Fluzone HD vs SD cluster randomized trial in US NHs

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Conflicts of Interest

• Grant, consultant and/or speaker for
  – Sanofi Pasteur, Seqirus (grant influenza vaccine, consultant, speaker)
  – Merck, Novartis, Janssen, GlaxoSmithKline (consultant shingles, flu, RSV, e coli, pneumococcal vaccines, antivirals)
  – Pfizer (speaker, vaccine contract)
  – Healthcentric Advisors (New England QIN), Catapult Consultants (for Informal Independent Dispute Resolution when CMS federal nursing home surveys are contested)

• Other support
  – NIAID (RO1, influenza, lymph nodes)
  – CDC (antibiotic stewardship in LTC)
  – Hartford, American Geriatrics Society (geriatrics co-management)
  – Gerontological Society of America (National Adult Vaccination Program)
Objectives

• A word about age, immune response, inflammation, complications from influenza
• Discuss results from a pragmatic large scale clinical effectiveness pilot and RCT
## Age-Adjusted Incidence Ratios (IR) of 1st MI and CVA after Vaccination or Infection

<table>
<thead>
<tr>
<th>Event (count) before First MI</th>
<th>Days 1-14 IR, n</th>
<th>Days 15-28 IR, n</th>
<th>Days 29-91 IR, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flu vaccine (20,486)</td>
<td>~0.72, 357</td>
<td>0.73, 417</td>
<td>~1, 2154</td>
</tr>
<tr>
<td>Td (7,966)</td>
<td>~1, 54</td>
<td>~1, 46</td>
<td>~1, 299</td>
</tr>
<tr>
<td>PPSV23 (5,925)</td>
<td>~1, 39</td>
<td>~1, 43</td>
<td>~1, 177</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Event (count) before First MI</th>
<th>Days 1-14</th>
<th>Days 15-28</th>
<th>Days 29-91</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flu vaccine (20,921)</td>
<td>~3.8, 1020</td>
<td>1.95, 576</td>
<td>1.4, 1658</td>
</tr>
<tr>
<td>UTI (10,448)</td>
<td>~1.6, 233</td>
<td>1.32, 217</td>
<td>1.23, 820</td>
</tr>
</tbody>
</table>

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*Note: SRTI = systemic respiratory tract infection, UTI = urinary tract infection*

“Thrombometer” – the propensity to clot

Increases with age
- Inflammatory markers of age
- IL-6, IL-8, C-reactive protein

Increases with disease
- Obesity
- Diabetes
- Arthritis, Vascular disease
- Dementia
- COPD

Increases with infection
- Influenza, pneumonia
- Bladder infection, pressure sores
Immune Senescence

- More permissive for infection including pneumonia
  - More permissive for severe infection that can result in hospitalization
- Lowers vaccine response
  - Need better vaccines to overcome declining response
- Slows recovery from infection
- Changes symptom presentation with age

High dose flu vaccine reduces clinical flu in outpatient elderly

Efficacy of High-Dose versus Standard-Dose Influenza Vaccine in Older Adults


- 31,989 volunteers, 2011-2013, 50:50 HD:SD
- Relative efficacy, ILI 24.2%; (95% CI 9.7 to 36.5)
  - Relative efficacy ILI hospitalization 30% (95% CI 9 to 46)

Comparative effectiveness of high-dose versus standard-dose influenza vaccines in US residents aged 65 years and older from 2012 to 2013 using Medicare data: a retrospective cohort analysis


- 900K HD vs 1600K SD, 2012-2013, retrospective cohort ≥65
- 22% fewer rapid test/oseltamivir in HD, and 22% fewer hospitalized
Pragmatic Large-Scale Cluster RCT on Comparative Effectiveness of HD vs SD Influenza Vaccine in Long-Term Care

• Review results from Pilot Study undertaken in 39 nursing facilities 2012-13 predominantly A/H3N2 influenza season

• Present findings from the Full cluster RCT of High Dose (HD) influenza vaccine vs. Standard Dose (SD) influenza vaccine in 823 nursing homes (NHs) 2013-2014 predominantly A/H1N1 influenza season
Patient Eligibility and Selection

Living Residents in study NHs on Oct 1, 2012
N=4,438

Residents over 65 years
N=3,784

Residents who became long-stay
N=2,957

Residents in HD group
N=1,461

Residents in SD group
N=1,496

a Residents who were 65 years old on October 1, 2012.
b Long-stay residents are NH residents with quarterly and annual MDS assessments. Residents who were discharged from the nursing home to: 1) the community, 2) inpatient rehabilitation facility, 3) hospice, 4) other location, or 5) as dead in the baseline period are excluded from the analytical sample. Residents are included if they were discharged to another nursing home, acute hospital, psychiatric hospital, or MR/DD facility.
## Pilot Results: Regression Models

