The Rationale and Evidence Base
Supporting the policy in most countries of vaccinating the frail/elderly rather than the “transmitters” (children/young adults)

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Foundation Merieux – Annecy – June 23-25
– Perspective on benefit-risk Decision-Making in Vaccinology
Benefit-Risk Equation for Influenza Vaccine

Serious risks: rare but have occurred (not zero)

Benefits difficult to measure due to seasonal variability, ethics constraints, need for modeling, 90% of deaths in seniors

Focus This Talk: Evidence of Benefits
Generally safe, but serious risk events do occur

<table>
<thead>
<tr>
<th>Type of Vaccine</th>
<th>Type of adverse event</th>
<th>Attributable cases per 1M vaccinees</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIV-Seasonal</td>
<td>Anaphylaxis*</td>
<td>2</td>
<td>Kawai, Pharmacoepi&amp;drugsafety 2014</td>
</tr>
<tr>
<td></td>
<td>Febrile Seizures*</td>
<td>10-50</td>
<td>Kawai, Pharmacoepi&amp;drugsafety 2014</td>
</tr>
<tr>
<td>TIV -2009 Pandemic GBS</td>
<td>GBS</td>
<td>1-6</td>
<td>Salmon et al Lancet 2013</td>
</tr>
<tr>
<td></td>
<td>Narcolepsy***</td>
<td>20-60</td>
<td>Barker&amp;Snape Lancet ID 2014</td>
</tr>
<tr>
<td></td>
<td>Hypersensitivity</td>
<td>8</td>
<td>Halsey et al, Vaccine 2013</td>
</tr>
<tr>
<td></td>
<td>Febrile seizures**</td>
<td>3300</td>
<td>Principi &amp;Esposito Expert Review 2013</td>
</tr>
<tr>
<td>LAIV</td>
<td>Asthma exascerb</td>
<td>3</td>
<td>Izurieta Jama 2005</td>
</tr>
<tr>
<td></td>
<td>Hypersensitivity</td>
<td>12</td>
<td>Halsey et al, Vaccine 2013</td>
</tr>
</tbody>
</table>

* for 2012-2013 season; using no. cases in brief risk window (table 2)

** only Australia; fluzone

*** rate seen in Finland, Sweden, England, Ireland (not Canada); still controversial
A bit of History.....

- **1940s**: Influenza vaccine for military pop
  - Goal: To protect the young, healthy
- **~1960s Policy**: Vaccinate high risk populations
  - Goal: reduce severe influenza outcomes, deaths
  - Especially elderly >65 years
- **1960-1994**: Concern – was it working in seniors?
  - Immune senescence?
- **mid-1990’s**: Concern gone
  - One randomized, placebo-controlled trial in seniors
  - Observational studies set in administrative db
How to Demonstrate Vaccine Effectiveness in Elderly

1. **Randomized, controlled vaccine trials**
   - “Gold standard” evidence not available
   - One Dutch study; VE for mild illness, young elderly

2. **Observational studies (cohort, case-control)**
   - Forms the evidence base
   - Potential for selection bias

3. **Trends in National excess mortality**
   - Mortality reduction achieved with vaccination
   - Potential for “ecological fallacy”
RTC: Large-scale Dutch study, 1994

set in young healthy elderly, mild outcomes only

post-hoc age stratification found 23% VE (NS) in seniors 70+ years old

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Proportion of 1838 member study population (%)</th>
<th>VE for laboratory-confirmed influenza illness (95% CI)</th>
<th>Results from national excess mortality studies*</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥60 years</td>
<td>100%</td>
<td>50% (35% to 61%)</td>
<td>84-90%†</td>
</tr>
<tr>
<td>60-69 years</td>
<td>70%</td>
<td>57% (33% to 72%)</td>
<td>7-14%‡</td>
</tr>
<tr>
<td>≥70 years</td>
<td>30%</td>
<td>23% (~51% to 61%)</td>
<td>76%</td>
</tr>
<tr>
<td>≥80 years</td>
<td>4%</td>
<td>..</td>
<td>55%</td>
</tr>
</tbody>
</table>

Vaccine efficacy (VE) estimates from a placebo-controlled randomised clinical trial in a group of younger, healthy elderly people. The VE point estimates suggest VE declines with age after 70 years, but the 95% CIs were wide. This study contributed no information on VE in elderly people ≥80 years, an age-group that accounts for about 55% of all US influenza-related deaths. ..=not reported. *Proportion of US excess deaths (1990–2001); percentages were estimated for each age-group from all-cause excess mortality by methods described by Simonsen et al.††Range based on ages ≥55 years and ≥65 years. ‡Range based on ages 55–69 years and 65–69 years (no estimate available for ages 60–69 years).

