Measuring Influenza Vaccine Effectiveness in Europe
The “I-MOVE” European CDC network

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on behalf of the I-MOVE network
Since 2007

I-MOVE

- European CDC
- 19 Member States
- EpiConcept
Large variation of Influenza vaccine effectiveness according to:

- **Outcomes**
  - ARI, ILI, Hospitalisation, Death, Lab. Confirmation
  - Case definitions
  - Lab. technique

- **Matching** between vaccine & circulating strains

- **Population** characteristics (age & risk groups)

- **Vaccination** ascertainment

- **Study** designs (cohort, case control, screening)
  - Biases
    - Health seeking behaviours
    - Confounding (+ & -)

- **Time** periods during seasons & pandemic
Study designs in seasons and pandemics to enable:

- Evidence from several studies representative of EU
- **Laboratory confirmation preferred**
- IVE by:
  - age and risk groups
  - vaccine brands
  - circulating strains
- Control for + & - confounders
- **Early** and repeated measurements in season
- Acceptable: easy source of information for cases & reference groups
- Vaccination = time dependant variable during pandemics
Influenza VE studies in EU: 2009-10

Case control
- Spain (2)
- Romania
- Hungary
- Portugal
- Ireland
- Italy
- France
- Valencia, Spain (hospital based)

Electronic cohorts & Nested case control
- England, UK
- Scotland, UK
- Navarra, Spain
- The Netherlands
- Denmark
- Italy

Screening method
- Italy
- France
- Spain
- Portugal
2009-10, GP based multicentre case control study: Methods

• **Study population**: Patients consulting for ILI in 1114 GP practices
• **Study period**: Start >14 days after vaccination campaigns begin
  End last case followed by 2 weeks with no case
• **ILI**: EU case definition EU
• **Cases**: ILI testing positive
• **Controls**: ILI testing negative
• **Systematic statistical sampling** for swabbing of ILI patients
  – ILI swabbed < 8 days after ILI onset
  – Confirmation with RT-PCR or culture
• **Vaccinated**: >14 days before ILI onset
• **Analysis**: VE = 1-OR * 100
  • Complete case analysis (missing excluded)
  • Imputed analysis (multiple multivariate imputation by chained equations procedure)
Methods

• **Pooled 1-stage model**
  – Study as fixed effect (assumption: true effect in each study is the same)
  – Common coding of covariates: age group, current smoker, sex, current and previous seasonal flu vaccinations, chronic diseases and related hospitalisations, functional status, number of GP visits in previous year, week of symptom onset.

• **Logistic regression:** adjustment for all confounding factors

<table>
<thead>
<tr>
<th>Total records: 2902</th>
</tr>
</thead>
<tbody>
<tr>
<td>No missing pandemic vaccination data: 2835</td>
</tr>
<tr>
<td>No missing data for covariates: 1502</td>
</tr>
<tr>
<td>Multiple imputation data: 2902</td>
</tr>
</tbody>
</table>
Number of vaccinated and unvaccinated cases (N=2835), by case / control status and country, multicentre case control study, EU, 2009-10

<table>
<thead>
<tr>
<th>Country</th>
<th>Case</th>
<th>Control</th>
<th>Case</th>
<th>Control</th>
<th>Case</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>3</td>
<td>63</td>
<td>6</td>
<td>100</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>695</td>
<td>1070</td>
<td>49</td>
<td>206</td>
<td>28</td>
<td>46</td>
</tr>
<tr>
<td>Hungary</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ireland</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>10</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>44</td>
<td>31</td>
<td>145</td>
<td>4</td>
<td>18</td>
</tr>
<tr>
<td>Total</td>
<td>1</td>
<td>9</td>
<td>12</td>
<td>185</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>58</td>
<td>226</td>
<td>883</td>
<td>1755</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Vaccinated with pandemic vaccine more than 14 days before onset of symptoms
VE of pandemic vaccine against pH1N1 by age group and chronic disease, missing excluded analysis, EU, 2009-10

* Study site in model as a fixed effect
‡ adjusted for age-group, sex, month of onset, chronic diseases and related hospitalisations, smoking, seasonal influenza vaccinations and number of practitioner visits in the previous year
VE of pandemic vaccine against pH1N1, by age group and chronic disease, imputed database, EU, 2009-10

* Study site in model as a fixed effect
‡ adjusted for age-group, sex, month of onset, chronic diseases and related hospitalisations, smoking, seasonal influenza vaccinations and number of practitioner visits in the previous year
VE of pandemic vaccine against pH1N1, by delay between vaccination and onset, missing excluded analysis, multicentre case control study, EU, 2009-10

![Graph showing vaccination efficacy (VE) percentages for different delay periods between vaccination and onset.](image)

<table>
<thead>
<tr>
<th>Delay Period</th>
<th>Crude* (N=1502)</th>
<th>Adjusted‡ (N=1502)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;8 days</td>
<td>21</td>
<td>19</td>
</tr>
<tr>
<td>8-14 days</td>
<td>60</td>
<td>66</td>
</tr>
<tr>
<td>15+ days</td>
<td>79</td>
<td>67</td>
</tr>
</tbody>
</table>

* Study site in model as a fixed effect
‡ adjusted for age-group, sex, month of onset, chronic diseases and related hospitalisations, smoking, seasonal influenza vaccinations and number of practitioner visits in the previous year
Limitations

• **Vaccination campaigns began after incidence peak in most countries:**
  – Low VC in study; few vaccinated cases
  – Impeded stratum-specific analysis
    • Brand
    • Type of vaccine (adjuvanted and not)
    • Early and late phase of the outbreak
  – Overestimation of VE
    if natural immunity differential
    between vaccinated and unvaccinated (children vs adults)