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Unadjusted</th>
<th>Adjusted*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard Ratio (LCL – UCL)</td>
<td>p-value</td>
</tr>
<tr>
<td>Death in NH</td>
<td>1.059 (0.827-1.357)</td>
<td>0.650</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Relative Risk (LCL – UCL)</th>
<th>p-value</th>
<th>Relative Risk (LCL – UCL)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Hospitalizations</td>
<td>0.617 (0.461-0.827)</td>
<td>0.001</td>
<td>0.647 (0.512-0.818)</td>
<td>0.000</td>
</tr>
<tr>
<td>Ever Hospitalized</td>
<td>0.658 (0.496-0.873)</td>
<td>0.004</td>
<td>0.701 (0.543-0.905)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

* Adjusted for prior year hospitalization rate, age of resident, mean age of residents in home, individual ADL score, mean ADL score in home, Cognitive Function Score (CFS), Mean CFS in home, history of CHF risk-group, prevalence of CHF risk-group in home
Pilot Results: Summary

• Large scale study feasible as pragmatic cluster RCT

• Can detect differential signal in hospitalization using MDS data
  – ~30% fewer people hospitalized in HD group in an A/H3N2 season predominant season, significant before and after adjustment

• Move forward to large trial
Pragmatic Cluster RCT of HD vs SD Flu Vaccine in Nursing Homes

- Recruit NH’s in areas adjacent to 122 cities in CDC Influenza Surveillance System
- Use Federally Mandated Nursing Home Resident MDS Assessment to identify permanent NH residents with selected demographic and functional characteristics AND to measure outcomes
- Use Medicare hospital claims to measure outcome of hospitalization for Influenza (P&I) and Cardiovascular exacerbations of Influenza
Study Design

• Recruit facilities within 50 miles of CDC cities
  – Excluded those facilities already using HD, with fewer than 50 permanent residents, hospital-owned NHs, or >20% of residents UNDER 65

• Randomly assign facilities to 4 groups
  – High-Dose for NHs residents
    • Free Staff Vaccine
    • No Free Staff Vaccine
  – Standard Dose for NHs residents
    • Free Staff Vaccine
    • No Free Staff Vaccine

• Educate facility staff on influenza, study procedures

• Link to facility data (OSCAR), MDS, and Medicare Part A, MDS (discharge destination, function), vital status files

• Collect Vaccination Data Reports

• Patient eligibility:
  – >3 months’ residence, over 65 years old on November 1, 2013, and Medicare Fee For Service (FFS)
Outcomes

1. All-cause hospitalization per person-year
2. Mortality
3. Functional Decline (activities of daily living, ADLs)
Outcome Determination

• PRIMARY. Medicare FFS permanent NH residents; risk of hospitalization due to Pulmonary and Influenza-related illness (P&I):
  – P&I hospitalization defined as: ICD9-CM codes 460–466, 480–488, 490–496, 500–518
Participating NHs by State (n=823)
**Nursing Home Facilities Selection and Randomization**

Facilities within 50 miles of one of 122 CDC surveillance cities (n=989 NHs screened)*

**Randomized (n= 823 NHs)**

- **Excluded facilities (n=166)**
  - Ineligible per protocol = 118
  - Not willing to participate = 48

**Allocation**

- **HD vaccine for residents**
  - Free SD vaccine for staff
  - 193 NHs
    - 21,926 residents
    - Median per NH=102, iqr 47

- **HD Vaccine for residents**
  - Usual care for staff
  - 216 NHs
    - 24,319 residents
    - Median per NH=108, iqr 53

- **SD vaccine for residents**
  - Free SD vaccine for staff
  - 226 NHs
    - 25,961 residents
    - Median per NH=111, iqr 58

- **SD vaccine for residents**
  - Usual care for staff
  - 226 NHs
    - 25,961 residents
    - Median per NH=111, iqr 58

**Analysis**

- **193 NHs**
  - 12,542 Long-Stay residents;
    - Median per NH=54, iqr 32
  - Excluded from analysis (0 NHs)

- **212 NHs**
  - 14,097 Long Stay residents
    - Median per NH=61, iqr 34
  - Excluded from analysis (5 NHs)
    - No Long Stay residents (1 NH)
    - No MDS @ baseline (2 NHs)
    - Does not bill Medicare (1 NH)

- **226 NHs**
  - 14,783 Long Stay residents
    - Median per NH=59, iqr 39
  - Excluded from analysis (0 NHs)

- **187 NHs**
  - 11,586 Long Stay residents;
    - Median per NH=58, iqr 31
  - Excluded from analysis (1 NH)
    - No Long Stay residents (1 NH)