Table 1: Gold-standard evidence for influenza vaccine benefits in elderly people, by age

Based on original Dutch RTC trial by Govaert JAMA 1994;
Table published in Simonsen et al, Lancet ID 2007
Observational Studies
Typical Design of a VE Cohort Study

- Set in large, managed-care populations of seniors
  - **Design**: Retrospective cohort study (ICD9 coded data)
  - **Exposure**: Influenza vaccination in Oct-Nov
  - **Outcome**: ALL deaths during December-March
  - **Measurement**: Vaccine Effectiveness $VE = 1 - RR$
  - **Adjustment**: Standard method, for co-morbidity patterns

<table>
<thead>
<tr>
<th>Vaccinated +/-</th>
<th>Died/lived through winter</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oct, Nov</strong></td>
<td><strong>Dec</strong></td>
</tr>
<tr>
<td>Vaccination period</td>
<td>Jan</td>
</tr>
<tr>
<td></td>
<td>Feb</td>
</tr>
<tr>
<td></td>
<td>Mar</td>
</tr>
<tr>
<td>Influenza period, winter months</td>
<td></td>
</tr>
</tbody>
</table>
How much reduction in ALL WINTER DEATHS in elderly do you think these observational studies consistently reported?

- 5–10%
- 10–25%
- 40–50%
SPECIAL ARTICLE

THE EFFICACY AND COST EFFECTIVENESS OF VACCINATION AGAINST INFLUENZA AMONG ELDERLY PERSONS LIVING IN THE COMMUNITY


Direct savings per year averaged $117 per person vaccinated (range, $21 to $235), with cumulative savings of nearly $5 million. Vaccination was also associated with reductions of 39 to 54 percent in mortality from all causes during the three influenza seasons (P<0.001).

BENEFITS. Influenza vaccine reported to prevent 1 death per 150-200 seniors vaccinated each winter.
Meta-Analyses of Observational Studies
Reported ASTONISHING Reductions of ~50% of ALL WINTER DEATHS in Vaccinated Elderly

<table>
<thead>
<tr>
<th>Meta-analyses</th>
<th>Study Population</th>
<th>% VE (reduction in all-cause deaths)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gross 1995</td>
<td>Nursing home seniors 65+</td>
<td>68%</td>
</tr>
<tr>
<td>Vu 2002</td>
<td>Community-living seniors 65+</td>
<td>50%</td>
</tr>
<tr>
<td>Rivetti 2006</td>
<td>Community-living seniors 65+</td>
<td>47%*</td>
</tr>
</tbody>
</table>

* Cochrane 2006 review; however, in 2009 Jefferson concluded this estimate was biased

If You Could Halve the Mortality Rate, Would You Do It?

Gregory A. Poland
Mayo Vaccine Research Group, Department of Medicine and Infectious Diseases, Molecular Pharmacology and Experimental Therapeutics, Mayo Clinic, Rochester, Minnesota

(See the article by Hak et al. on pages 370–7)

Remarkably translates into:
1 death saved per 150-200 seniors vaccinated
Rupture of the paradigm of extraordinary influenza vaccine benefits

A New Era of Approaches and Evidence Accumulating since 2005
Trends in US Excess Mortality: Attributing winter-seasonal deaths to influenza, elderly $\geq$65 years

15% Influenza vaccination programme intensifies 65%

Yellow areas above baseline = Seasonal Excess Mortality

Model baseline

- P&I mortality/100,000pop
- model baseline
A Paradox From Trends Studies:
Influenza-related mortality increased in US, Italian elderly while vaccine coverage rose from 15% to 65%

US Pneumonia Excess Mortality study

Disappointing Age-Adjusted National Mortality Trends as Vaccination in Seniors Rose to 70%

EXPECTED 35% decline for coverage 15% to 65% assuming vaccine is 60-70% effective

Simonsen 2005; Rizzo 2006; Reichert 2007
Influenza Cannot Possibly Cause 50% of All Deaths

Ocean of Deaths with influenza “foam”

Monthly deaths in elderly 65+, all causes, US, 1980–2000

Can half of all winter deaths be prevented with vaccine? NO!

Nationally, influenza explained less than 10% of all winter deaths
Even in mis-matched seasons. Max what a vaccine can reduce.
An Elegant Demonstration of Profound Bias in Observational Studies: Using Seasonality for Bias Detection

**EXPECTATION**

Vaccine benefits should ONLY occur DURING influenza epidemics, NOT before.

