Influenza vaccine effectiveness in Europe, 2010-11: Estimates from the I-MOVE multi-centre case control study

E. Kissling on behalf of the I-MOVE multi-centre case control study team
Background

- **I-MOVE:** Monitoring IVE in EU and EEA Studies since 2008/9
- Multi-centre case control
  - 8 flu VE case-control studies in 2010/11 season

Very similar protocols ➔ Pooled analysis

- To obtain summary, preliminary VE measures
- To enable controlling for all covariates
Methods

- **Study population**: patients consulting for ILI in 1035 GP practices
  - Systematic selection of ILI/ARI patients to swab (incl. all elderly)
  - Confirmation with RT-PCR or culture
  - EU ILI; swabbed <8 days after symptom onset

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

- **Test-negative design**
  - **Case**: 1) Influenza + 2) AH1N1 + 3) B+
  - **Control**: influenza -

- **Vaccinated**: onset >14 days after vaccination

- **Analysis**: VE=(1-OR)*100; logistic regression
  - Complete case analysis
  - Multiple imputation using chained equations
Methods

Pooled 1-stage model

- Study as fixed effect
  (true exposure effect in each study is the same)
- Covariates for adjustment: age group (10y groups), sex, current smoker, presence of chronic disease and related hospitalisations, previous seasonal and pandemic flu vaccination, number of GP visits, week of onset.

Stratified analysis by:
  age group, influenza type, target group for vaccination

Pooled 2-stage random effects model

- IVE by study site, adjusted for age group, presence of chronic disease, month of onset
- Pooled average of results
Sample size for complete case and imputed datasets, multi-centre case control study, EU, 2010-11

Total records: 4410

No missing seasonal vaccination data: 4390

No missing data for covariates: 3254

Multiple imputation data: 4410

Complete case analysis
ILI influenza positive (n=2019) and negative cases (n=2391), AH1N1 cases (n=1179), influenza B cases (n=765), by week of symptom onset (N=4410), multi-centre case control study, EU, 2010-11

![Graph showing the number of ILI influenza positive and negative cases, AH1N1 cases, and influenza B cases by week of symptom onset from ISO week 45 to 52, 2010 and 2011. The graph indicates a peak in cases around ISO week 1 to 3, with a decline thereafter. The lines represent controls and any flu cases.](image-url)
ILI influenza positive (n=2019) and negative cases (n=2391), AH1N1 cases (n=1179), influenza B cases (n=765), by week of symptom onset (N=4410), multi-centre case control study, EU, 2010-11

Controls
Any flu cases
AH1N1 cases
Influenza B cases

ISO week of symptom onset, 2010 and 2011
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cases</th>
<th>Controls</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age</td>
<td>23</td>
<td>32</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Fever</td>
<td>1964/2016 (97.5)</td>
<td>2246/2381 (94.3)</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>Cough</td>
<td>1891/2018 (93.7)</td>
<td>2049/2382 (86.0)</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>Pandemic vaccination, 2009-10</td>
<td>148/1994 (7.4)</td>
<td>300/2348 (12.8)</td>
<td>0.001†</td>
</tr>
<tr>
<td>Heart disease</td>
<td>62/1296 (4.8)</td>
<td>201/1715 (11.7)</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>2+ GP visits previous 12 months</td>
<td>916/1611 (56.9)</td>
<td>1379/2010 (68.6)</td>
<td>&lt; 0.001†</td>
</tr>
<tr>
<td>Current smoker</td>
<td>165/1791 (9.2)</td>
<td>319/2137 (14.9)</td>
<td>&lt;0.001†</td>
</tr>
</tbody>
</table>

* Nonparametric equality-of-medians test; † Fisher’s exact test;
VE of seasonal vaccine against all influenza, AH1N1 and influenza B, imputed analysis, multi-centre case control study, EU, 2010-11

<table>
<thead>
<tr>
<th></th>
<th>Crude*</th>
<th>Adjusted‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>All influenza (N=4410)</td>
<td>64</td>
<td>52</td>
</tr>
<tr>
<td>H1N1 (N=3344)</td>
<td>68</td>
<td>55</td>
</tr>
<tr>
<td>B (N=2944)</td>
<td>66</td>
<td>50</td>
</tr>
</tbody>
</table>

* Study site in model as a fixed effect
‡ adjusted for 10 year age groups, sex, week of onset, chronic diseases and related hospitalisations, smoking, pandemic and seasonal influenza vaccination in 2009-10 and number of practitioner visits in the previous year
VE of seasonal vaccine against all influenza, by age group, imputed analysis, multi-centre case control study, EU, 2010-11

* Study site in model as a fixed effect
‡ adjusted for 10 year age groups, sex, week of onset, chronic diseases and related hospitalisations, smoking, pandemic influenza vaccination in 2009-10 and number of practitioner visits in the previous year
Overall and strain-specific adjusted VE of seasonal vaccine, among target group for vaccination, imputed analysis, multi-centre case control study, EU, 2010-11

Study site in model as a fixed effect
Adjusted for 10 year age groups, sex, week of onset, chronic diseases and related hospitalisations, smoking, pandemic influenza vaccination in 2009-10 and number of practitioner visits in the previous year
## Comparison of overall IVE using 1-stage and 2-stage pooled models, multi-centre case control study, EU, 2010-11.

