Influenza vaccine effectiveness
I-MOVE multicentre case control study 2013-14

Moderate but heterogeneous effectiveness by country

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and the I-MOVE multicentre case control study team
from
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Background

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

Multicentre case control, 2013-14
- Six countries involved
- Very similar protocols
- Pooled analysis
  - early and final VE measures in season
  - sample size large enough for stratified estimates
Methods

- **Study population**
  Patients consulting for ILI/ARI in 435 GP practices
  - systematic selection of ILI/ARI patients to swab
  - EU ILI; swabbed < 8 days after symptom onset

- **Test-negative design** (strain-specific analysis)
  - cases: A(H3N2), A(H1N1)pdm09 RT-PCR or culture positive
  - controls: influenza negative

- **Study period**
  - start: >14 days after vaccination campaign begin
  - end: last subtype-specific case followed by 2 w. of no cases

- **Vaccinated**
  - ILI onset >14 days after vaccination
Methods

- **Pooled analysis**
  - Evaluation of heterogeneity between study sites
    - I², Q-test; qualitative
  - **1-stage model** – study as fixed effect
    (more weight for larger studies provided that vaccine effect in each study is the same)
  - **2-stage model** using random effects meta-analysis
    (smaller studies weighted more than in 1-stage)

- **Logistic regression** \( VE = (1 - OR) \times 100 \)
  - complete case analysis
  - adjusted where sample size allows for week of onset, chronic condition, sex, age (restricted cubic spline)
Characteristics of influenza A(H1N1) (n=531) and A(H3N2) cases (n=623) and corresponding ILI influenza negative controls, I-MOVE pooled analysis, influenza season 2013-14

<table>
<thead>
<tr>
<th></th>
<th>A(H1N1) cases [531]</th>
<th>Controls [1712]</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (years)</td>
<td>35.5</td>
<td>26.0</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Seasonal vaccination, 2013-14</td>
<td>34/523 (6.5)</td>
<td>206/1634 (12.6)</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>Any chronic condition</td>
<td>102/529 (19.3)</td>
<td>340/1664 (20.4)</td>
<td>0.619†</td>
</tr>
<tr>
<td>Swabbed &lt;4 days</td>
<td>469/531 (88.3)</td>
<td>1348/1712 (78.7)</td>
<td>&lt;0.001†</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>A(H3N2) cases [623]</th>
<th>Controls [1920]</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age</td>
<td>33.0</td>
<td>22.0</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Seasonal vaccination, 2013-14</td>
<td>72/617 (11.7)</td>
<td>215/1813 (11.9)</td>
<td>0.942†</td>
</tr>
<tr>
<td>Any chronic condition</td>
<td>128/616 (20.8)</td>
<td>372/1854 (20.1)</td>
<td>0.728†</td>
</tr>
<tr>
<td>Swabbed &lt;4 days</td>
<td>532/623 (85.4)</td>
<td>1643/1920 (78.5)</td>
<td>0.001†</td>
</tr>
</tbody>
</table>

* Nonparametric equality-of-medians test
† Fisher’s exact test
Crude and adjusted VE against A(H1N1), by age group, 1-stage pooled estimates*, I-MOVE pooled analysis, influenza season 2013-14

Vaccine effectiveness (%)

- Crude estimate includes study site. Heterogeneity all ages, crude: $I^2 = 0.0\%$, $p=0.434$; adjusted: $I^2 = 0.0\%$, $P=0.695$.
- Adjusted by: study site, age (cubic spline), sex, chronic condition, onset week (onset month for 0-14 yrs);
- 0-14 yrs: 4 controls unvaccinated in PT dropped
Crude VE by vaccine type against influenza A(H1N1), 1-stage pooled estimate*, I-MOVE multicentre case control study, influenza season 2013-14

* Adjuvanted includes Fluval AB. Crude estimates adjusted by study site;
Adjusted VE against A(H3N2), total population, by country and 2-stage pooled estimate*, I-MOVE pooled analysis, influenza season 2013-14

* Crude: Heterogeneity $I^2$ = 54.3%. Cochrane’s p-value: 0.053.

