Protecting the vulnerable in health care
Who is vulnerable?

- Health workers - high risk of disease
- Health care workers aOR of 2.14 (95%CI: 1.25-3.66) of being an outpatient influenza case
- Patients - high risk of disease and complications
- Risk groups
- Hospitals - sites of outbreaks. Attack rates 25%.

Pregnant women

• Higher risk for hospitalization in pregnant versus non-pregnant patients (odds ratio [OR] 2.44, 95% CI 1.22-4.87)

• No significant difference in mortality (OR 1.04, 95% CI 0.81-1.33) or other outcomes.

• Ecologic studies confirmed the association between hospitalization risk and pregnancy and 4 of 7 studies reported higher mortality rates in pregnant women.

Foetal outcomes in vaccinated pregnant women

- A review of 19 cohort studies.
- The use of vaccines during any period of pregnancy was associated with lower risk of stillbirth (adjusted hazard ratio 0.80, 95% confidence interval 0.69-0.92).
- No significant differences were found between the vaccinated versus unvaccinated groups in terms of the risks of spontaneous abortion, premature birth, and small for gestational age.

Obesity

- Not recognised as a risk factor until 2009
- Analysis of seasonal data confirms risk
- Effect of seasonal influenza 19% greater in obese individuals than normal-weight individuals (HR, 1.19; 95% CI, 1.01-1.42).

Chronic diseases and immunosuppression

- Asthma, COPD
- Renal
- Diabetes
- Cardiac
- Malignancy
- Immunosuppression
• PPE
• New influenza vaccines for the elderly
Relevant disciplines for IPC

PPE decision-making

Hospital Infection control

Patient safety

Occupational Health and Safety

Responder safety
Infection prevention

- Removing the worker from the hazard (principle of having focused locations, such as treatment units, and personnel dedicated to treating the infectious disease)
- Drugs
- Vaccines
- Pre-exposure prophylaxis
- Post-exposure prophylaxis
- Non-pharmaceutical interventions
  - Surveillance and early detection
  - Contact tracing and screening
  - Cohorting and environmental controls
  - Hand hygiene
  - Personal protective equipment
    - Masks, respirators
Fig. 3. Emergency Department (metropolitan Perth) attendances with influenza-like illness by week for June to December 2009 (compared with 2007 and 2008).
Respiratory protection

- PPE is only a part of the hierarchy of controls
- Respiratory protection is part of PPE
- All PPE is important
- PPE must be tailored to the hazard - think of routes of transmission
Contact, droplet, airborne

- An artificial paradigm that has driven hospital infection control practice for >60 years.
- Belief that only large droplets are emitted close to the patient, and small droplet nuclei at a greater distance.
- Based on experiments of aerobiologists from 1940’s and 50’s using.
- Newer research shows both small and large droplets can be present close to the patient*

Transmission of respiratory infections

- Contact, fomite spread

- Droplet, aerosol, airborne
Health workers and infections

• Health workers known to be at risk all infections - influenza (25% attack rate), meningococcal, measles, VHF.

Dogma vs clinical complexity

- Pathogens are recognised as having predominant modes of transmission
- But transmission rarely unimodal
- Relative contribution of different modes hard to quantify
- Experimental data do not account for complexities in the clinical setting nor inter-host variation

- Influenza - predominantly droplet,
  - but numerous studies show airborne,
  - contact and other transmission.
Other modes of influenza transmission

- Self-contamination through hand-to-nose, hand-to-eye, hand-to-mouth transmission
- Direct contact
- Indirect contact
- Small particle transmission at several metres (aerosol)
Surgical masks

- Designed to protect surgical wounds from infection.
- 3 RCTs showed no efficacy against original purpose
- Not designed as respiratory protection
- No fit or seal, significant leakage, poor filtration
- No regulation of quality

Respirators

• Designed for gas, chemicals and infections

• **Air purifying** (can be disposable filtering facepiece half-mask respirators - N95, re-usable, half mask, full face or powered air-purifying respirator - PAPR) - require cartridges, batteries.

