Influenza vaccine effectiveness estimates from the I-MOVE multicentre case-control studies in Europe, 2011-12 to 2012-13: is there evidence of waning of vaccine-induced immunity?

Esther Kissling on behalf of the I-MOVE multicentre case control study team
Introduction

Decrease of vaccine effectiveness (VE) over time suggested in European influenza studies in 2011-12 (UK, I-MOVE, Navarra)

- Higher early vs. late season VE; lower VE by days since vaccination
Introduction

Decrease of vaccine effectiveness (VE) over time suggested in European influenza studies in 2011-12 (UK, I-MOVE, Navarra)
• Higher early vs. late season VE; lower VE by days since vaccination

Virological changes across season (e.g. antigenic drift)

Waning of vaccine effect within individual
Introduction

Decrease of vaccine effectiveness (VE) over time suggested in European influenza studies in 2011-12 (UK, I-MOVE, Navarra)

- Higher early vs. late season VE; lower VE by days since vaccination

Virological changes across season (e.g. antigenic drift)

Waning of vaccine effect within individual

- Later begin of vaccination campaigns
- 2nd dose of vaccine for some target groups
Introduction

Decrease of vaccine effectiveness (VE) over time suggested in European influenza studies in 2011-12 (UK, I-MOVE, Navarra)

- Higher early vs. late season VE; lower VE by days since vaccination

Virological changes across season (e.g. antigenic drift)

Waning of vaccine effect within individual

- Later begin of vaccination campaigns
- 2nd dose of vaccine for some target groups

Hypothesis: Virological changes may be greater later in season.
- Decrease in VE with more days since vaccination in early season more likely attributable to waning of immunity?
Methods

I-MOVE multicentre case control study data
- 2011-12 for A(H3N2); 2012-13 for influenza B: seasons of greater sample size

Test-negative design: Patients consulting GP for ILI/ARI
- Case Influenza A(H3)/B positive
- Control Influenza negative

Early/late influenza phase based on equal numbers of cases

VE=(1-OR)*100

Logistic regression, adjusting for age, onset week, sex and presence of chronic conditions
- VE overall and early/late phase
**Methods**

- **Time since vaccination:**
  - days between date of vaccination and onset of ILI symptoms

- **Binary cutoff (Before/after: 3 months ~93 days)**

- **Model days since vaccination as restricted cubic spline**
  - Segments of polynomials fitted together as curve
  - 3 or 4 knots depending on sample size
  - Knots at 0, 15 days (a priori) and then at 75th or 40th and 90th centile
  - Calculate adjusted VE by day since vaccination
RESULTS
Number of ILI vaccinated by week of vaccination, A(H3) cases and controls by week of symptom onset, I-MOVE multicentre case control study, EU, 2011-12
A(H3) cases and controls by week of symptom onset, I-MOVE multicentre case control study, EU, 2011-12
Adjusted VE against influenza AH3N2 by time since vaccination, by age group, I-MOVE multicentre case control study, EU, 2011-12

Vaccinated cases / vaccinated controls

<table>
<thead>
<tr>
<th>Age Group</th>
<th>&lt;94 days</th>
<th>&gt;93 days</th>
<th>VE%</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ages</td>
<td>148/116</td>
<td>49/133</td>
<td>35</td>
</tr>
<tr>
<td>0-14 year olds</td>
<td>11/8</td>
<td>6/11</td>
<td>-7</td>
</tr>
<tr>
<td>15-59 year olds</td>
<td>34/38</td>
<td>28/37</td>
<td>-9</td>
</tr>
<tr>
<td>60 years and over</td>
<td>109/70</td>
<td>25/61</td>
<td>4</td>
</tr>
</tbody>
</table>
Adjusted VE against influenza AH3N2 by time since vaccination, by age group, early influenza phase, I-MOVE multicentre case control study, EU, 2011-12

VE %

- 31/115 <94 days (All ages)
- 38/30 >93 days (All ages)
- 5/10 <94 days (0-14 year olds)
- 6/2 >93 days (0-14 year olds)
- 12/44 <94 days (15-59 year olds)
- 7/12 >93 days (15-59 year olds)
- 14/54 <94 days (60 years and over)
- 25/16 >93 days (60 years and over)
Adjusted VE against A(H3N2) by days between vaccination and onset of symptoms, I-MOVE multicentre case control study, season 2011-12

