Challenges when measuring Influenza Vaccine Effectiveness In Europe

Collaboration between
- I-MOVE, Europe
- EU-Member states
- EU CDC
- REVELAC
- Australia
- Canada

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On behalf of
The I-MOVE network
The I-MOVE network 2007 – 2015

- **I-MOVE network**
  - 24 institutes + ECDC
  - 17 Member States in EU / EEA
  - Collaboration with:
    - WHO, WHO-EURO, EMA, USA, Canada, Australia, Latin America

- **Studies in 15 sites since 2007**
  - Generic protocols
  - National test negative design (TND) studies based on GP sentinel networks
  - **Multicentre TND in up to 10 countries**
  - Cohorts based on computerised registers
  - Rapid case coverage VE estimates

![Map of Europe with institutes marked]

- **Legend:**
  - Test negative design (TND)
  - Cohort with nested TND
  - Case coverage method
  - Partner institutes
Influenza vaccine effectiveness
Unanswered questions

- What is the average VE for H1N1, H3N2 & B over time?
- Is immunity waning in the season?
- What is the role of vaccinations in previous seasons?
- Can we / should we measure VE by vaccine type / brand?
- Can we provide robust VE results to guide WHO Committee on vaccine content?
Methods: Multicentre test negative design study
I-MOVE network, 8 EU countries, 2008-15

- **Study population**
  Patients consulting for ILI/ARI in >1000 GP practices
  - **Systematic statistical sampling**
    of ILI/ARI patients to swab
  - Confirmation with RT-PCR or culture
  - EU ILI, swabbed <8 days after symptom onset

- **Test-negative design** (sub type-specific analysis)
  Case: Influenza (type/subtype) positive
  Control: Influenza negative

- **Study period**
  Start: >14 days after vaccination campaign begin
  End: Two weeks after last case

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

- **Sentinel GPs:** sample of ILI patients
- **Ref lab:** PCR, culture
- **Cases:** ILI PCR +
- **Controls:** ILI PCR -
Adjusted VE, all ages, by type/subtype and season
I-MOVE 2008/9-2014/15

* Among those ages 65 and older; ** Imputed analysis, *** 2-stage model, **** Estimates up to w9, 2015
<table>
<thead>
<tr>
<th>Type/sub-type</th>
<th>Sample size Cases/controls</th>
<th>VE%</th>
<th>Lower limit</th>
<th>Upper limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>A(H1N1)</td>
<td>10193 (3013;7180)</td>
<td>50.5</td>
<td>39.1</td>
<td>59.7</td>
</tr>
<tr>
<td>Influenza B</td>
<td>9406 (3195;6211)</td>
<td>52.0</td>
<td>40.9</td>
<td>61.0</td>
</tr>
<tr>
<td>A(H3N2)</td>
<td>12477 (4437;8040)</td>
<td>20.5</td>
<td>8.1</td>
<td>31.3</td>
</tr>
</tbody>
</table>
Waning immunity?

VE against **A(H1N1)** by time since vaccination (days), all ages, **whole season**, I-MOVE 2010-11 to 2014-15

![Graph showing VE against A(H1N1) over time since vaccination with confidence intervals.](Image)
Waning immunity?

VE against influenza B by time since vaccination (days), all ages, overall season, I-MOVE 2010-11 to 2014-15

The graph shows the efficacy (VE) of influenza B vaccines over time since vaccination. The blue line represents the efficacy of influenza B, with the upper and lower confidence intervals indicated by the light blue lines. As timesince vaccination increases, the efficacy decreases, indicating a waning immunity effect.
VE against influenza B by time since vaccination (days), all ages, early season, I-MOVE 2010-11 to 2014-15

Waning immunity?
Waning immunity?

VE against A(H3N2) by time since vaccination (days), all ages, overall season, I-MOVE 2010-11 to 2014-15

VE (%)

Time since vaccination (days)
Waning immunity?

VE against A(H3N2) by time since vaccination (days), all ages, early season, I-MOVE 2010-11 to 2014-15

VE (%) vs Time since vaccination (days)
Is former vaccination affecting current VE?