• **Supplied air** (not generally used for infectious diseases)
Examples of respirators

- PAPR
- Full face respirator
- Half face elastomeric respirator
- Disposable N95
N95 respirators

• Specifically designed as respiratory protection
• Superior filtration capacity (defines N95 status)
• Designed to fit, seal and prevent leakage around the face
• Protection factors that were 8 to 12 times greater than those of medical masks \(^{(4,5)}\)
• Must be fit tested
• Wide variation in quality of available N95s

Fit testing
Current evidence around efficacy of masks/respirators

- Some evidence around efficacy of masks and respirators
- Most studies are in-vivo or observational and carried out during outbreaks and pandemic situations
- 5 RCTs were conducted in healthcare setting to examine efficacy of masks and respirators
- 3 RCTs compared N95 respirators and medical masks
- No RCTs have compared respirators with masks for TB, Ebola or other infections
- No RCTs on PAPRs
## 5 HCW RCTs

<table>
<thead>
<tr>
<th>Author, year</th>
<th>N HCWs, country</th>
<th>Interventions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jacobs 2009</td>
<td>32 Japan</td>
<td>Medical masks Control</td>
<td>NS</td>
</tr>
<tr>
<td>Loeb 2009</td>
<td>446 Canada</td>
<td>Medical masks, targeted N95, targeted</td>
<td>NS</td>
</tr>
<tr>
<td>MacIntyre 2011</td>
<td>1441 China</td>
<td>Masks N95 respirators, fit tested N95 respirators, non-fit tested Control</td>
<td>N95 protective</td>
</tr>
<tr>
<td>MacIntyre 2013</td>
<td>1669 China</td>
<td>Medical Mask N95, continuous N95, targeted</td>
<td>N95 protective</td>
</tr>
<tr>
<td>MacIntyre 2014</td>
<td>1441 China (bacterial outcomes)</td>
<td>Medical Masks N95 respirators, fit tested N95 respirators, non-fit tested Control</td>
<td>N95 protective</td>
</tr>
<tr>
<td>MacIntyre 2015</td>
<td>1607 Vietnam</td>
<td>Medical masks Cloth masks Control</td>
<td>Medical masks protective</td>
</tr>
</tbody>
</table>
Observed attack rates

MacIntyre et al 2011
A Randomized Clinical Trial of Three Options for N95 Respirators and Medical Masks in Health Workers

C. Raina MacIntyre, Quanyi Wang², Holly Seale¹, Peng Yang², Weixian Shi², Zhanhai Gao¹, Bayzid Rahman¹, Yi Zhang², Xiaoli Wang², Anthony T. Newall¹, Anita Heywood¹, and Dominic E. Dwyer³

Am J Respir Crit Care Med Vol 187, Iss. 9, pp 960–966, May 1, 2013

Figure 2. Adjusted and unadjusted Kaplan-Meier survival curves for CRI and bacteria detection for the three intervention arms. Adjusted for all variables included in the multivariate Cox model and clustering (Table 3). CRI = clinical respiratory illness.
The efficacy of medical masks and respirators against respiratory infection in health workers. Influenza and Other Respiratory Viruses, 11 Aug 2017.
Cloth masks

• Most guidelines fail to discuss cloth masks, which are used widely in developing countries

• RCT of cloth masks vs surgical masks showed that cloth masks increase the risk of infection.


Risk analysis framework for making recommendations for respiratory protection of health workers

- OHS obligations
- Disease severity and case fatality rate
- Uncertainty around outbreak parameters or modes of transmission
- Modes/routes of transmission of the infection
- Availability prevention or treatment (vaccines, post-exposure prophylaxis or drugs)
- Equity and consistency with recommendations for other exposed groups (e.g., laboratory staff)
- Cost, supply, logistics
Principles of PPE

• PPE should be appropriate to mode of disease transmission and occupational hazard,
• Removal of PPE must be done safely, and observed (risk of contamination)
• Removal (doffing) poses the highest risk of self-contamination
• Order of donning (dressing) determines risk of doffing
• Clothing used in treatment room must not be taken home
• Comfort, breathing, heat stress and duration of tolerability are a problem
PPE

- All skin, hair and mucous membranes should be covered.
- Water-resistant materials
- Double gloves
- Gown or suit
- Apron
- Boots or rubber shoes with shoe/boot covers to knee
- Head and neck cover
- Goggles or face shield
- Surgical scrubs
- Order of donning and doffing matters
Donning PPE

1. Apply boot covers. 2. Surgical cap. and 3. Surgical gown. NOTE: ALL TIES should be properly secured with a SIMPLE BOW. Ensure all fit well and cover the intended areas.
4. Perform hand hygiene.

