Influenza vaccination: past, present and future

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The pathogen

- Family of enveloped RNA viruses with a segmented genome
  - Influenza A – strain shift and drift
  - Influenza B – strain drift
  - Influenza C – rarely causes disease

- Influenza A has a large number of animal hosts:
  - Birds, Pigs, Horses, Seals
The pathogen

- Protective immunity is through antibodies against haemogglutinin.
- RNA polymerases lack the ability to proof-read.
  - Mutations occur more frequently with RNA viruses.
- Mutations result in periodic changes in haemogglutinin: **Strain drift**.
- Strain drift makes immunity short-lived: **annual epidemics**.
The pathogen

- A segmented genome allows the genetic reassortment of the influenza genome: **Strain shift**
- No (little) protective immunity exists against new reassorted viruses: **episodic pandemics**
Why influenza?

Vaccine Preventable Diseases in Australia: 2012
Why influenza?

Vaccine Preventable Diseases in Australia: 2012

- Deaths
- ICU Admissions
- Hospital Admissions

Influenza (lab confirmed)
Influenza burden

Laboratory proven influenza 2012

NNDSS December 2013
Influenza burden

Estimated costs of influenza: hospitalisation

Estimated costs of influenza: GP visits

$115 million ($72.3–$170.1M) dollars per annum

Newall AT et al, Vaccine 2008
Influenza prevention

Circ. 1918: http://science.nationalgeographic.com/science/photos/influenza/
Influenza prevention

Influenza prevention
Influenza prevention: 2013

Live-attenuated

Split-inactivated
Influenza prevention: 2013

- Monovalent (pandemic)
- Trivalent
  - H1N1
  - H3N2
- B – Victoria or Yamagata
- Quadrivalent
  - H1N1
  - H3N2
  - Both B lineages
Influenza prevention

- Measurements of vaccine efficacy / effectiveness
- Summary points:
  - VE varies each season
  - VE is greatest against laboratory-proven influenza (not ILI or pneumonia)
  - Immunogenicity and VE is lower in the elderly and young children
Vaccination: direct effects

- Population: Adults (20-64 years) presenting to sentinel general practices in Victoria
- Years: 2007-2011 (2009 excluded)
- Methods: Test negative design
- Endpoint: PCR proven influenza

<table>
<thead>
<tr>
<th>Population</th>
<th>Adjusted Vaccine Effectiveness (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>62% (43 to 75%)</td>
</tr>
</tbody>
</table>
Vaccination: direct effects

- Population: Adults (≥18 years) presenting to Tertiary hospitals in all states/territories
- Years: 2010-2011
- Methods: Test negative design
- Endpoint: PCR proven influenza

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<thead>
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<th>Population</th>
<th>Adjusted Vaccine Effectiveness (95% confidence interval)</th>
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<tr>
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<td>37% (12 to 55%)</td>
</tr>
</tbody>
</table>
Vaccination: indirect effects

- Cluster RCT of vaccination in Hutterite colonies
  - Vaccination of children 3 to 15 years

  49 colonies included
  - 25 colonies randomised to receive TIV influenza vaccine
    - 502 children received vaccine
    - 1773 included in primary analysis
  - 24 colonies randomised to receive HepA vaccine
    - 445 children received vaccine
    - 1500 included in primary analysis

Loeb M et al JAMA 2010
Vaccination: indirect effects

Laboratory proven influenza in child or adult not receiving study vaccine

Protective effectiveness of vaccination

Loeb M et al JAMA 2010
WA preschool influenza program

Flu kills three young children

PETA KOLE and DEBBIE GUEST

Three children have been killed by the flu in Perth in the past few days, prompting experts to issue an urgent warning that parents should take their children to the doctor as soon as they show signs of the illness.

The three children were all under five and lived in the metropolitan area. It is understood each of them died within 24 hours of showing the first signs of the flu, which doctors say was a form of the common influenza A strain. They warned that listlessness, cough and fever were the key symptoms parents should look for and urged them to seek medical advice immediately.

“While we do not want to create unnecessary panic, it is important for parents to be aware that the disease can cause serious illness within 24 hours,” Health Department director of communicable diseases control Paul Van Beynder said last night.

Two of the deaths were at Princess Margaret Hospital and at least two of the children had also contracted pneumonia as a result of the virus, which could have contributed to their deaths.

Doctors across the State have been warned that they may be inundated by worried parents, prompting the Health Department to advise them of the details of the deaths.

Australian Medical Association president Geoff Dobbs said influenza A strain was one of the most common during winter and that West Australians were particularly vulnerable because it had been several years since the last flu epidemic.

He said parents should not be worried if their children simply had a runny nose and headache, though they should look out for a fever above 38°C.

“The critical thing is the combination of a fever and a cough,” he said.

“What we’re talking about here is not just having a runny nose and feeling unwell, often people refer to that loosely as having the flu. A true influenza will make you feel really unwell, more severe with cough fever and muscular aches and pain.”

He said that unlike the flu, people with a cold may have sore throat and runny nose, followed by a cough, but without a significant fever.