**Influenza epidemic intensity**

- Highest expected VE when influenza peaks
- Expected VE=0 pre-influenza
- Expected VE=0 post-influenza
Observed Seasonal “VE” Pattern
Highest “VE” measured in pre-influenza period when no benefits were expected

% “VE” (=1-RR)

October Early flu Peak flu Late flu Post flu Next summer

“VE” estimate based on:

… and standard ICD-code adjustment for co-morbidities enhanced the bias

Frailty Selection Bias Explains Pattern

SIR model simulation (dotted line):
5% frail seniors at ½ coverage and 20-fold higher risk explains pattern

Simonsen L and Viboud C, unpublished.
**Table 1. Relative Risk of Death or Hospitalization among Vaccinated Elderly Persons vs. Unvaccinated Elderly Persons in the Studies by Nichol et al. and Jackson et al., According to Period.**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Relative Risk (95% CI)*</th>
<th>Nichol et al.</th>
<th>Jackson et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Death from any cause</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before influenza season</td>
<td>Not reported</td>
<td>0.36 (0.30–0.44)</td>
<td></td>
</tr>
<tr>
<td>During influenza season</td>
<td>0.52 (0.50–0.55)</td>
<td>0.51 (0.47–0.55)</td>
<td></td>
</tr>
<tr>
<td>After influenza season</td>
<td>Not reported</td>
<td>0.66 (0.61–0.72)</td>
<td></td>
</tr>
<tr>
<td><strong>Hospitalization for pneumonia or influenza</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before influenza season</td>
<td>Not reported</td>
<td>0.65 (0.53–0.80)</td>
<td></td>
</tr>
<tr>
<td>During influenza season</td>
<td>0.73 (0.68–0.77)</td>
<td>0.71 (0.65–0.78)</td>
<td></td>
</tr>
<tr>
<td>After influenza season</td>
<td>0.94 (0.74–1.19)</td>
<td>0.82 (0.73–0.92)</td>
<td></td>
</tr>
</tbody>
</table>

* Relative risks were adjusted for age, sex, and disease covariates. CI denotes confidence interval.

**"VE"**

**Outcome: AC Mortality**

<table>
<thead>
<tr>
<th>Period</th>
<th>Nichol</th>
<th>Jackson</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>---</td>
<td>64%</td>
</tr>
<tr>
<td>During</td>
<td>48%</td>
<td>49%</td>
</tr>
<tr>
<td>After</td>
<td>---</td>
<td>34%</td>
</tr>
</tbody>
</table>

**"VE"**

**Outcome: Pneumonia Hospital**

<table>
<thead>
<tr>
<th>Period</th>
<th>Nichol</th>
<th>Jackson</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>---</td>
<td>35%</td>
</tr>
<tr>
<td>During</td>
<td>27%</td>
<td>39%</td>
</tr>
<tr>
<td>After</td>
<td>6%</td>
<td>18%</td>
</tr>
</tbody>
</table>

We conclude that frailty selection bias and use of non-specific endpoints such as all-cause mortality have led cohort studies to greatly exaggerate vaccine benefits. The remaining evidence base is currently insufficient to indicate the magnitude of the mortality benefit, if any, that elderly people derive from the vaccination programme.
Next Generation Bias-Adjusted Admin db Studies
More Specific Outcomes and Measurement During Influenza Periods
Provided Improved VE Estimates for Elderly

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Outcome</th>
<th>VE [95% CI] Seniors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mangtani JID 2004</td>
<td>GP databases Cohort study</td>
<td>Pneumonia deaths All-cause deaths</td>
<td>12% 0%</td>
</tr>
<tr>
<td>Jackson LANCET 2008</td>
<td>HMO data + chart review Case-control study</td>
<td>X-ray confirmed Pneumonia hospitalizations All-cause deaths</td>
<td>8% (–4% in peak) Low; no est possible</td>
</tr>
<tr>
<td>Fireman AJE 2009</td>
<td>HMO data + chart review Cohort study</td>
<td>Resp/circulatory hospitalizations All-cause deaths</td>
<td>9% 4.6% [0.7 to 8.3%]</td>
</tr>
</tbody>
</table>