- Headcovers which covered more of the neck and tie at the lower rear neck were identified. 5. The ties for the head and neck covers cross in front and then tie a bow in the back. It is worn under the gown. 6. The mask and face shield are worn over it. 7. Ensure the faceshield and headcover overlap to protect the forehead.
## WHO and CDC guidelines

<table>
<thead>
<tr>
<th></th>
<th>High risk HCW</th>
<th>Routine care HCW</th>
<th>Lab workers</th>
<th>High risk community</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pandemic influenza</strong></td>
<td>Respirator</td>
<td>Respirator (CDC)</td>
<td>Respirator</td>
<td>Mask</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mask (WHO)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Seasonal influenza</strong></td>
<td>Mask</td>
<td>Mask</td>
<td>Masks (rapid testing)</td>
<td>Masks</td>
</tr>
<tr>
<td><strong>MERS-CoV</strong></td>
<td>Respirator</td>
<td>Respirator (CDC)</td>
<td>?</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mask (WHO)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TB</strong></td>
<td>Respirator</td>
<td>Respirator</td>
<td>Respirator</td>
<td>Not recommended</td>
</tr>
</tbody>
</table>
Other PPE – gloves

- There is very little research on other types of PPE.
- The use of gloves is recommended when there are chances of contact with the blood and body fluids, including respiratory secretions.
- There is evidence of the transmission of virus from the contaminated hands and other surfaces.
- Gloves are single use and hand hygiene should be done after gloves removed.
- Double gloves are also recommended in some high risk situations (e.g. Ebola) to protect wearer and aid in safer doffing.


Other PPE – goggles, cap and boots

• Goggles are used to protect the transmission of microorganism into the eyes from the contaminated hands or transferring of infection from the eyes to others
• Face shield can be used instead of goggles
• Boot are recommended in certain situations.
  • Rubber boots/ or shoes covers are recommended for Ebola
  • Chemical-resistant Boots, steel toe and shank are recommended in event of a bioterror attack

Summary

• In many situations, drugs and vaccines are unavailable, delayed or in short supply
• Non-pharmaceutical means of infection control are just as effective and need to be used
• These include social distancing, hospital infection control, quarantine, hand hygiene and PPE.
• PPE is only one measure
• Donning and doffing is critical
• Understanding modes of transmission of infections assists with choice of PPE
• Mode of transmission is not the only consideration - need a risk analysis framework
Masks for source control

- Rates of clinical respiratory illness (relative risk (RR) 0.61, 95% CI 0.18 to 2.13), ILI (RR 0.32, 95% CI 0.03 to 3.13) and laboratory-confirmed viral infections (RR 0.97, 95% CI 0.06 to 15.54) were lower in the mask arm compared with control, although not statistically significant.

- A post hoc comparison between the mask versus no-mask groups showed a significant protective effect against clinical respiratory illness, but not against ILI and laboratory-confirmed viral respiratory infections.

Influenza Vaccines
Influenza and ischaemic heart disease

Influenza virus infection

- Tachycardia
- Hypoxia
- Acute inflammation
- Cytokine release
- Vasoconstriction
- Effect on receptors
- Coronary plaque disruption
- Thrombogenesis

Atherosclerosis

Acute myocardial infarction

Influenza infection and AMI diagnosis

**Study ID**
- Guan et al, 2012: influenza A
- Guan et al, 2012: influenza B
- MacIntyre et al, 2013
- Ponka et al, 1980
- Warren-Gash et al, 2013
- Subtotal (I-squared = 82.5%, p = 0.000)

**Influenza infection (lab diagnosis) vs AMI**

<table>
<thead>
<tr>
<th>Study ID</th>
<th>OR (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guan et al, 2012: influenza A</td>
<td>5.50 (1.30, 23.27)</td>
<td>3.47</td>
</tr>
<tr>
<td>Guan et al, 2012: influenza B</td>
<td>20.30 (5.60, 73.59)</td>
<td>4.05</td>
</tr>
<tr>
<td>MacIntyre et al, 2013</td>
<td>1.97 (1.09, 3.56)</td>
<td>8.38</td>
</tr>
<tr>
<td>Ponka et al, 1980</td>
<td>0.37 (0.08, 1.75)</td>
<td>3.12</td>
</tr>
<tr>
<td>Warren-Gash et al, 2013</td>
<td>0.82 (0.34, 1.98)</td>
<td>6.22</td>
</tr>
<tr>
<td>Subtotal (I-squared = 82.5%, p = 0.000)</td>
<td>2.29 (0.74, 7.06)</td>
<td>25.25</td>
</tr>
</tbody>
</table>