* Matched with Medicare metadata and geocodes. Exception was state of New Jersey of which all facilities were eligible.
The trials follows an intent-to-treat analysis at random assignment, therefore there is no loss to follow-up.
HD, high-dose; IQR, interquartile range (p75-p50); MDS, minimum data set assessment; NHs, nursing homes; SD, standard dose
## NH groups are similar (N=823 NHs)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>HD Vaccine for Residents</th>
<th>SD Vaccine for Residents</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Staff Free (mean, SD)</td>
<td>Staff Usual Care (mean, SD)</td>
</tr>
<tr>
<td>NHs randomized (N)</td>
<td>193</td>
<td>216</td>
</tr>
<tr>
<td>Facilities-Reported Data&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Residents per home (N)</td>
<td>118.0 (82.3)</td>
<td>118.7 (52.1)</td>
</tr>
<tr>
<td>% residents vaccinated</td>
<td>81.7 (14.4)</td>
<td>79.9 (16.6)</td>
</tr>
<tr>
<td>% LTC residents</td>
<td>77.4 (15.9)</td>
<td>78.2 (14.8)</td>
</tr>
<tr>
<td>% LTC residents vaccinated</td>
<td>86.0 (14.8)</td>
<td>86.5 (13.8)</td>
</tr>
<tr>
<td>% staff vaccinated</td>
<td>53.5 (26.2)</td>
<td>56.3 (26.9)</td>
</tr>
<tr>
<td>Medicare Claims/Facility Data&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Medicaid</td>
<td>59.9 (18.1)</td>
<td>64.2 (16.1)</td>
</tr>
<tr>
<td>Ratio of RN/RN+LPN</td>
<td>0.361 (0.15)</td>
<td>0.355 (0.16)</td>
</tr>
<tr>
<td>Average ADL score (0-28)</td>
<td>17.0 (1.77)</td>
<td>16.9 (2.10)</td>
</tr>
</tbody>
</table>
Cohort Selection, 2013-14
(ALL Long-stay NH residents over 65 years)

Living in study NHs on 1 October, 2013; N=91932

Residents over 65 years;\textsuperscript{a} N=75,960

Residents who became Long-Stay;\textsuperscript{b} N=53,008

MDS Analytic Sample

\textbf{405 NHs HIGH DOSE}
26,639 Long Stay residents
Median per NH=58

\textbf{413 NHs STANDARD DOSE}
26,369 Long Stay residents
Median per NH=58

FFS Analytic Sample

\textbf{405 NHs HIGH DOSE}
19,127 Long Stay residents
Median per NH=43

\textbf{413 NHs STANDARD DOSE}
19,129 Long Stay residents
Median per NH=42

\textsuperscript{a} Residents who were 65 years old on October 1, 2013.
\textsuperscript{b} Long-stay residents are NH residents with quarterly and annual MDS assessments. Residents who were discharged from the nursing home to: 1) the community, 2) inpatient rehabilitation facility, 3) hospice, 4) other location, or 5) as dead in the baseline period are excluded from the analytical sample. Residents are included if they were discharged to another nursing home, acute hospital, psychiatric hospital, or MR/DD facility.

[Note: We could not obtain MDS records for 6 NH facilities (i.e., 1 veteran’s home; 2 rehabilitation facilities that were randomized prior to their withdrawal; 1 facility stopped operation in Nov/Dec 2013)]
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>HD Vaccine for Residents</th>
<th>SD Vaccine for Residents</th>
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<tbody>
<tr>
<td></td>
<td>Free Vaccine for Staff</td>
<td>Usual Care for Staff</td>
</tr>
<tr>
<td></td>
<td>(N, %)</td>
<td>(N, %)</td>
</tr>
<tr>
<td>LS residents &gt;65 yo</td>
<td>12,542 (14.097)</td>
<td>14,097 (14.783)</td>
</tr>
<tr>
<td>Age (mean, sd)</td>
<td>83.7 (8.7)</td>
<td>83.5 (8.8)</td>
</tr>
<tr>
<td>Female</td>
<td>9,014 (71.9)</td>
<td>10,248 (72.7)</td>
</tr>
<tr>
<td>African American</td>
<td>1,800 (14.4)</td>
<td>2,088 (14.8)</td>
</tr>
<tr>
<td>White</td>
<td>9,469 (75.5)</td>
<td>10,690 (75.8)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>715 (5.7)</td>
<td>681 (4.8)</td>
</tr>
<tr>
<td>Married</td>
<td>2,326 (18.6)</td>
<td>2,687 (19.1)</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>2,547 (20.3)</td>
<td>2,868 (20.3)</td>
</tr>
<tr>
<td>Stroke/ CVA/ TIA</td>
<td>2,452 (19.6)</td>
<td>2,807 (19.9)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>9,953 (79.4)</td>
<td>11,156 (79.1)</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>4,229 (33.7)</td>
<td>4,826 (34.2)</td>
</tr>
<tr>
<td>Asthma/COPD/CLD</td>
<td>2,405 (19.2)</td>
<td>2,869 (20.4)</td>
</tr>
</tbody>
</table>
Results: Censoring is Balanced