• **Pooled analysis:**
  – No two-stage model, no evaluation of statistical heterogeneity

• **Missing data** for some variables
  – Flu vaccination in previous 2 years, GP visits
Strengths of I-MOVE pooled case control studies

- Pooled analysis feasible
- **Common protocol** for 7 study sites
- Collection of many covariates and ability to **adjust for many confounders**
  - Time, age, health seeking behaviour, chr. diseases
- **Large sample size** for overall analysis
- **Systematic sampling** rather than ad hoc sampling
- Attempt to show **representatively VE in Europe**
- Excellent cross-European collaboration
Next steps

- Increase number of countries in multicentre studies
  - Increase ILI sample size in each study site
  - Stratified analysis by risk groups, strains and vaccine brands
- Earlier measurements in season
  - 2009-10: early February
  - 2010-11: early March
Case control studies (test negative design) nested in cohorts, adjusted VE of pandemic vaccine against pH1N1, 2009-10

NESTED CASE CONTROL STUDIES

<table>
<thead>
<tr>
<th>Country</th>
<th>N</th>
<th>VE %</th>
</tr>
</thead>
<tbody>
<tr>
<td>England*</td>
<td>1149</td>
<td>55</td>
</tr>
<tr>
<td>Navarra, Spain†</td>
<td>646</td>
<td>100</td>
</tr>
<tr>
<td>Scotland</td>
<td>1492</td>
<td>70</td>
</tr>
</tbody>
</table>

* Adjusted for age, seasonal vaccination, onset month
† Adjusted for age, high risk group
‡ Adjusted for age and onset month
Influenza vaccine effectiveness estimates, test negative case control studies, Europe, 2010-11 (until January 28, 2011)

VE %

England  Spain  7 EU sites  England  Spain  England  Spain

Seasonal V  2010-11  Pandemic V only  Both pandemic & seasonal V

pH1N1  All  pH1N1  All  pH1N1  All
Electronic cohort study, Navarra, Spain

- Navarra region, 600 000 inhabitants
- 600 GPs and paediatricians, public practices sharing same software
- Linked data bases
  - GP medical records
  - Hospital discharge records
  - Vaccination registries
  - Laboratory data
  - Death registries
- Real time vaccine effectiveness
Incidence of ILI by week and periods of virus circulation
Navarra, 2008-9
Weekly mortality in the cohort of ≥65 years by vaccine status, Navarra, Spain, 2008-9

Flu A/H3N2
Flu B

Weeks
Rate per 100,000
Unvaccinated
Vaccinated

Weeks
47 48 49 50 51 52 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21
Adjusted seasonal vaccine effectiveness for all causes of death, population ≥ 65 years by 3 week periods, Navarra, Spain, 2008-9.
Next steps

- Electronic cohort studies
  - Validate ICD codes
  - Laboratory confirmed outcome (validation subset)
  - To further adjust for confounding by indication carry out before/during/after-season IVE analyses for clinical, hospitalisation & death outcomes
Conclusion

• Since 2007
  a network of European study sites has helped:
  – Basing decision making on estimates of Influenza vaccine effectiveness from several countries and designs
  – Carry out representative multicentre studies
  – Provide early estimates in seasons or pandemics
  – Identify and develop electronic cohort studies (using quality data!)
  – Create a momentum for hospital based VE studies on severe influenza outcomes
Merci

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  - Sweden, SMI
  - The Netherlands, RIVM
ILI pH1N1 positive and negative cases by onset week (N=2902), ILI cases vaccinated with pandemic vaccine (N=197), multicentre case control study, EU, 2009-10
ILI: EU case definition

• Sudden onset of symptoms
• and at least one of the following four systemic symptoms:
  – fever or feverishness,
  – malaise,
  – headache,
  – myalgia
• and at least one of the following three respiratory symptoms:
  – cough,
  – sore throat,
  – shortness of breath
• who was swabbed and tested positive for the pH1N1 using real-time polymerase chain reaction (RT-PCR) or culture.
## Pandemic vaccines used by study site, multicentre case-control study, influenza season 2009-10

<table>
<thead>
<tr>
<th>Vaccines</th>
<th>Adjuvant</th>
<th>Date Marketing 2009</th>
<th>Countries</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cevalpan (Baxter)</strong></td>
<td>None</td>
<td>2 Oct</td>
<td>Fr, Ir</td>
</tr>
<tr>
<td><strong>Focetria (Novartis)</strong></td>
<td>MF59</td>
<td>25 Sept</td>
<td>Fr, It, Sp</td>
</tr>
<tr>
<td><strong>Pandemrix (GSK)</strong></td>
<td>ASO3</td>
<td>25 Sept</td>
<td>Fr, Ir, Pt, Sp</td>
</tr>
<tr>
<td><strong>Fluval P</strong> Omninvest</td>
<td>Aluminium phosphate</td>
<td>28 Sept</td>
<td>Hu</td>
</tr>
<tr>
<td><strong>Panenza (Sanofi Pasteur)</strong></td>
<td>None</td>
<td>16 Nov</td>
<td>Fr, Sp</td>
</tr>
<tr>
<td><strong>Cantgrip (Cantacuzino)</strong></td>
<td>None</td>
<td>26 Nov</td>
<td>Ro</td>
</tr>
</tbody>
</table>
start vaccination, week 43

start vaccination, week 44

Incidence

start vaccination, week 45

start vaccination, week 46

start vaccination, week 48
ILI pH1N1 positive and negative cases by age N=(2895), multicentre case control study, EU, 2009-10