**Influenza infection (ILI case definition) vs AMI**

<table>
<thead>
<tr>
<th>Study ID</th>
<th>OR (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mattila, 1989</td>
<td>2.99 (1.09, 8.21)</td>
<td>5.41</td>
</tr>
<tr>
<td>Ponka et al, 1980</td>
<td>1.15 (0.30, 4.41)</td>
<td>3.83</td>
</tr>
<tr>
<td>Warren-Gash et al, 2013</td>
<td>3.17 (0.61, 16.47)</td>
<td>2.86</td>
</tr>
<tr>
<td>Subtotal (I-squared = 0.0%, p = 0.491)</td>
<td>2.29 (1.11, 4.73)</td>
<td>12.10</td>
</tr>
</tbody>
</table>

**Influenza infection (RTI case definition) vs AMI**

<table>
<thead>
<tr>
<th>Study ID</th>
<th>OR (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clayton et al, 2005</td>
<td>0.92 (0.60, 1.41)</td>
<td>9.70</td>
</tr>
<tr>
<td>Clayton et al, 2008</td>
<td>2.55 (1.71, 3.80)</td>
<td>9.92</td>
</tr>
<tr>
<td>MacIntyre et al, 2013</td>
<td>1.98 (1.20, 3.27)</td>
<td>9.12</td>
</tr>
<tr>
<td>Meier et al, 1998</td>
<td>3.00 (2.10, 4.29)</td>
<td>10.24</td>
</tr>
<tr>
<td>Penttinen et al, 1996</td>
<td>1.77 (1.07, 2.93)</td>
<td>9.08</td>
</tr>
<tr>
<td>Spodick et al, 1984</td>
<td>2.15 (1.22, 3.80)</td>
<td>8.56</td>
</tr>
<tr>
<td>Warren-Gash et al, 2013</td>
<td>1.39 (0.56, 3.45)</td>
<td>6.03</td>
</tr>
<tr>
<td>Subtotal (I-squared = 69.9%, p = 0.003)</td>
<td>1.89 (1.35, 2.65)</td>
<td>62.65</td>
</tr>
</tbody>
</table>

**Overall (I-squared = 68.4%, p = 0.000)**

<table>
<thead>
<tr>
<th>OR (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.99 (1.45, 2.74)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

**NOTE:** Weights are from random effects analysis

---

Acute myocardial infarction and influenza: a meta-analysis of case-control studies.
Acute myocardial infarction and influenza: a meta-analysis of case-control studies.
Table 1  Efficacy of accepted coronary interventions and influenza vaccine in the prevention of myocardial infarction

<table>
<thead>
<tr>
<th>Coronary intervention</th>
<th>Prevention</th>
<th>Intervention efficacy/effectiveness against acute myocardial infarction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking cessation$^4 23–25$</td>
<td>Secondary</td>
<td>32–43</td>
</tr>
<tr>
<td>Statins$^{38}$</td>
<td>Secondary</td>
<td>19–30</td>
</tr>
<tr>
<td>Antihypertensive drugs$^{26–29 32}$</td>
<td>Secondary</td>
<td>17–25</td>
</tr>
<tr>
<td>Influenza vaccine$^5 9 18$</td>
<td>Secondary</td>
<td>15–45</td>
</tr>
</tbody>
</table>
Immunosenescence: age-based CMI decline and risk of HZ/PHN

Rate per 1000 per annum

HZ per 1000 per annum

PHN per 1000 per annum

Age (years)

Rate per 1000 per annum

0 10 20 30 40 50

60 70 80+

11

10

9

8

7

6

5

4

3

2

1

0

Levine M et al. CMI to VZV.
“Pneumonia is the old man’s friend”

- Demented frail elderly (73/144, 51%) less likely (OR 0.28, 95% CI 0.18-0.42, p<0.0001) to be vaccinated than non-demented (402/509, 79%).
- Patients >80 years less likely to be vaccinated (OR 0.69, 95% CI 0.47-1.02, p 0.052).
- Nursing home residents and staff less likely to be vaccinated
- Explosive outbreaks in nursing homes – Illness in residents and staff

Ridda, MacIntyre et al. Predictors of pneumococcal vaccination uptake in hospitalised patients aged 65 years and over shortly following the commencement of a publicly funded national pneumococcal vaccination program in Australia. *Human Vaccines*, 2007;3(3):57-60.
How is pneumonia anyone’s friend?....