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>VE</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total population</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete case 1-stage fixed effect pooled analysis(^1,2)</td>
<td>4141</td>
<td>48.7</td>
<td>29.7-62.6</td>
</tr>
<tr>
<td>2-stage random effects pooled analysis(^2)</td>
<td>4129</td>
<td>47.7</td>
<td>25.3-63.4</td>
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<tr>
<td><strong>Target group for vaccination</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete case 1-stage fixed effect pooled analysis(^1,3)</td>
<td>903</td>
<td>52.8</td>
<td>30.8-67.8</td>
</tr>
<tr>
<td>2-stage random effects pooled analysis(^3)</td>
<td>885</td>
<td>57.1</td>
<td>16.4-78.0</td>
</tr>
</tbody>
</table>

Models adjusted for: age group, chronic disease, month of onset
1 Study site in model as fixed effect.
2 Ireland excluded as no vaccinated cases (N=190)
3 Ireland excluded as no vaccinated cases (N=46)
Discussion

Lower VE against A(H1N1) 2009 in 2010/11 compared to monovalent 2009/10 pandemic vaccine
– Perfect match of circulating and vaccine strain 09/10
– 2009/10: Adjuvanted vaccines
– Overestimation 2009/10?

Main confounder age
– Confounding different by age group
– Low confounding among other covariates
Discussion

- Age group 15-59: lower VE in overall population
  - Not among target group for vaccine

- 1-stage pooled analysis
  - Similar results to 2-stage analysis
  - Comparison hampered by small sample size by study site
Conclusions

- I-MOVE network can support 8 countries for multicentre case control study
  - Good data quality, communication
  - Rapid results (preliminary: February 2011)
  - Strain-specific, stratified results

- Moderate IVE 2010/11

- Increase in sample size needed for precise estimates and 2-stage pooling
  - More study sites contributing 2011/12
  - More GPs recruited
Thank you
I-MOVE multi-centre case control team

- **National partners:**
  - **France, OpenRome / GROG:** Jean-Marie Cohen, Anne Mosnier, Isabelle Daviaud
  - **Hungary, NCE:** Beatrix Oroszi, Krisztina Horvath, Marta Melles, Agnes Csohan, Mónika Rózsa
  - **Ireland, HSE:** Joan O’Donnell, Darina O’Flanagan, Aidan O’Hora, Anne-Sophie Barret
  - **Italy, ISS:** Caterina Rizzo, Silvia Declich, Antonino Bella, Maria Cristina Rota
  - **Poland, IPH:** Pawel Stefanoff, Małgorzata Gluchowska, Iwona Paradowska-Stankiewicz
  - **Portugal, Inst Nac Saude Dr Ricardo Jorge:** Baltazar Nunes, José Marinho Falcão, Raquel Guiomar, Pedro Pechirra, Ausenda Machado
  - **Romania, Cantacuzino Institut:** Viorel Alexandrescu, Daniela Pitigoiti, Emilia Lupulescu, Claudiu Sbarcea
  - **Spain, ISCIII:** Amparo Larrauri, Salvador De Mateo, Silvia Jiménez

- **ECDC:** B Ciancio, Piotr Kramarz, A Nicoll, Johan Giesecke
- **EpiConcept:** A Moren, E Kissling, C Savulescu, A Halm, T Seyler, M Valenciano, V Nancey, N Colombo, G Jeannerod
References:

Kissling E, Valenciano M; I-MOVE case-control studies team. Early estimates of seasonal influenza vaccine effectiveness in Europe, 2010/11: I-MOVE, a multicentre case-control study. 2011 Mar 17;16(11)


Backup slides
Number vaccinated by ISO-week of seasonal vaccination of ILI cases (N=350), mult-icentre case control study, EU, 2010-11
ILI influenza positive and negative cases, all and all vaccinated, by age N=(4410), multicentre case control study, EU, 2010-11

ILI flu positive vaccinated
ILI flu negative vaccinated
ILI flu positive unvaccinated
ILI flu negative unvaccinated
Crude VE estimates against all influenza, by country, multi-centre case control study, EU, 2010-11

Ireland using exact logistic regression
Crude 2 by 2 tables, by study site, multi-centre case control study, EU, 2010-11

<table>
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<tr>
<th></th>
<th>France</th>
<th>Hungary</th>
<th>Ireland</th>
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<tbody>
<tr>
<td></td>
<td>Case</td>
<td>Control</td>
<td>Case</td>
</tr>
<tr>
<td>Vaccinated</td>
<td>15</td>
<td>39</td>
<td>4</td>
</tr>
<tr>
<td>Unvaccinated</td>
<td>576</td>
<td>542</td>
<td>115</td>
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<th>Poland</th>
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<tbody>
<tr>
<td></td>
<td>Case</td>
<td>Control</td>
<td>Case</td>
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<tr>
<td>Vaccinated</td>
<td>17</td>
<td>64</td>
<td>6</td>
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<tr>
<td>Unvaccinated</td>
<td>99</td>
<td>235</td>
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<tbody>
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<td>Case</td>
<td>Control</td>
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<tr>
<td>Vaccinated</td>
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<td>13</td>
</tr>
<tr>
<td>Unvaccinated</td>
<td>147</td>
<td>88</td>
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