Note: data truncated at -100
Adjusted VE against A(H3N2) by days between vaccination and onset of symptoms, early and late phase, I-MOVE multicentre case control study, season 2011-12

Note: data truncated at -150
Number of ILI vaccinated by week of vaccination, influenza B cases and controls by week of symptom onset, complete case analysis, I-MOVE multicentre case control study, EU, 2012-13

- Controls (N=2484)
- Influenza B cases (N=1860)
- Vaccinated patients (N=336)

15th February, 2013
Adjusted VE against influenza B by days between vaccination and onset of symptoms, all ages, overall, early and late influenza phase, I-MOVE multicentre case control study, season 2012-13

Note: data truncated at -150
Discussion

Analysis suggests in 2011/12 decline in VE by time since vaccination for A(H3N2) for all ages

- Peak VE at 31-43 days (71%)
- Lower VE in late phase suggesting virological changes
- Decline seen also in early phase, suggesting possibility of waning immunity
Discussion

Analysis suggests in 2012/13 mild decline in VE by time since vaccination for influenza B for all ages

– Small sample sizes overall do not exclude no decline

– Peak VE at 54-55 days (63%)
Discussion

- Low number of vaccinated and vaccinated cases brings uncertainty into models
  - Greater sample sizes needed for conclusions

- Loss of information when using binary cutoffs
  - Modelling of time since vaccination as a continuous variable recommended

- Careful when partitioning early/late influenza phase and +/- 3 months since vaccination in a multicentre study:
  - Different epidemic timing and vaccination campaigns by country may bias results if heterogeneity between countries
Conclusions

- Waning of immunity may be a real phenomenon, but greater sample size needed to obtain precise results by age group and influenza type/subtype.

- Individual detailed virological data in VE studies are needed to disentangle changes in immune response from virological changes over time.
Acknowledgements

For statistical advice & discussions:
- Chris Robertson, Stathclyde University/Health Protection Scotland
- Baltazar Nunes, Inst Nac Saude Dr Ricardo Jorge, Portugal

Multicentre case control team:
- France, OpenRome / GROG: Jean-Marie Cohen, Anne Mosnier, Isabelle Daviaud
- Germany: Udo Buchholz, Annicka Reuss
- Hungary, Office of the Chief Medical Officer: Beatrix Oroszi, Krisztina Horvath
- Ireland, HSE: Joan O'Donnell, Darina O’Flanagan, Justyna Rogalska
- Italy, ISS: Caterina Rizzo, Silvia Declich, Antonino Bella, Maria Cristina Rota
- Poland, IPH: Malgorzata 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, Silvia Jiménez, Salvador De Mateo

ECDC: Bruno Ciancio, Piotr Kramarz, Angus Nicoll, Johan Giesecke
EpiConcept: Alain Moren, Marta Valenciano, Camelia Savulescu, Marc Rondy, Ariane Halm, Thomas Seyler
Sources of funding

- ECDC
- National institute’s own funding
- WHO-EURO/US CDC
- EpiConcept
Backup slides
Decline in VE 2011-12

UK multicentric, Spanish and Navarra (Spain) TND study show lower VE in later influenza phase 2011-12

– UK: Early influenza phase: 43% (95% CI: -34 to 75),
  late influenza phase: 17% (95% CI: -24 to 45)

– Navarra: Early influenza phase: 37% (95% CI: -18 to 67),
  late influenza phase 19% (95% CI: -176 to 76)

– Spain: Early influenza phase: 52% (95% CI: 4–76),
  late influenza phase: 28% (95% CI: -124 to 77)
Decline in VE 2011-12

- UK multicentric, Spanish and Navarra (Spain) TND study show lower VE in later influenza phase 2011-12
  - UK: VE 53% (95% CI: 0 to 78) <3 months after vaccination, VE 12% (95% CI: -31 to 41) 3 or more months after vaccination
  - Navarre: VE 61% (95% CI: 5 to 84) in the first 100 days after vaccination, 42% (95% CI: -39 to 75) between 100 and 119 days, and zero thereafter
  - Spain: persons ≥65 years VE 85% (95% CI, 18-97) < 3 months after vaccination, null estimate > four months after vaccination
Adjusted VE against A(H3N2) by days between vaccination and onset of symptoms, among those aged 60 and older, overall, early and late phase, I-MOVE multicentre case control study, season 2011-12