- Communicable diseases impact more than the individual Transmission to others
- Individual suffering
- Closure of ACFs during outbreaks (economic impacts)
- Demented and frail elderly admitted to hospital with pneumonia
- Pneumonia can cause acute delirium and acute loss of autonomy and mental capacity
- Seniors are more vulnerable when acutely
Vaccine efficacy

• Vaccines in children are often >90% effective
  Vaccinologists think of vaccines as poor if efficacy is <80%
  • and totally unworthy if efficacy is <60%
• Yes, vaccines are less effective in the elderly.
• Is it appropriate to compare vaccines in the elderly to vaccines in infants?
• How do vaccines in the elderly compare to other accepted preventive strategies in public health?
Accepted prevention strategies in public health

• 30 years ago, having a myocardial infarction led to reduced life expectancy
• Today, with innovations such as rapid time from chest pain to catheter lab, early revascularisation and statins for lipid lowering, people with IHD can have a normal life expectancy.
• IHD is never referred to as “the old man’s friend” Statins have an efficacy as secondary prevention of
  • approximately 25% and are accepted worldwide
Vaccines in the elderly look good!

- In public health, accepted worthy preventive strategies often have efficacy of <25%
- Anti-hypertensive treatment has lower efficacy than statins in
  - prevention of IHD.
- Vaccines in the elderly look favourable when compared to statins
- A pneumococcal vaccine that prevents IPD or vaccine-type pneumonia is good news!
- A flu vaccine that protects against the strains it is matched for is good news!
Is efficacy the be all and end all?

Efficacy is not the full story! It is only part of the equation.

Public health benefit = burden of disease \times \text{preventive efficacy}
## IPD cases prevented

<table>
<thead>
<tr>
<th>Age group</th>
<th>Cases (n)</th>
<th>VE</th>
<th>Cases prevented</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>50</td>
<td>95</td>
<td>47</td>
</tr>
<tr>
<td>50-95</td>
<td>45</td>
<td>80</td>
<td>36</td>
</tr>
<tr>
<td>&gt;65</td>
<td>160</td>
<td>70</td>
<td>112</td>
</tr>
<tr>
<td>&gt;65</td>
<td>160</td>
<td>60</td>
<td>96</td>
</tr>
<tr>
<td>&gt;65</td>
<td>160</td>
<td>50</td>
<td>96</td>
</tr>
<tr>
<td>&gt;65</td>
<td>160</td>
<td>40</td>
<td>64</td>
</tr>
<tr>
<td>&gt;65</td>
<td>160</td>
<td>30</td>
<td>64</td>
</tr>
</tbody>
</table>

*A vaccine with lower efficacy can still have public health benefit if disease burden is high*
Vaccines for the frail elderly

• 2017 influenza season: VE 33% against influenza, 10% against H3N2, no effectiveness in older adults

• Effectiveness decreases with age

• Adjuvanted and high dose products available for >65 year age group.

FLUAD: MF59 OIL-IN-WATER ADJUVANTED SEASONAL INFLUENZA VACCINE

AN ENHANCED INFLUENZA VACCINE FOR OLDER ADULTS

For Scientific or Medical Use Only
First approved for use as an adjuvant in 1997, as part of aTIV®

MF59 is an oil-in-water emulsion composed of squalene, which is stabilised by Tween 80 and Span 85

Squalene

- Biodegradable and biocompatible oil
- Intermediate precursor in the cholesterol biosynthetic pathway
- Synthesised in the liver (>1g/day) and derived from dietary sources (50–200 mg/day)
- Single dose of FLUAD contains ~10 mg
Proposed MF59 Mode of Action at Injection Site

**Injection Site**
1. MF59 recruits immune cells

   - Antigen
   - Chemo attractants
   - Release
   - Recruit
   - Macrophages
   - Monocytes & Neutrophils
   - Increased antigen reuptake

2. Differentiates recruited immune cells into antigen presenting cells (APCs)

   - APCs
   - Increased APC migration

3. T-cell activation and B-cell expansion

   - Vaccine-specific Responses
     - T-cell activation
     - B-cell activation
     - Antibody release
     - Neutralising flu specific antibodies

---

Seubert et al., J Immunol, 2008; Schultze et al., Vaccine, 2008.
Calabro et al., Vaccine, 2011.
# Homologous Strains - Greater Differences in SC and GMT with aTIV vs Comparator TIV

## Non-inferiority – PPS GMT Ratio

<table>
<thead>
<tr>
<th>Strain</th>
<th>aTIV:TIV (95% CI)</th>
<th>Non-inferiority Bound</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1N1</td>
<td>1.40 (1.32-1.49)</td>
<td></td>
<td>3225 3257</td>
</tr>
<tr>
<td>H3N2</td>
<td>1.61 (1.52-1.70)</td>
<td></td>
<td>3225 3256</td>
</tr>
<tr>
<td>B</td>
<td>1.15 (1.08-1.21)</td>
<td></td>
<td>3227 3259</td>
</tr>
</tbody>
</table>