New Generation VE estimation using lab confirmed endpoints set in surveillance

Low non-significant VE in European Elderly in 2011–12

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Number</th>
<th>Influenza vaccine effectiveness in % (case-negative analysis)</th>
<th>95% confidence intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allage</td>
<td>Crude</td>
<td>1016</td>
<td>12.2</td>
</tr>
<tr>
<td></td>
<td>Adjusted</td>
<td>1014</td>
<td>24.8</td>
</tr>
<tr>
<td>&lt;15</td>
<td>Crude</td>
<td>78</td>
<td>19.4</td>
</tr>
<tr>
<td></td>
<td>Adjusted</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>15–59</td>
<td>Crude</td>
<td>431</td>
<td>59.3</td>
</tr>
<tr>
<td></td>
<td>Adjusted</td>
<td>431</td>
<td>63.3</td>
</tr>
<tr>
<td>60 +</td>
<td>Crude</td>
<td>505</td>
<td>6.4</td>
</tr>
<tr>
<td></td>
<td>Adjusted</td>
<td>503</td>
<td>15.1</td>
</tr>
</tbody>
</table>
MMWR 2012-13 interim analysis
US Flu VE Network

2,697 influenza ILI outpatients; case-negative controlled
adjusted for age, site, race/ethnicity, self-rated health, days of illness

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Vaccine Effectiveness (adjusted) Influenza A+B</th>
<th>Vaccine Effectiveness (adjusted) A/H3N2 only</th>
</tr>
</thead>
<tbody>
<tr>
<td>6mo – 17 yrs</td>
<td>64% (51-73)</td>
<td>58% (38-71)</td>
</tr>
<tr>
<td>18-49 yrs</td>
<td>52% (38-79)</td>
<td>46% (20-63)</td>
</tr>
<tr>
<td>50-64 yrs</td>
<td>63% (43-76)</td>
<td>50% (15-71)</td>
</tr>
<tr>
<td>≥ 65 yrs</td>
<td>27% (-31 to 59)</td>
<td>9% (-84 to 55)</td>
</tr>
</tbody>
</table>

MMWR, Feb 22, 2013 / 62(07):119-123
What about other approaches to the control of influenza?
“….. children in school and day care are the most important disseminators of virus in the community”

“Consideration should be given to providing protection for all children against influenza when effective methods and strategies have been found”

“Such prophylaxis would decrease not only morbidity and serious disease in children but also the risk of exposure of high-risk adult patients”

Evidence of Herd Protection From Vaccinating School Children

- Types of study design
  - Observational
    - Japanese school children study
  - Modelling
    - Longini and colleagues
    - HPA Vynnycky et al.
- Interventions
  - Trial versus control community
    - Ontario, Texas, Tennessee
Indirect Effects of Vaccinating School Children on Influenza Mortality in Japan

**Finding:** ~50% drop in influenza related deaths during the childhood vaccine programme
Higher rates before programme and after it phased out

UK: HPA Modelling Study demonstrating herd benefits if 60% children aged 6mo to 16 yrs were vaccinated

- **Projecting** a 65%–97% reduction in ALL clinical cases if 6 month–16 year olds vaccinated
- No reduction if only seniors vaccinated

Strong evidence of herd immunity from infant PCV7 vaccine in the US since 2000.

Invasive Pneumococcal Disease reduction seen in all ages.

CDCs ABC surveillance (lab confirmed)

Pilishvili et al, JID 2010

7 serotypes virtually Eliminated

90% of IPD cases reduced were in unvaccinated adults Including elderly (Simonsen…Klugman, mbio 2008 and Lancet Resp Med 2013)
A Way Forward

- Conduct more appropriate VE studies
  - Bias adjust administrative data cohort studies
  - Lab-confirmed case-negative controlled studies (I-MOVE)
- Use more immunogenic formulations for seniors
  - Higher antigen dose, adjuvants, intradermal delivery, more
- Protect seniors/frail populations also indirectly
  - Increase vaccine coverage in children, younger adults, care takers to achieve lower influenza transmission to high-risk pop
  - Universal immunisation
Recent Movement Towards Universal Coverage in some countries

<table>
<thead>
<tr>
<th>Year</th>
<th>Country</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>Canada/Ontario</td>
<td>Universal</td>
</tr>
<tr>
<td>2004</td>
<td>USA</td>
<td>+ children 6–23 months</td>
</tr>
<tr>
<td>2010</td>
<td>USA</td>
<td>Universal</td>
</tr>
<tr>
<td>2013</td>
<td>England &amp; Wales</td>
<td>+ children</td>
</tr>
</tbody>
</table>
Acknowledgments

- **National Institutes of Health**
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  - Katherine Goodwin
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  - Michael Jackson
  - Jennifer Nelson

- **Others**
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  - Paul Glezen
  - Heath Kelly


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None at the time this work was undertaken and published