Influenza

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Director, Infection Prevention and Healthcare Epidemiology Unit, Alfred Health
Outline

Influenza surveillance; transmission, severity and impact

Summary of 2017 season; vaccine coverage and effectiveness

Influenza A/H3 vaccine problems

New strategies to reduce burden of influenza
   New vaccines
   Paediatric immunisation programs
   Staff vaccination

Vaccine safety
   Active surveillance for adverse events following immunisation (AEFI)
   Systematic review of flu vaccines in pregnancy
Surveillance pyramid

- **Deaths**
  - Notified deaths
  - NSW influenza/pneumonia
  - FluCAN hospital mortality

- **ICU**
  - FluCAN
  - FluCAN-PAEDS

- **Hospitalisations**
  - FluCAN
  - FluCAN-PAEDS
  - EpiLog (Qld)

- **Emergency department**
  - NSW, WA ED ILI surveillance

- **Primary care**
  - Sentinel GP surveillance systems
  - Notification data (NNDSS)

- **Mild respiratory tract symptoms**
  - FluTracking
  - Call centre data
  - Absenteeism

- **Asymptomatic illness**
21 hospitals (incl 6 paediatric hospitals)

17 hospitals used for surveillance

All states/territories

Metropolitan/regional

Temperate/tropical

>14% of national bed capacity

(TSANZ/ASID collaboration 2009)
Incidence density test-negative

Case = influenza
Control = non influenza ILI matched for date of presentation
Case/control status assigned when test result known
Adjust for confounders

“Exposure”
Vaccinated
Not vaccinated

“Outcome”
Flu
Non flu ILI
2017 season

4259 cases at surveillance hospitals (excluding 4 PAEDS sites - >2x 2016)

78% chronic comorbidities
31% influenza B

(~31 000 admissions nationally)

Mortality 155/4236 (3.7%)
Severity – proportion admitted to ICU

Overall 8.7%
Paediatric 10.1%
Non-elderly adults 11.1%;
Elderly 6.3%
Indigenous Australians (10.0%)
Pregnant women (8.7%).
Patients admitted with acute respiratory symptoms at sentinel sites

All lab-confirmed influenza (n=4974)

Sample of test negative patients (n=2264)

Vaccination status not ascertained (n=1228)

Vaccination status not ascertained (n=493)

Vaccination status ascertained (n=3746)

Vaccination status ascertained (n=1771)
Vaccine coverage

![Bar chart showing vaccine coverage by age group and comorbidity status.

- For age group <18 years:
  - No comorbidities: 17%
  - Comorbidities: 53%

- For age group 16-64 years:
  - No comorbidities: 76%
  - Comorbidities: 61%
Vaccine effectiveness (reduction in risk of hospitalisation in vaccinated compared to unvaccinated)
Historical context

All types

<table>
<thead>
<tr>
<th>year</th>
<th>VE (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2011</td>
<td>0.40 (0.02, 0.64)</td>
<td>2.78</td>
</tr>
<tr>
<td>2012</td>
<td>0.38 (0.23, 0.51)</td>
<td>14.13</td>
</tr>
<tr>
<td>2013</td>
<td>0.50 (0.33, 0.63)</td>
<td>11.61</td>
</tr>
<tr>
<td>2014</td>
<td>0.50 (0.40, 0.59)</td>
<td>30.93</td>
</tr>
<tr>
<td>2015</td>
<td>0.49 (0.38, 0.58)</td>
<td>29.03</td>
</tr>
<tr>
<td>2016</td>
<td>0.19 (0.02, 0.32)</td>
<td>11.51</td>
</tr>
<tr>
<td>Subtotal (I-squared = 66.2%, p = 0.011)</td>
<td>0.44 (0.39, 0.49)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Elderly