### Risk Ratio (95% CI)

- 0.5: Favors TIV
- 2.0: Favors aTIV
- 1.0: Non-inferiority Bound

## Non-inferiority – PPS Seroconversion

<table>
<thead>
<tr>
<th>Strain</th>
<th>aTIV – TIV (95% CI)</th>
<th>Non-inferiority Bound</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1N1</td>
<td>9.8% (7.5-12.1)</td>
<td></td>
<td>3225 3257</td>
</tr>
<tr>
<td>H3N2</td>
<td>13.9% (11.7-16.1)</td>
<td></td>
<td>3225 3256</td>
</tr>
<tr>
<td>B</td>
<td>3.2% (1.1-5.3)</td>
<td></td>
<td>3227 3259</td>
</tr>
</tbody>
</table>

### Percent Difference (95% CI)

- -20: Favors TIV
- 20: Favors aTIV

---

SC: Seroconversion  
GMT: Geometric Mean Titer  
PPS: Per Protocol Set  
### Heterologous Strains - Greater Differences in GMT and SC with aTIV vs comparator TIV

#### Non-inferiority – PPS GMT Ratio

<table>
<thead>
<tr>
<th>Strain</th>
<th>aTIV: TIV (95% CI)</th>
<th>aTIV</th>
<th>TIV</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>H3N2 (Brisbane)</td>
<td>1.45 (1.29-1.63)</td>
<td>834</td>
<td>814</td>
<td></td>
</tr>
<tr>
<td>H3N2 (Wisconsin)</td>
<td>1.36 (1.23-1.50)</td>
<td>834</td>
<td>815</td>
<td></td>
</tr>
<tr>
<td>B (Malaysia)</td>
<td>1.09 (0.98-1.21)</td>
<td>834</td>
<td>814</td>
<td></td>
</tr>
</tbody>
</table>

#### Risk Ratio (95% CI)

- **0.5** favors TIV
- **0.67**
- **1.0** favors TIV
- **1.5**
- **2.0** favors aTIV

#### Non-inferiority – PPS Seroconversion

<table>
<thead>
<tr>
<th>Strain</th>
<th>Percent Difference (95% CI)</th>
<th>aTIV</th>
<th>TIV</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>H3N2 (Brisbane)</td>
<td>11.9% (7.3-16.5)</td>
<td>834</td>
<td>814</td>
<td></td>
</tr>
<tr>
<td>H3N2 (Wisconsin)</td>
<td>11.5% (6.9-16.2)</td>
<td>834</td>
<td>815</td>
<td></td>
</tr>
<tr>
<td>B (Malaysia)</td>
<td>3.9% (0.0-8.3)</td>
<td>834</td>
<td>814</td>
<td></td>
</tr>
</tbody>
</table>

#### Percent Difference (95% CI)

- **-20**
- **-15**
- **-10**
- **-5**
- **0**
- **5**
- **10**
- **15**
- **20**

SC: Seroconversion  
GMT: Geometric Mean Titer  
PPS: Per Protocol Set

Pivotal Study: Safety Profile of aTIV and TIV

<table>
<thead>
<tr>
<th></th>
<th>Assessment Period</th>
<th>aTIV N=3,545</th>
<th>TIV N=3,537</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td></td>
<td>1.5%</td>
<td>1.3%</td>
</tr>
<tr>
<td>SAEs</td>
<td>Day 1-366</td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>AEs leading to withdrawal</td>
<td></td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Unsolicited AEs</td>
<td>Day 1-22</td>
<td>16%</td>
<td>16%</td>
</tr>
<tr>
<td>N=3,515</td>
<td></td>
<td>N=3,502</td>
<td></td>
</tr>
<tr>
<td>*Solicited AEs</td>
<td>Day 1-7</td>
<td>46%</td>
<td>33%</td>
</tr>
</tbody>
</table>

*Greater incidence of mild-moderate local and systemic AEs with aTIV vs TIV. Most were transient.