Parents can call Health Direct on 1800 020 080 for advice and locations of their nearest after-hours clinic.

West Australian Newspaper: 7th July 2007
WA preschool influenza program

Little data demonstrating vaccine efficacy / effectiveness in children < 2 years
WAIVE

- Prospective incidence density case-control study
- Enrolling children with influenza-like illness:
  - Measured or history of temperature $\geq 37.5^\circ C$
  - At least one respiratory symptom
- Case – influenza test positive
- Control 1 – influenza test negative
- Control 2 – other virus detected
WA preschool influenza program

2008-09: vaccine uptake

<table>
<thead>
<tr>
<th></th>
<th>2008</th>
<th>Laboratory confirmed influenza (95% confidence interval)</th>
<th>Influenza related hospitalisations (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fully vaccinated</td>
<td>51%</td>
<td>51% (-21% to 80)</td>
<td>83% (-54 to 98%)</td>
</tr>
<tr>
<td>Partially vaccinated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unvaccinated</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Dixon G et al, IoRV 2010; Kelly H et al, PIDJ 2011
2010: a problematic year

Under-5s will get free vaccine to combat flu

CATHY O'LEARY
MEDICAL EDITOR

WA children under the age of five will be offered a free vaccine against three strains of influenza, including human swine flu, as health authorities try to prevent a repeat of last year's high rate of serious illness in the very young.

The Health Department has confirmed authorities will fund the vaccine because of concerns that babies, toddlers and pre-schoolers are at highest risk of developing serious illness from the flu this winter.

Last year, 130 children under the age of five were admitted to WA hosptals suffering complications from seasonal flu or the pandemic H1N1 strain. Children in that age group had young children who were at highest risk of becoming seriously ill from the flu.

This year's seasonal flu vaccine would protect against the swine flu strain which emerged last year as well as two additional strains expected to cause illness this winter.

"The data from last year indicates that right across Australia more children are once again providing free seasonal influenza vaccine to all children aged six months to four years.

"WA is the only State taking this proactive approach to help make sure one of our most vulnerable groups has ready access to influenza vaccine."

Dr Effer said parents should contact their doctor or health care continue to be available for school-age children through their doctors. Parents, which only protects against the H1N1 virus, is still available from GPs for all adults and children aged six months and over.

But it is estimated that only 1.3 per cent of the population has been vaccinated.

Last winter, 4,549 West Australians
2010: a problematic year

R56 febrile convulsions: 9 emergency departments

T88.8 other vaccination reactions: 9 emergency departments
2010: a problematic year

8th March 2010: Trivalent vaccine launched

13th April 2010: TGA notified

Reports of children requiring admission with ‘sepsis’ or fever following trivalent influenza vaccine

Reports of febrile convulsions presenting to ED follow TIV

22nd April 2010: Health Department suspends preschool influenza vaccination program
Not all vaccines are equal

- All febrile convulsions (R56 and non-R56 coded) in WA were reported following Fluvax® or Fluvax Junior®

<table>
<thead>
<tr>
<th>Age</th>
<th>Fluvax or Fluvax Junior</th>
<th>Influvac</th>
<th>Compared</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>Rate per 1000 doses</td>
<td>n/N</td>
</tr>
<tr>
<td>&gt;5 yrs</td>
<td>62/14096</td>
<td>4.4 (3.4-5.6)</td>
<td>0/4720</td>
</tr>
</tbody>
</table>

Armstrong PK et al. BMJ Online 2011
Not all vaccines are equal

- WA Central Immunisation Clinic survey

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Fluvax or Fluvax Junior</th>
<th>Influvac</th>
<th>Odds ratio</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>56.5%</td>
<td>17.3%</td>
<td>5.1 (2.9-9.2)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Fatigue</td>
<td>33.0%</td>
<td>10.9%</td>
<td>3.5 (1.8-7.0)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Vomiting</td>
<td>17.2%</td>
<td>2.7%</td>
<td>6.0 (1.8-20.3)</td>
<td>0.0037</td>
</tr>
<tr>
<td>Rigors</td>
<td>15.3%</td>
<td>0.9%</td>
<td>16.0 (2.1-119.5)</td>
<td>0.0070</td>
</tr>
<tr>
<td>Swelling</td>
<td>12.9%</td>
<td>10.9%</td>
<td>1.1 (0.5-2.3)</td>
<td>0.7914</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>5.3%</td>
<td>0.9%</td>
<td>5.3 (0.7-43.0)</td>
<td>0.1160</td>
</tr>
<tr>
<td>Rash</td>
<td>3.8%</td>
<td>0.9%</td>
<td>3.8 (0.5-31.2)</td>
<td>0.2193</td>
</tr>
<tr>
<td>Headache</td>
<td>3.4%</td>
<td>0.9%</td>
<td>4.3 (0.5-37.5)</td>
<td>0.1843</td>
</tr>
<tr>
<td>Convulsions</td>
<td>1.4%</td>
<td>0.0%</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Armstrong PK et al. BMJ Online 2011; Blyth CC et al. Vaccine 2011
2010: later that year

“Children under 5 years of age can now be vaccinated against influenza using Vaxigrip® or Influvac® seasonal influenza vaccine.”
Post 2010

2008-09: vaccine uptake

- Fully vaccinated
- Partially vaccinated
- Unvaccinated

2010-12: vaccine uptake

- Fully vaccinated
- Partially vaccinated
- Unvaccinated
Finding solutions

What was the problem?
Does the vaccine work?
Is the vaccine safe?
What is being done about adverse events following immunisation?
What else can be done?