<table>
<thead>
<tr>
<th>year</th>
<th>VE (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011</td>
<td>0.41 (-0.62, 0.79)</td>
<td>1.53</td>
</tr>
<tr>
<td>2012</td>
<td>0.36 (0.11, 0.54)</td>
<td>17.06</td>
</tr>
<tr>
<td>2013</td>
<td>0.53 (0.22, 0.71)</td>
<td>12.46</td>
</tr>
<tr>
<td>2014</td>
<td>0.49 (0.31, 0.62)</td>
<td>32.79</td>
</tr>
<tr>
<td>2015</td>
<td>0.42 (0.23, 0.56)</td>
<td>29.25</td>
</tr>
<tr>
<td>2016</td>
<td>-0.21 (-0.59, 0.08)</td>
<td>6.90</td>
</tr>
<tr>
<td>Subtotal (I-squared = 67.5%, p = 0.009)</td>
<td>0.40 (0.31, 0.49)</td>
<td>100.00</td>
</tr>
</tbody>
</table>
Summary of 2017 season

2017 was a big flu season for hospitals
A/H3N2 and B/Yamagata dominant strains
Much higher activity than 2014, 2015, 2016

Vaccination in 2017
Small reduction in the risk of hospitalisation with influenza.
Estimated vaccine effectiveness: 23% (95% CI: 9%, 35%) – similar to 2016 but much less than 2015

Based on point estimates, VE:
Higher in non-elderly adults (50%) than the elderly (7%)
Higher in A/H1 (51%) and influenza B (26%) than A/H3 (21%).
Limitations

Likely underestimate of true influenza burden
Much greater burden when estimating excess admissions/mortality

Observational case control study
Potential selection biases
Misascertainment
Unmeasured confounding
The “perfect storm”

A/H3 subtype predominating
Tends to affect elderly
Genetically diverse subtype compared to A/H1 and B

Egg adaptation of H3 vaccine strain
Fewer vaccine candidates
Difficult to match against diverse H3 strains

Poorly protective vaccine-induced antibodies
Vaccine poorly immunogenic in high risk groups
A/H3 vaccine issues
H3N2 diversity

Significant genetic diversity within H3N2 circulating strains

Various clades – recent strains in 3C.2a1

Recent diversification in 2a1 clade

Hong Kong vaccine strain (2016-17)

Singapore vaccine strain (2018)

3C.2a1 clade
H3 vaccine issues

K160T glycosylation site in H3 clade 3C.2a strains

Emerged 2014/15, now common

Impaired binding of antibodies from egg grown vaccine strains (adapted strains - not glycosylated)

Zost PNAS 2017
Repeated vaccination

Vaccination serially correlated

Mixed results – some studies demonstrate impaired vaccine protection with repeated doses

Potential for confounding by natural infection

No evidence of impaired VE in FluCAN

Cheng CID 2017
Policy options to control influenza

Access to better vaccines for elderly

Improve vaccine coverage, esp high risk groups
Elderly
Comorbidities
Pregnancy
Young children

Herd protection

Use antivirals

Prevent pneumonia?
New vaccines for elderly – FluZone HD

4x antigen content of standard IIV

TIV (not QIV)

Evidence of increased protection in RCT
24% more effective than TIV

Single season

Also protection demonstrated against non-specific endpoints eg pneumonia

24% represents relative protection
If standard vaccine 40% effective, expect 50% effectiveness with new vaccine

DiazGrandos NEJM 2014
New vaccines for elderly - Flud

MF59 adjuvanted vaccine

Also TIV (not QIV)

Evidence of increased protection in observational study
Hospitalisation with influenza
17% more effective than TIV
Multiple seasons

Original Contribution
Effectiveness of Adjuvanted Influenza Vaccination in Elderly Subjects in Northern Italy


* Correspondence to Dr. Salvatore Mannino, O.R. Villa Sofia—Cervello, Viale Stasburgo, 233, 90146 Palermo, Italy (e-mail: salvatore.mannino@villasofia.it).

Mennino AJE 2012
Herd protection

Immunisation protects individual as well as community
Local level – households and closed communities
Community level – reducing public health burden

Who should we target with vaccination?
Elderly
Individuals with chronic medical comorbidities
Children? (WA, Qld, NSW, Vic, ACT, Tas in 2018)
Healthcare workers and other contacts of high risk people?
UK paediatric influenza program

Paediatric program gives both direct and indirect protection

Greater effect if more children vaccinated (and if uptake rapid)

May be more cost effective than vaccinating elderly

Hodgson Lancet Pub Health 2017
Current estimated paediatric coverage
Active surveillance systems to detect common and less common adverse events following vaccination. SMS/email based follow up

Complements other adverse event reporting systems – spontaneous reports, linkage studies