Adjusted VE by current and previous season vaccination status, by type/subtype, I-MOVE 2010-11 to 2014-15

<table>
<thead>
<tr>
<th>Vaccine Status</th>
<th>Virus Type</th>
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<tr>
<td>Current season only</td>
<td>AH3N2</td>
</tr>
<tr>
<td>Previous season only</td>
<td>AH1N1</td>
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<tr>
<td>Both seasons' vaccine</td>
<td>Influenza B</td>
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</thead>
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<tr>
<td>Current season only</td>
<td>28.7%</td>
<td>56.4%</td>
<td>49.8%</td>
</tr>
<tr>
<td>Previous season only</td>
<td>29.9%</td>
<td>45.7%</td>
<td>-8.5%</td>
</tr>
<tr>
<td>Both seasons' vaccine</td>
<td>19.2%</td>
<td>13.8%</td>
<td></td>
</tr>
</tbody>
</table>

Cases/noncases: 88/205, 92/270, 380/670, 50/266, 104/316, 93/508, 44/239, 110/299, 112/410
Does VE vary by vaccine type?

**Adjusted vaccine type-specific VE, by type/subtype, I-MOVE 2010-11 to 2014-15**

- **A(H3N2)**
  - Subunit: 25.2%
  - Split virion: 21.6%
  - Adjuvanted: 15.7%
- **A(H1N1)**
  - Subunit: 58.0%
  - Split virion: 48.9%
  - Adjuvanted: 50.3%
- **Influenza B**
  - Subunit: 49.6%
  - Split virion: 54.3%
  - Adjuvanted: 54.3%
Does VE vary by vaccine brand?

Adjusted vaccine brand-specific VE, by type/subtype, I-MOVE 2010-11 to 2014-15

VE (%)
GIVE: Estimates of influenza vaccine effectiveness all age groups provided to WHO by virus type/subtype, 2013 season, eight study sites (six North & two South hemisphere)

Source: United Kingdom National; Canada National, Europe I-MOVE network, Navarra Spain, Spain National, UK National, USA Flu VE Network; Denmark National; Australia GP network..
How can we respond to the challenge?

- Larger sample size
- Multicentre studies / Pooling countries & years?
- Joint large laboratory and VE studies
  - Increase number and representativeness of strains characterised
  - Quantified viral change in season
  - Robust vaccine effectiveness results early in season
- International collaboration
- Sustainable national & international funding
Patients
Influenza Sentinel networks
Study sites I-MOVE

- Denmark: A Mazick, K Molbak (2008-9)
- England, Wales RCGP: D Fleming, H Durnall, S de Lusignan
- France OpenRome / GROG: JM Cohen, A Mosnier, I Daviaud
- Germany, RKI: A Ruess, U Buchholz
- Hungary, NCPHMOS, : B Oroszi, K Horvath
- Ireland, HSE: AS Barret , J Rebolledo, C Giese, L Domegan, O'Donnell
- Italy, ISS: C Rizzo, A Bella , MC Rota, S Erlich
- Poland National Institute of Public Health: I Paradowska-Stankeiwicz, M Fluchowska
- Portugal, Inst Nac Saude Dr Ricardo Jorge: B Nunes, A Machado, J Marinho Falcão, R Guiomar, P Pechirra
- Romania, Cantacuzino Institut: V Alexandrescu, D Pitigoiti, E Lupulescu,
- Scotland, HPS: J McMenamin, C Robertson, B V Wissmann
- Spain, CNE, ISCIII: A Larrauri, S Jiménez, S De Mateo, A Gherasim
- Spain, Navarra Public Health Institute: J Castilla, I Martinez
- UK, PHE: R Pebody, N Andrews

ECDC: B Ciancio, K Johansen, P Kramarz, A Nicoll, P Penttinnen
EpiConcept: E Kissling, A Moren, M Valenciano, M Rondy, C Savulescu, T Seyler, A Halm, V Nancey, N Colombo, G Jeannerod

Other partners Institutes
- Croatia, National Insitute of Public Health
- Denmark, SSI
- Finland. THL
- France, InVS
- France, Sentinelles
- France, Innovative clinical research network in vaccinology : I-RE
- Lithuania, Lithuanian University of Health Sciences
- Norway, FHI
- The Netherlands, RIVM
- The Netherlands, NIVEL
- Sweden, PH IAgency