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HD vaccine (N, %)</th>
<th>SD vaccine (N, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Follow Up</td>
<td>21,639 (80.2)</td>
<td>21,382 (80.1)</td>
</tr>
<tr>
<td>Death</td>
<td>4,542 (17.1)</td>
<td>4,531 (17.2)</td>
</tr>
<tr>
<td>Lost: Acute Impatient discharge, no return</td>
<td>173 (0.65)</td>
<td>158 (0.60)</td>
</tr>
<tr>
<td>Lost: Other institutional discharge, no return</td>
<td>31 (0.12)</td>
<td>35 (0.13)</td>
</tr>
<tr>
<td>Lost: Discharge to community or hospice</td>
<td>223 (0.84)</td>
<td>250 (0.95)</td>
</tr>
<tr>
<td>Lost: No discharge record</td>
<td>31 (0.12)</td>
<td>13 (0.05)</td>
</tr>
<tr>
<td>Total</td>
<td>26,639</td>
<td>26,369</td>
</tr>
</tbody>
</table>
Analytic Approach

- Unit of analysis: individual residents
  - Adjusted for clustering by NHs using robust variance estimates
- Multivariable logistic, Poisson, and Cox regression
  - Initial model assessed interaction between treatments
  - Adjusted for pre-specified NH- and resident-level covariates
- Analysis by Intention-To-Treat
  - Sensitivity analysis to assess effect of excluding deaths
- Number Needed to Treat (NNT)

Seasonal Index Hospitalizations by Month

Count of Index Hospitalization for Influenza Season
(November 2013 to May 2014)

Number of Index Hospitalizations by Month

0 500 1,000

1: Nov 2: Dec 3: Jan 4: Feb 5: Mar 6: Apr 7: May

Standard-Dose Vaccine
High-Dose Vaccine
Number Needed to Treat  
(for Ever Hospitalized)

\[ NNT = \frac{1}{ARR} \text{ where } ARR^* = CER - EER \]

\[ \frac{1}{(0.2090 - 0.1967)} = 81.3 \text{ (CI: 53, 182)} \]

To prevent 1 person from being hospitalized, ~81 long-stay 65+ NH residents need to be treated with high-dose instead of standard dose influenza vaccine

Definitions

NNT= Number Needed to Treat  
ARR = Absolute Risk Reduction  
CER = Control Event Rate (i.e., Probability of Hospitalization for SD group)  
EER = Experimental Event Rate (i.e., Probability of Hospitalization for HD group)

* Using unadjusted event rates.
FluView

Laboratory-Confirmed Influenza Hospitalizations
Preliminary rates as of Jun 27, 2015

FluSurv-NET :: Entire Network :: 2014-15 Season

FluSurv-NET :: Entire Network :: 2013-14 Season

FluSurv-NET :: Entire Network :: 2012-13 Season

FluSurv-NET :: Entire Network :: 2011-12 Season

Pilot Year

Full Study Year
Summary

- HD vaccine has been shown to reduce laboratory confirmed influenza among outpatient elderly
- NH residents have higher event rates (e.g., hospitalization) than others, enables health services impact study; cluster-randomized approach overcomes selection biases
- 2013-2014 season is of special interest because it offers a conservative estimate of relative benefit in this population
  - A(H1N1) predominated, and relative benefit of HD vaccine for this strain in a NH population has been unknown
  - A relatively low influenza attack rate to comparison seasons
- FFS claims differences consistent with biologic plausibility of effect on hospitalization based on diagnoses
Discussion

• Reasons our estimate may be conservative
  – Severity of influenza season

• ITT approach
  – Over 10% of residents not vaccinated

• Type of influenza virus circulating (A/H1N1)

• Reduced hospitalization likely underestimates net benefits to nursing home residents’ health outcomes

• When ~20% of population is hospitalized, even a 1% absolute reduction in hospitalization can be cost effective (e.g., 81 vaccines at ~$30/vaccine = $2430, or less than the average cost of hospitalization)

• Limitations:
  – No laboratory data to confirm influenza
  – HD:SD relative benefit on A(H1N1) may underestimate difference when other strains dominate, especially A(H3N2)
  – Have not estimated relative benefit to no vaccine
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- **UH/ CWRU**
  - Stefan Gravenstein

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  - Vincent Mor
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  - Lisa Han

- **University of Ottawa**
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