Effectiveness data supporting enhanced protection against Influenza and Influenza Related Outcomes

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Lombardi Influenza Vaccine Effectiveness (LIVE)</th>
<th>Canadian Comparative Effectiveness</th>
<th>Serious Outcomes Surveillance (SOS) Network</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Design</td>
<td>Prospective, observational</td>
<td>Test negative - community based case control study</td>
<td>Test negative – hospital based case control study</td>
</tr>
<tr>
<td>Outcome Measure</td>
<td>Hospitalisation due to influenza or pneumonia</td>
<td>PCR confirmed influenza</td>
<td>PCR confirmed influenza</td>
</tr>
<tr>
<td>Results</td>
<td>ATIV relative to TIV = 25% reduction in hospitalisation for influenza or pneumonia</td>
<td>aTIV VE = 35% (whole population) aTIV VE = 58% (multivariate)</td>
<td>aTIV VE ~ 61.3% (representing an increase of ~30% over TIV)[NS]</td>
</tr>
</tbody>
</table>

Characteristics of HD vaccine (Fluzone High-Dose, Sanofi)

- For 65+
- 4x antigen of standard dose vaccine
  - Single 0.5-mL dose; intramuscular
- Trivalent formulation
  - H3N2, H1N1 & one B strain
  - Quadrivalent under development
- Extensively studied: ~30 publications
- The most widely used influenza vaccine in 65+ in USA
  - ~60% of vaccinated 65+ received HD vaccine in 2016-17

Reference: Fluzone High-Dose vaccine [Product Information]. Australia: Sanofi Pasteur Inc.; 2018
Clinical development & registration milestones

1999:
- Concept development of HD

2000–2007:
- Pre-licensure studies (phase I, II & III)¹-³

2009:
- Licensure via FDA’s Accelerated Approval Program in USA
- Launch in 2009-10 season
- Commitment to post-licensure efficacy study

2009–2013:
- Post-licensure studies (phase IV)⁴,⁵

2015:
- Licensure in Canada

2017:
- Registration in Australia approved in Dec
- NACI statement


Abbreviations: FDA=Food & Drug Administration; NACI=Canada’s National Advisory Committee on Immunization; TGA=Therapeutic Goods Administration
Studies comparing the relative benefits
HD vaccine vs SD TIV in 65+

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Design</th>
<th>Studies (sample size)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease</td>
<td>RCT (gold standard)</td>
<td>Pivotal study by Sanofi(^1,2) (N≈32,000)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cluster RCT in nursing home by independent researchers(^3) (N≈53,000)</td>
</tr>
<tr>
<td></td>
<td>Cohort study</td>
<td>CDC/FDA/CMS study-a(^4) (N≈2.5 million)</td>
</tr>
<tr>
<td></td>
<td>(real world)</td>
<td>CDC/FDA/CMS study-b(^5) (N≈6.1 million)</td>
</tr>
<tr>
<td>Immunogenicity</td>
<td>RCT</td>
<td>Phase III study by Sanofi(^6,7) (N≈3,850)</td>
</tr>
</tbody>
</table>

Abbreviations: CDC=US Centers for Disease Control & Prevention; CMS=Centre of Medicare & Medicaid Services; FDA=Food & Drug Administration; RCT=randomised controlled trial; SD TIV=standard dose trivalent inactivated influenza vaccine

References
2. DiazGranados et al. Vaccine 2015;33:4988-93
6. Fluzone High-Dose Prescribing Information
Relative efficacy of HD vaccine to SD TIV

31,989 participants 65+ from 126 sites in USA & Canada

Relative Efficacy

- **Primary Endpoint**
  - Year 1 (2011-2012): 45.3
  - Year 2 (2012-2013): 20.7

- **Influenza A**: 23.6
- **Influenza B**: 27.4
- **Similar to Vaccine Strains**: 35.3

---

a Laboratory-confirmed influenza caused by any viral type or subtype (regardless of similarity) associated with a protocol-defined influenza-like illness. 
b Type A & B combined, similar to the vaccine strains by ferret antisera or genomic sequencing data.
Relative effectiveness of HD vaccine to SD TIV

Secondary endpoint post hoc analysis: serious events possibly related to influenza

* The % pneumococcal vaccination was 65% in both study groups. Therefore, HD vaccine effect on pneumonia was not due to differences of pneumococcal vaccination between groups.
Fewer SAEs observed in HD group than SD TIV group

Relative risk of SAE: 0.92 (95% CI 0.80-0.99)