Fevers, fits, brain damage… by the time the seasonal flu vaccine was banned for kids under five last year, its side-effects were being felt around the country. So what went wrong? Natasha Bita reports.
What was the problem?

- Partially unsplit products are more reactogenic compared with other split influenza vaccines
- Two new viruses with CSLs novel splitting process resulted in an increased volume of partially split products
- Although first noted in 2010, this is not restricted to 2010
Does the vaccine work?

- Population: Children 6-59 months
- Years: 2008-2012 (2009 excluded)
- Methods: Test negative design
- Endpoint: PCR proven influenza

<table>
<thead>
<tr>
<th>Population</th>
<th>Test negative controls</th>
<th>Other virus detected controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>All children</td>
<td>64.7% (33.7 to 81.2%)</td>
<td>65.8% (32.1 to 82.8%)</td>
</tr>
<tr>
<td>Children &lt; 2 years</td>
<td>85.8% (37.9 to 96.7%)</td>
<td>85.5% (34.7 to 96.8%)</td>
</tr>
<tr>
<td>Children ≥ 2 years</td>
<td>52.1% (-0.1 to 77.1%)</td>
<td>55.0% (-3.6 to 80.5%)</td>
</tr>
</tbody>
</table>

2013: unadjusted vaccine effectiveness: 64%

Blyth CC et al, IDWeek 2013; Manuscript submitted
Is the vaccine safe?

- The Western Australian Children’s Follow up and Active Surveillance of Trivalent influenza vaccine (FAST) Study
  - Rheola Street Immunisation Clinic and PMH
  - Children 6 – 59 months receiving TIV
  - Parental questionnaire after 72-120 hours

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>0%</td>
</tr>
<tr>
<td>Rigors</td>
<td>0%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0%</td>
</tr>
<tr>
<td>Rash</td>
<td>0%</td>
</tr>
<tr>
<td>Local AE</td>
<td>0%</td>
</tr>
</tbody>
</table>

n = 685
### What is being done about AEFI?

#### National Initiatives
- National review (Horvath)
- Australian Committee of the Safety of Vaccines
- Improved TGA processes
- Active Surveillance for adverse events following the introduction of new vaccines

#### State Initiatives
- State review (Stokes)
- WA Vaccine Safety Advisory Committee
- WA Vaccine Safety Surveillance system
- Adult and paediatric adverse events clinics established
- Active Surveillance

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Clear lines of communication between states / commonwealth
What is being done about AEFI?

What else can be done?

- Parents who discuss influenza immunisation with their vaccine provider are 10 times more likely to immunise their children (WAIVE 2008-2012)

2008-09: Provider recommendation

2010-12: Provider recommendation

- Recommended for
- Recommended against
- No specific advice
The future

- Quadrivalent vaccines
- Adjuvanted vaccines
- Live attenuated vaccines
Quadrivalent vaccines

Since 1985, two antigenically distinct lineages of influenza B have circulated globally.
Adjuvanted vaccines

- The immune response to inactivated influenza vaccine is lower in those at greatest risk of severe disease
- Options: Increase haemagglutinin or Adjuvants

<table>
<thead>
<tr>
<th>Adjuvant</th>
<th>Immunostimulatory component</th>
<th>Mode of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alum</td>
<td>Aluminum salts</td>
<td>Increased attraction and uptake of APCs; Activation of inflammasome complex with increased efficiency of innate immunity</td>
</tr>
<tr>
<td>Oil in water emulsions MF59 AS03</td>
<td>Squalene Squalene + a tocopherol</td>
<td>Innate inflammatory responses; increased attraction and uptake of APCs; increased antigen persistence at injection site and presentation to immune-competent cells</td>
</tr>
<tr>
<td>Virosomes</td>
<td>Virosomes</td>
<td>Stronger interaction with B lymphocytes and APCs with a strong TH1 response</td>
</tr>
</tbody>
</table>
Live attenuated vaccines

- Cold-adapted, temperature sensitive, attenuated influenza virus (will not replicate at body temperature)

Advantages of LAIV
- Invokes mucosal and systemic immunity
- Greater protection against mismatched strains

Not recommended for:
- Children < 2 years
- Adults (>49 years in US; > 18 years in Europe)
- History of bronchospasm
Conclusions

- Influenza remains a significant pathogen in Australia
- Vaccination is the most effective preventative strategy
- Vaccination has both direct and indirect effects
- Influenza vaccine in young children is both effective and safe
- Further work is required to improve the effectiveness of influenza vaccines
Acknowledgments

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All staff from the Emergency, DPAM and Microbiology Departments of PMH.

All staff from PathWest Laboratory Medicine, WA, involved in processing and reporting study samples.

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