Influenza vaccine effectiveness in Europe, 2012-13: Estimates from the I-MOVE multicentre case control study by influenza type/subtype

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I-MOVE
Monitoring IVE in EU and EEA Studies since 2008-9

Multicentre case control, 2012-13
7 flu VE case control studies

Very similar protocols → Pooled analysis
– To obtain summary, preliminary VE measures
– Sample size big enough for stratified estimates
Methods

Study population
Patients consulting for ILI/ARI in 787 GP practices
- Systematic selection of ILI/ARI patients to swab
- Confirmation with RT-PCR or culture
- EU ILI; swabbed <8 days after symptom onset

Test-negative design (strain-specific analysis)
Case Influenza A(H3), A(H1N1)pdm09, B positive
Control Influenza negative

Study period
Start >14 days after vaccination campaign begin
End Last case followed by at least 2 weeks of no cases

Vaccinated
Onset >14 days after vaccination
Methods

**Complete case analysis**
- $VE = (1-OR) \times 100$; logistic regression

**Pooled 1-stage model**
- Study as fixed effect (true vaccine effect in each study is the same)
- Covariates for adjustment: age (restricted cubic spline with 4 knots), sex, presence of chronic conditions, week of symptom onset

**Analysis by**
- Influenza type/subtype
- Age group (0-14; 15-59; 60+ years)
- Vaccine group (split virion or subunit vaccine)
Sample size for complete case analysis, I-MOVE multicentre case control study, influenza season 2012-13

Total records received: 7954

Application of exclusion criteria

B analysis 4627
-283
B analysis 4344
-73
B analysis 4271

A(H1N1)pdm09 analysis 3516
-367
A(H1N1)pdm09 analysis 3249
-64
A(H1N1)pdm09 analysis 3185

A(H3) analysis 3340
-283
A(H3) analysis 3057
-60
A(H3) analysis 2997
Number of ILI reports by influenza type/subtype and week of symptom onset, I-MOVE multicentre case control study, influenza season 2012-13

Number of ILI cases

ISO week of onset of symptoms

- Influenza A(H3) (N=730)
- Influenza A(H1N1)pdm09 (N=1068)
- Influenza B (N=1937)
Characteristics of influenza cases by type/subtype and test-negative controls, I-MOVE multicentre case control study, influenza season 2012-13

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Influenza B cases (N=1937)</th>
<th>A(H1N1) cases (N=1068)</th>
<th>A(H3) cases (N=730)</th>
<th>“Any flu” controls (N=2874)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (interquartile range)</td>
<td>15 (7-43)</td>
<td>31 (10-46)</td>
<td>20 (5-46)</td>
<td>22 (4-45)</td>
</tr>
<tr>
<td>Seasonal vaccination, 2012-13</td>
<td>94/1898 (5.0)</td>
<td>48/1031 (4.7)</td>
<td>47/699 (6.7)</td>
<td>255/2772 (9.2)</td>
</tr>
<tr>
<td>At least one chronic condition</td>
<td>278/1896 (14.7)</td>
<td>154/1014 (15.2)</td>
<td>91/690 (13.2)</td>
<td>495/2733 (18.1)</td>
</tr>
<tr>
<td>Female</td>
<td>95/1933 (49.9)</td>
<td>562/1059 (53.1)</td>
<td>355/727 (48.8)</td>
<td>1458/2854 (51.1)</td>
</tr>
<tr>
<td>Swabbed &lt;4 days after symptom onset</td>
<td>1675/1937 (86.5)</td>
<td>972/1068 (91.0)</td>
<td>658/730 (90.1)</td>
<td>2577/2874 (89.7)</td>
</tr>
<tr>
<td>Belongs to target group for vaccination</td>
<td>376/1916 (19.6)</td>
<td>199/1045 (19.0)</td>
<td>140/707 (19.8)</td>
<td>624/2801 (22.3)</td>
</tr>
</tbody>
</table>
Crude and adjusted VE against influenza B, A(H1N1) and A(H3N2), I-MOVE multicentre case control study, influenza season 2012-13

Adjusted for week of onset, chronic disease, age group as restricted cubic spline and sex
Adjusted VE against influenza B, A(H1N1) and A(H3N2), by age group, I-MOVE multicentre case control study, influenza season 2012-13

Adjusted for week of onset, chronic disease, age group as restricted cubic spline and sex
Adjusted vaccine effectiveness by vaccine group (N;cases) against influenza B, A(H1N1) and A(H3N2), I-MOVE multicentre case control study, influenza season 2012-13

1 Adjusted for week of onset, chronic disease, age group as restricted cubic spline and sex
Adjusted vaccine effectiveness against any influenza by vaccine group (N;cases), by age group, I-MOVE multicentre case control study, influenza season 2012-13