<table>
<thead>
<tr>
<th></th>
<th><strong>HD Vaccine</strong>&lt;sup&gt;a&lt;/sup&gt; (N=15,992)</th>
<th><strong>SD TIV</strong>&lt;sup&gt;a&lt;/sup&gt; (N=15,991)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>(Number of participants)</strong></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>SAE</td>
<td>1323</td>
<td>8.3</td>
</tr>
<tr>
<td>Related SAE</td>
<td>3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.02</td>
</tr>
<tr>
<td>Death (any cause)</td>
<td>83</td>
<td>0.5</td>
</tr>
</tbody>
</table>

<sup>a</sup> Full analysis set (subjects categorized by vaccine received)  
<sup>b</sup> Related SAEs: HD vaccine group: left cranial nerve VI palsy (Day 1), hypovolemic shock with diarrhea (Day 1), & acute disseminated encephalomyelitis (ADEM; Day 117)
Cluster RCT in 823 nursing homes with 53,008 residents
Conducted by Stefan Gravenstein from Brown University

- Evaluating the relative effectiveness of HD vaccine to SD TIV against hospitalisations
  - 2013-14 season (mild; H1N1 predominant); 1:1 ratio for two vaccines

**Distribution of 823 Study Nursing Homes**

References
## Key results

*Gravenstein et al. Lancet Respir Med 2017*

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Relative effectiveness of HD vaccine vs SD TIV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary endpoint</strong></td>
<td></td>
</tr>
<tr>
<td>Respiratory-related hospitalisation</td>
<td>13% (95% CI 2% to 22%, p=0.02)</td>
</tr>
<tr>
<td><strong>Secondary endpoint</strong></td>
<td></td>
</tr>
<tr>
<td>Pneumonia hospitalisation</td>
<td>21% (95% CI 5% to 73%, p=0.013)</td>
</tr>
<tr>
<td>All-cause hospitalisation</td>
<td>9% (95% CI 3% to 14%, p=0.003)</td>
</tr>
<tr>
<td>All-cause death</td>
<td>2% (95% CI -4% to 7%, p=0.567)</td>
</tr>
</tbody>
</table>

*Abbreviations: CI=confidence interval; SD TIV=standard dose trivalent inactivated influenza vaccine*
Two large-scaled cohort studies in USA for 65+

Indepedently conducted by US authorities

<table>
<thead>
<tr>
<th>Study design</th>
<th>Izurieta et al. 2015</th>
<th>Shay et al. 2017</th>
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<tbody>
<tr>
<td></td>
<td>Retrospective cohort studies using administrative data (Medicare database in USA)</td>
<td></td>
</tr>
<tr>
<td>Seasons*</td>
<td>2012-13</td>
<td>2012-13 &amp; 2013-14</td>
</tr>
<tr>
<td>N of vaccinees</td>
<td>2.5 million</td>
<td>6.1 million</td>
</tr>
<tr>
<td>Endpoints</td>
<td>a. Probable influenza†</td>
<td>Post-influenza death‡</td>
</tr>
<tr>
<td></td>
<td>b. Influenza hospitalisation</td>
<td></td>
</tr>
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</table>

* H3N2 predominated 2012-13; H1N1 predominated in 2013-14
† Defined by receipt of a rapid influenza test followed by dispensing of neuraminidase inhibitor oseltamivir
‡ Death within 30 days following an inpatient or emergency department encounter coded as influenza (ICD-9)
Relative benefits consistent with pivotal study

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<td>2012-13</td>
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</tr>
<tr>
<td>N of vaccinees</td>
<td>2.5 million</td>
<td>6.1 million</td>
</tr>
<tr>
<td>% ≥1 medical condition</td>
<td>59-60%</td>
<td>62-65%</td>
</tr>
<tr>
<td>Endpoints</td>
<td>a. Probable influenza†</td>
<td>Post-influenza death‡</td>
</tr>
<tr>
<td></td>
<td>b. Influenza hospitalisation</td>
<td></td>
</tr>
<tr>
<td>Relative effectiveness</td>
<td>a. 22% (95% CI 15-29%)</td>
<td>24% (95% CI 0.6-42%)</td>
</tr>
<tr>
<td></td>
<td>b. 22% (95% CI 16-27%)</td>
<td></td>
</tr>
</tbody>
</table>

* H3N2 predominated 2012-13; H1N1 predominated in 2013-14
† Defined by receipt of a rapid influenza test followed by dispensing of neuraminidase inhibitor oseltamivir
‡ Death within 30 days following an inpatient or emergency department encounter coded as influenza (ICD-9)
Summary

• More immunogenic vaccines for older people are available
• At least 25% relative gain in efficacy compared to standard TIV
• Relative benefits vs QIV unknown, but flu B preferentially affects children
Thank you!