Note: data truncated at -150
Introduction

- Duration of vaccine-induced immunity against influenza complex and debated, may be lower among elderly
- However antibody response studies show high seroprotection rates for A(H1N1) and A(H3N2) after 4 months, less consistency for B
- But do antibody response studies correlate with vaccine effectiveness (VE)?
- If waning of immunity within a season is real
  - Later begin of vaccination campaigns
  - 2\textsuperscript{nd} dose of vaccine for some target groups
Number of A(H3) cases by year of age, I-MOVE multicentre case control study, EU, 2011-12
Number of influenza B cases by year of age, I-MOVE multicentre case control study, EU, 2012-13
Adjusted VE against influenza B by time since vaccination, by age group, I-MOVE multicentre case control study, EU, 2012-13

Vaccinated cases / vaccinated controls

- <94 days: 22/86 (58%), 70/150 (46%)
- >93 days: 6/20 (36%), 20/20 (15%)

0-14 year olds
- <94 days: 7/29 (24%), 21/66 (32%)
- >93 days: 9/31 (29%), 28/63 (44%)

15-59 year olds
- <94 days: 67%, 62%
- >93 days: 51%, 54%

60 years and over
Adjusted VE against influenza AH3N2 by time since vaccination, by age group, early influenza phase, I-MOVE multicentre case control study, EU, 2011-12

<table>
<thead>
<tr>
<th>Age Group</th>
<th>&lt;94 days</th>
<th>&gt;93 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ages</td>
<td>47%</td>
<td>60%</td>
</tr>
<tr>
<td>0-14 year olds</td>
<td>29%</td>
<td>43%</td>
</tr>
<tr>
<td>15-59 year olds</td>
<td>53%</td>
<td>65%</td>
</tr>
<tr>
<td>60 years and over</td>
<td>55%</td>
<td>71%</td>
</tr>
</tbody>
</table>
Adjusted VE against A(H3N2) by days between vaccination and onset of symptoms, total influenza season, I-MOVE multicentre case control study, season 2012-13
Adjusted VE against A(H3N2) by days between vaccination and onset of symptoms, early influenza season, I-MOVE multicentre case control study, season 2012-13
Adjusted VE against A(H3N2) by days between vaccination and onset of symptoms, late influenza season, I-MOVE multicentre case control study, season 2012-13
Number of cases by week of symptom onset and age group for influenza B, I-MOVE multicentre case control study, season 2012-13
Number of cases by week of symptom onset and age group for influenza A(H3N2), I-MOVE multicentre case control study, influenza season 2011-12

- Cases: 0-14 years
- Cases: 15-59 years
- Cases: 60 years and over
Proportion of vaccinated controls by early/late influenza phase, I-MOVE multicentre case control study, influenza seasons 2009/10 to 2012/13

<table>
<thead>
<tr>
<th>Year</th>
<th>Early</th>
<th>Late</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009-10</td>
<td>AH1N1</td>
<td>N=1188</td>
</tr>
<tr>
<td>2010-11</td>
<td>AH1N1</td>
<td>N=793</td>
</tr>
<tr>
<td>2011-12</td>
<td>B</td>
<td>N=1461</td>
</tr>
<tr>
<td>2011-12</td>
<td>AH3</td>
<td>N=1190</td>
</tr>
<tr>
<td>2012-13</td>
<td>B</td>
<td>N=977</td>
</tr>
<tr>
<td>2012-13</td>
<td>AH3</td>
<td>N=1222</td>
</tr>
<tr>
<td>2012-13</td>
<td>B</td>
<td>N=470</td>
</tr>
<tr>
<td>2012-13</td>
<td>AH1N1</td>
<td>N=1380</td>
</tr>
<tr>
<td>2012-13</td>
<td>AH3</td>
<td>N=926</td>
</tr>
<tr>
<td>2012-13</td>
<td>B</td>
<td>N=1513</td>
</tr>
<tr>
<td>2012-13</td>
<td>AH1N1</td>
<td>N=11177</td>
</tr>
<tr>
<td>2012-13</td>
<td>AH3</td>
<td>N=1252</td>
</tr>
<tr>
<td>2012-13</td>
<td>B</td>
<td>N=1196</td>
</tr>
<tr>
<td>2012-13</td>
<td>AH3</td>
<td>N=1300</td>
</tr>
<tr>
<td>2012-13</td>
<td>B</td>
<td>N=1310</td>
</tr>
</tbody>
</table>