Adjusted for:
DE, ES: Age (cubic spline), sex, chronic condition, onset month (cubic spline)
IE, RO: Age group (3 categories), chronic condition, onset month
HU: Age group (3 categories); PT: Age (2 categories), chronic condition, onset month
Heterogeneity $I^2$ = 52%. Cochrane’s p-value: 0.064
In summary
VE against A(H1N1)

- No statistical heterogeneity between country-specific VE estimates
  - VE: 47.5% (95% CI: 16.4-67.0)
  - similar to VE in 2012-13 (50.4%)

- VE by age group
  - higher among youngest: 64.4%
  - lower among adults: 38.8%

- VE by vaccine type
  - higher VE for adjuvanted vaccine (NS)
  - similar VE subunit, split virion
  - sample size needs to increase
Reasons for heterogeneity in A(H3N2)

- **Low vaccine coverage** in controls & **low sample size**
  ✔ high variability

- **Different vaccines** used?
  ✔ need much larger sample sizes to analyse by type and brand

- **Different age** distributions
  ✔ but pattern not consistent between countries
  ✔ estimates are age adjusted

- **Other biases**: information / selection?
  ✔ but why only for A(H3N2), and not for A(H1N1)?

- **Virological changes**?
  ✔ Changes in amino acid positions in B antigenic site
    but no correlation with low or high VE.
  ✔ Isolated viruses antigenically similar to vaccine virus
Conclusion

- Interesting season with higher heterogeneity than usual
  - cannot conclude for VE against A(H3N2)

- I-MOVE multicentre case-control study
  - a strong network using the right and robust methods to answer VE related questions
  - due to low vaccination coverage in EU, we need larger sample sizes than in USA, Canada & Australia

- Pending questions
  - Can we guide WHO vaccine selection committee?
  - How fast is immunity waning in the season?
  - What is the role of former vaccinations?
  - Can we measure brand specific VE?

- EU vaccine scientists
  - to request a stronger commitment from EC and EU agencies for an independent evaluation of vaccine performances
I-MOVE multi-centre case control team 2013-14

- **Germany, RKI**: Udo Buchholz, Annicka Reuss
- **Hungary, Office of the Chief Medical Officer**: Krizstina Horvath, Beatrix Oroszi
- **Ireland, HSE**: Joan O'Donnell, Coralie Giese, Lisa Domegan, Darina O’Flanagan,
- **Portugal, Inst Nac Saude Dr Ricardo Jorge**: Baltazar Nunes, Raquel Guiomar, Pedro Pechirra, Ausenda Machado
- **Romania, Cantacuzino Institut**: Daniela Pitigoi, Emilia Lupulescu, George Necula, Carmen Marica, Maria Elena Mihai, Viorel Alexandrescu
- **Spain, ISCIII**: Amparo Larrauri, Silvia Jiménez, Salvador De Mateo, Francisco Pozo
- **EpiConcept**: Esther Kissling, Marta Valenciano, Alain Moren
Sample size for complete case analysis, I-MOVE multicentre case control study, EU, 2013-14

Total records before restriction: 4292

**A(H1N1)**
- After restriction/exclusion: 2243
  - Cases: 531\(^a\)
  - Controls 1712
- No missing seasonal vaccination status/date: 2157

**A(H3N2)**
- After restriction/exclusion: 2543
  - Cases: 623\(^a\)
  - Controls 1920
- No missing seasonal vaccination status/date: 2430

Complete case analysis total population:
- No missing data for covariates
  - **A(H1N1)**: 2113
  - **A(H3N2)**: 2370

\(a\): One A(H1N1) A(H3N2) coinfection
Sources of funding 2013-14

- National institute’s own funding
- WHO/US CDC
- EpiConcept