Measuring Influenza VE in EU
I-MOVE pooled analysis
using case control studies

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I-MOVE

• **ECDC project**: Monitoring seasonal and pandemic influenza vaccine effectiveness in Europe

• Need for study designs enabling:
  – Early, repeated, reliable, stratified (age, virus, etc.) estimates

• Feasible designs
  – Based on routine influenza surveillance in EU
  – Little additional workload

• Cohort studies, **case-control studies**, screening method
I-MOVE case control studies 2008-9 (pilot phase)

- 5 flu VE case-control studies in 2008-9
- Sentinel GPs (128) swabbed all elderly consulting for influenza-like symptoms (ILI)
- Influenza cases confirmed by RT-PCR or culture
- Controls: influenza negative ILI

![Diagram showing the process of swabbing elderly individuals presenting to GPs for influenza-like symptoms (ILI) and classifying them as cases or controls based on the results of RT-PCR or culture tests.]

Elderly with ILI (presenting to GP) → GP → Swabbing → Cases: ILI flu+ → Controls: ILI flu-
I-MOVE case control studies 2008-9 (pilot phase)

- Very similar, but not identical protocols
- Small sample sizes of individual studies

Pooled analysis
Pooled analysis: objectives

• To obtain summary VE measure
• To enable controlling for all confounders
• To enable large enough sample size for stratified VE estimates
Methods

• Individual data received from all 5 countries
• Common minimum set of covariates, including
  – Age, sex, presence of chronic disease, hospitalisations in previous 12 months, smoking status, functional status, any influenza vaccination in past 2 years
• Vaccinated
  >14 days before onset of ILI symptoms
Methods

• Restriction to
  – EU ILI case definition
  – <8 days delay between onset of symptoms and swabbing
  – Controls selected within interval of week of first and last case
  – >=65 years
Methods

• Evaluation of heterogeneity
  – Qualitative and statistical ($I^2$ index)
• Pooled 1-stage model
  – Study as fixed effect
  – Logistic regression, adjusting for age, sex, smoking status, functional status, presence of chronic disease, previous influenza vaccination, previous hospitalisations
Sample characteristics by country, influenza vaccine effectiveness multicentre case control study, EU, 2008-9

<table>
<thead>
<tr>
<th>Study</th>
<th>GPs (n)</th>
<th>Sample size</th>
<th>Swab date first enrolled case</th>
<th>Cases (n)</th>
<th>Proportion of ILI flu positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spain</td>
<td>48</td>
<td>81</td>
<td>28th Nov, 2008</td>
<td>44</td>
<td>54.3</td>
</tr>
<tr>
<td>Portugal</td>
<td>5</td>
<td>29</td>
<td>2nd Dec, 2008</td>
<td>14</td>
<td>48.3</td>
</tr>
<tr>
<td>Denmark</td>
<td>23</td>
<td>41</td>
<td>9th Jan, 2009</td>
<td>20</td>
<td>48.8</td>
</tr>
<tr>
<td>Romania</td>
<td>28</td>
<td>98</td>
<td>22nd Jan, 2009</td>
<td>30</td>
<td>30.6</td>
</tr>
<tr>
<td>Hungary</td>
<td>24</td>
<td>79</td>
<td>23rd Jan, 2009</td>
<td>30</td>
<td>40.0</td>
</tr>
</tbody>
</table>
Study-specific differences

• No evidence of statistical heterogeneity between studies: $I^2=0\%$

• Different case definition: Portugal

• Covariates: Previous hospitalisations, functional status collected differently

• In 3/5 studies, delay between onset of symptoms and swabbing shorter for cases than test-negative controls ($p<0.05$)
Study-specific and pooled adjusted Influenza VE in 5 test negative design case control studies, EU, 2008-9

- Pooled: 138 ILI flu+ cases, 189 ILI flu- controls

![Chart showing vaccine effectiveness (%)](chart)

- Spain: 82.9
- Portugal: 82.3
- Denmark: 90.9
- Romania: 86.8
- Hungary: 43.6
- Pooled estimate (65+): 59.1

Adjusted for age, sex, presence of chronic disease, smoking: PT
Adjusted for above and previous flu vaccination: RO, DK, HU
Adjusted for age, sex, presence of chronic disease, smoking, functional status: ES
Adjusted for above and previous flu vaccination, hospitalisation in previous 12 months: Pooled
Overall, stratified & type-specific adjusted Influenza VE in 5 test negative design cc studies, EU, 2008-9, 1-stage pooled analysis model

Vaccine effectiveness (%)
Study limitations

• Low study-specific sample sizes
  – Due to low influenza incidence in elderly
  – Comparison of individual studies difficult
  – Adjusting for all covariates only possible with pooled analysis (sample size)

• Pooling: greater sample size for better precision, strain-specific & stratified analysis
  – But: sample size needs to increase further
Study limitations

• 1-stage model: effect of vaccine and covariates same in all the studies. Valid assumption?
  – Next season: 2-stage pooled estimate incorporating random effects of studies

• Representativity of test-negative controls?
  – Difference in delay between symptom onset and swabbing
  – Different health-seeking behaviour/severity?
2009-10 season: VE against pandemic influenza

• Early estimates needed for decision-making
• Estimates for all age groups, by vaccine brand
  – Greater sample size needed
• Collection of covariates & exposure more difficult
  – Higher workload of GP
  – Vaccination not always carried out in GP practice
    (need to collect vaccination date(s), brand, doses)
Next steps

• More countries carrying out studies
• More GPs per country
• All age groups systematically swabbed
• Interim (pooled) analyses
Conclusions

• 2008-9 pilot phase results suggest protective effect of vaccine in elderly

• Feasible, acceptable study design for VE against seasonal influenza

• Pandemic situation challenging in terms of:
  – Sample size needed
  – Collection of information

• Excellent cross-European collaboration enables pooled analysis
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Reference

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Thank you