Adjusted for week of onset, chronic disease, age group as restricted cubic spline and sex
Discussion

- Long season with substantial proportions of A(H1N1)pdm09, A(H3N2) and influenza B
- VE all ages around 50% for all types/subtypes
  - 42.2% to 50.4%
- VE slightly higher for 15-59 year olds
  - 43.6% to 63.6%
- VE lower among <15 year olds
  - 22.3% to 36.5%
  - Info on number of doses not collected everywhere
- Low sample sizes amongst elderly
Discussion

- VE estimates by vaccine group possible
  - Data completeness good
  - Suggestion of similar VE for B and slightly higher subunit VE for A
  - Need for type/subtype and age-specific estimates for valid comparison

- Sample size large enough to estimate type/subtype and age-specific VE
  - Important for 2012-13 season
Conclusions

VE moderate
- But vaccine still best preventive measure
- Virological component of VE study necessary to understand variation in VE estimates

Sample sizes need to increase to obtain vaccine type-specific estimates by age group and influenza type/subtype
I-MOVE multi-centre case control team

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- **EpiConcept:** Alain Moren, Marta Valenciano, Marc Rondy
Sources of funding

- National institute’s own funding
- WHO-EURO/US CDC
- EpiConcept
Backup slides
Adjusted VE of seasonal vaccine against all influenza, imputed and complete case analysis, overall and by target population, I-MOVE pooled analysis, influenza season 2012-13
Comparison of categorical and spline modelling of a continuous variable

From Orsini, 3rd Nordic and Baltic countries Stata Users Group meeting, 2009
Splines

- Polynomial line segments
- Pieces are joined together to make a curve
- Boundaries of segments are called knots
- Linear, quadratic and cubic splines: continuous variable: \(x^1\), \(x^2\) and \(x^3\) respectively
- Stata: mkspline2 and xbrcspline
  - User-written routines
Age distribution of influenza cases by type and subtype, I-MOVE pooled analysis, influenza season 2012-13

Influenza B cases
Influenza A(H1N1) cases
Influenza A(H3) cases
Crude and adjusted\textsuperscript{1} VE of seasonal vaccine against all influenza, A(H1N1), A(H3N2) and influenza B, target population, I-MOVE pooled analysis, influenza season 2012-13

When adjusting for onset week, some onset weeks dropped, resulting in different sample size for crude and adjusted

\begin{itemize}
  \item VE against any influenza
  \item VE against A(H1N1)
  \item VE against A(H3N2)
  \item VE against influenza B
\end{itemize}

\textsuperscript{1} Adjusted for week of onset, chronic disease, age group as restricted cubic spline and sex

\begin{tabular}{|c|c|}
  \hline
  \textbf{VE \%} & \textbf{Sample Size} \\
  \hline
  Crude (1082) & 43,7 \\
  Adjusted (1059) & 48,2 \\
  Crude (604) & 58,0 \\
  Adjusted (561) & 44,5 \\
  Crude (512) & 50,9 \\
  Adjusted (483) & 50,4 \\
  Crude (777) & 43,0 \\
  Adjusted (763) & 50,4 \\
  \hline
\end{tabular}
Percentage change in OR of influenza vaccination when omitting covariates from the model, total population, I-MOVE pooled analysis, influenza season 2012-13

Onset weeks

Age

Sex

Any reported chronic disease

% relative difference in OR of influenza vaccination when omitting variable from full model
Smoking and GP visits confounders?
I-MOVE pooled analysis, complete case analysis, excluding Germany, influenza season 2012-13

Adj 1: Adjusted for onset week, age as cubic spline, chronic condition, sex
Adj 2: Adjusted for onset week, age as cubic spline, chronic condition, sex, current smoker, GP visits
Crude and adjusted\(^1\) VE of seasonal vaccine against all influenza, A(H1N1), A(H3N2) and influenza B, total population, delay between swabbing and onset of symptoms 1-3 days inclusive, I-MOVE pooled analysis, influenza season 2012-13

<table>
<thead>
<tr>
<th></th>
<th>Crude</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any influenza</td>
<td>45.4</td>
<td>51.3</td>
</tr>
<tr>
<td>A(H1N1)</td>
<td>57.9</td>
<td>54.5</td>
</tr>
<tr>
<td>A(H3N2)</td>
<td>29.2</td>
<td>48.7</td>
</tr>
<tr>
<td>Influenza B</td>
<td>45.1</td>
<td>51.2</td>
</tr>
</tbody>
</table>

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When adjusting for onset week, some onset weeks dropped, resulting in different sample size for crude and adjusted