<td>Generic</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Influvac</td>
<td>34 (1.7%)</td>
</tr>
<tr>
<td>Vaxigrip</td>
<td>1403 (69.3%)</td>
</tr>
<tr>
<td>Vaxigrip Junior</td>
<td>518 (25.6%)</td>
</tr>
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Additional WA data

SMS follow-up
Pregnant women (1000’s !!)
- flu and pertussis vaccines safe
HCW (1000’s !!)
- flu vaccine safe
Conclusions
(and what can I tell my patients?)

- Flu vaccine use is safe
- Don’t use bioCSL Fluvax brand in children but other vaccines used are SAFE
- Australia has some new great safety surveillance systems for vaccines – GPs and clinics can actively participate
- Influenza is a terrible illness.
- Vaccination works !!
Top four reasons your children need the FREE Influenza Vaccine

1. Prevents influenza related illness and death
   Children can get really sick and die from the flu, especially children aged less than 5 years, Aboriginal and Torres Strait Islander children and those with medical conditions predisposing them to severe illness.

2. Vaccination is safe and effective
   The brands of influenza vaccine approved for use in children are shown to be safe. Getting the vaccine each year helps prevent influenza related illnesses.

3. Protects other people
   Protecting your child will stop the spread of flu to others who may be at particular risk, such as grandparents and those with chronic illness.

4. Reduced time off work and school
   Children infected with flu may not be able to attend school or childcare for several weeks. Parents and carers need to take time away from work to care for them.

Follow the green footprints to the Clinic on level one for vaccinations today.

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NATIONAL CENTRE FOR IMMUNISATION RESEARCH & SURVEILLANCE