**Cumulative Participation**
From 1 April 2017

- **Enrolled**: 102,663
- **Participants**: 73,560 (71.7%)
- **Any reaction**: 4,857 (6.6%)
- **Medically attended**: 299 (0.4%)
<table>
<thead>
<tr>
<th>Reaction</th>
<th>6 months - 4 years</th>
<th>5 years - 64 years</th>
<th>≥65 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any reaction</td>
<td>517/6,155 (8.4%)</td>
<td>2,534/37,363 (6.8%)</td>
<td>1,688/28,050 (6.0%)</td>
</tr>
<tr>
<td>Fever</td>
<td>138/5,957 (2.3%)</td>
<td>340/36,097 (0.9%)</td>
<td>210/27,121 (0.8%)</td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>157/5,957 (2.6%)</td>
<td>831/36,097 (2.3%)</td>
<td>431/27,121 (1.6%)</td>
</tr>
<tr>
<td>Rash</td>
<td>31/5,957 (0.5%)</td>
<td>75/36,097 (0.2%)</td>
<td>70/27,121 (0.3%)</td>
</tr>
<tr>
<td>Seizure</td>
<td>0/5,957 (0.0%)</td>
<td>0/36,097 (0.0%)</td>
<td>2/27,121 (0.01%)</td>
</tr>
<tr>
<td>Other reaction</td>
<td>213/5,957 (3.6%)</td>
<td>893/36,097 (2.5%)</td>
<td>549/27,121 (2.0%)</td>
</tr>
<tr>
<td>Medical advice</td>
<td>36/5,957 (0.6%)</td>
<td>68/36,097 (0.2%)</td>
<td>31/27,121 (0.1%)</td>
</tr>
<tr>
<td>Medical attendance</td>
<td>58/6,155 (0.9%)</td>
<td>159/37,363 (0.4%)</td>
<td>72/28,050 (0.3%)</td>
</tr>
</tbody>
</table>

**Median age (range)**
- Female: 196/299 (65.6%)
- Pregnant: 10/299 (3.3%)

**Brand**
- Afluria Quad: 16/299 (5.4%)
- Fluarix Tetra: 122/299 (40.8%)
- FluQuadri: 112/299 (37.5%)
- FluQuadri Junior: 46/299 (15.4%)
- Fluarix: 2/299 (0.7%)
- Influvac: 1/299 (0.3%)

**Reaction**
- Fever: 79/164 (48.2%)
- Injection site reaction: 82/164 (50.0%)
- Other: 126/164 (76.8%)

**Medical attendance type**
- GP: 88/108 (81.5%)
- ED: 20/108 (18.5%)
- Hospitalised: -
- Concomitant vaccine: 83/299 (27.8%)
Healthcare workers

Alfred Health (all campuses) 2012-17

81%
Conclusions

**Vaccine effectiveness moderate at best**

**Vaccine match issues persist**

**Available tools to reduce impact of influenza**

Improve vaccine coverage esp in vulnerable groups

More immunogenic vaccines. FluZone HD, Fluad in 2018 – marginal benefit over QIV

Childhood immunisation

**Research required**

Evaluate effectiveness of new vaccines

Determine whether alternative vaccine platforms may reduce adaptation problems

Universal flu vaccine
Acknowledgements

FluCAN investigators
Dominic Dwyer
Mark Holmes
Louis Irving
Grant Waterer
Tony Korman
Louise Cooley
Anna Howell
Deb Friedman
Peter Wark
Graham Simpson
John Upham
Simon Bowler
Sanjaya Senenayake
Tom Kotsimbos
Paul Kelly

FluCAN is funded by the Commonwealth Department of Health
PAEDS-FluCAN sites are funded by a NHMRC Partnership Grant
Thanks to Jill Garlick, Janine Roney and study staff at each site

PAEDS/AusVaxSafety
Kristine Macartney
Christopher Blyth
Helen Marshall
Julia Clark
Josh Francis
Jim Buttery

Infection Prevention Unit, Alfred Health
Pauline Bass
Kristine Heinrich- Morrison
Sue McLellan
Jonathan Chrimes

Systematic review
TGA, OHP, NCIRS
Michelle Giles, Sush Krishnaswamy
Alternate Vax
Dont get Trumped by the Flu

Just give me the vax.