Effectiveness and safety of seasonal and pandemic influenza vaccines: European Perspectives

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Declaration of Interest Statement
I have no relevant commercial interests www.europa.eu/transparency
The most entrenched conflict of interest in medicine is a disinclination to reverse a previous opinion

John Yudkin, Bernd Richter & Edwin Gale
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- Epiconcept and I-MOVE Collaboration
- VAESCO & the Brighton Collaboration
- National Collaborators and Regulatory Agencies
- World Health Organization Europe and HQ
- The VENICE-II Collaboration

Many many people in each of these
Background

- Potentially a new seasonal influenza in Europe – A(H1N1)2009 based
  - Affecting younger people
  - Clinical risk group more important
  - Significant numbers of severe cases in healthy people

- Flu vaccine used to varying degrees routinely in Europe

- Political commitment – since 2009
Vaccination coverage for seasonal influenza vaccine in older people (65 years & older) in EU and EEA countries

Latest seasonal data available in spring 2009 - For season 2007/8

Data available in 2009. No data available from: Austria, Cyprus, Czech Republic, Greece, Latvia
Background

• Potentially a new seasonal influenza in Europe – A(H1N1)2009 based
  – ? Affecting younger people
  – ? Clinical risk group more important
  – ? Significant numbers of severe cases in healthy people

• Flu vaccine used to varying degrees routinely in Europe

• Political commitment since 2009

• Mixed experience in Europe in the pandemic - but things that worked well outside the pandemic functioned in the pandemic - conversely …….
Pandemic Vaccination coverage in the population (n=21 countries)

- Sweden: High coverage
- Finland: High coverage
- Iceland: High coverage
- Norway: High coverage
- The Netherlands: High coverage
- Spain: High coverage
- Hungary: High coverage
- Ireland: High coverage
- Malta: High coverage
- Romania: Mid coverage
- Germany: Mid coverage
- France: Mid coverage
- Luxemburg: Mid coverage
- Portugal: Low coverage
- Slovenia: Low coverage
- Italy: Low coverage
- Estonia: Low coverage
- Greece: Low coverage
- Cyprus: Low coverage
- Austria: Low coverage
- Czech Republic: Low coverage

Vaccination coverage %

Vaccine Effectiveness
# Efficacy and Effectiveness of Vaccines – both important

## Efficacy
- **Seen in trials** – but usually optimal subjects
- **Can study mild infection only**
- **Simple**
- **Through serology** – a correlate of protection
- **Key in Regulation and annual licensing**

## Effectiveness
- **Observed in the field**
- **Estimates subject to various biases**
- **Estimates less stable**
- **Complex – Varying methods**
- **Can study severe disease and death**
- **Closer to the individual experience**
Monitoring influenza vaccine effectiveness in EU: why?

- Not the most effective vaccine but recommended in all EU MS
- Evaluate influenza vaccination programme
- Maintain confidence in vaccination programmes
- Influenza VE (IVE) varies from year to year
  - clinical IVE cannot be predicted based on antigenic distance
  - IVE can vary by age, subgroups and virus subtype
- Detect variations in effectiveness due to
  - changes in the target population
  - changes in the epidemiology of disease
  - poor virus-vaccine match
  - special field conditions
Monitoring influenza vaccine effectiveness in EU: why?

- Trigger other public health measures
  - use of antivirals

- For new vaccines IVE could be incorporated as component of post-licensure surveillance

- ILI /ARI incidence does not predictably decrease with increased vaccination coverage
  - VE cannot be inferred from surveillance data

- Trigger research on more effective vaccines
  - mode of administration
  - adjuvanted vs non-adjuvanted vaccines
  - dosages
I-MOVE Collaboration
(Influenza monitoring VE in Europe)
Objectives

- To identify and pilot test methods to measure seasonal and pandemic IVE in EU and EEA

- To develop a system to monitor on a routine and real-time basis IVE in EU and EEA
  - have early estimates during the influenza season
  - have a system ready to assess and monitor IVE in a pandemic
I-MOVE

- ECDC
- 20 EU & EEA Member States
- Coordination, EpiConcept

- Collaboration with
  ✓ Australia
  ✓ Canada
  ✓ USA

- Smittskäddsinstitutet, Stockholm, Sweden
- Statens Serum Institut, Copenhagen, Denmark
- Scottish Centre for Infection and Environmental Health (CIHE)
- Istituto Superiore Di Sanita, Rome, Italy
- Greece, National Institute of Health
- Royal College of General practitioners
  Brimingham Research Unit, UK
- Instituto Nacional de Saude Dr. Ricardo Jorge, Lisboa, Portugal.
Three Methodologies – all based on laboratory confirmed end-points

- Case control
- Cohort studies and nested case controls
- Screening method

Published Results

- 2008/9  Pre pandemic elderly – seasonal vaccine
- 2009  Pandemic vaccines – predominately adjuvanted
- 2010-2011  Post pandemic seasonal vaccine
Seasonal vaccine effectiveness 2008-9 pooled analysis pilot season (older people) – 5 sites

- **Crude**
  - Overall sample size: N = 327
  - Influenza A only: 55.1
  - Influenza AH3: 59.1

- **Full model**
  - Age: 65 - 74
    - Overall sample size: N = 327
    - Influenza A only: 65.4
    - Influenza AH3: 59.6
  - Age: 75+
    - Influenza A only: 57.4
    - Influenza AH3: 56.4

* Study site in model as a fixed effect
‡ adjusted for sex, chronic diseases and related hospitalisations, smoking, previous seasonal influenza vaccination, functional status,

Pandemic vaccine effectiveness 2009-10, imputed dataset, pooled analysis – 7 study sites

Overall sample size N = 2902


http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1000388

* 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

PIVE %

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<td>All</td>
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<td>&lt; 15 years</td>
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<td>No chronic disease</td>
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Seasonal vaccine 2010-11 effectiveness by influenza subtype, imputed dataset, pooled analysis – 8 study sites

Importance of Laboratory Confirmed End-points
Cohort study to evaluate the IVE in preventing MA-ILI and lab confirmed influenza in pop with chronic conditions, Navarra

Test negative case-control study to evaluate the IVE in preventing laboratory-confirmed influenza

* Euro Surveill 2011;16(7):pii=19799.
I-MOVE future

- To monitor influenza VE against severe outcomes
- Network of EU hospitals
  - similar protocol pooling
  - can be used for other diseases
- ECDC EVER programme
  - collect, analyse, communicate data and information on immunisation programmes in EU
  - bring under same umbrella activities previously covered by different projects
  - integrate the elements of vaccine preventable disease surveillance programme: disease surveillance, vaccine effectiveness, vaccination safety and vaccination coverage
Effectiveness Acknowledgements

- Sentinel networks
- Partners conducting studies in 2010/11
  - England and Wales, RCGP: Douglas Fleming, Haylay Durnall,
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  - Italy, Campobasso, Catholic University
  - Greece, KEEPNO
  - Norway, FHI
  - Spain, Valencia CSISP
  - Sweden, SMI
  - The Netherlands, RIVM
  - The Netherlands, Erasmus University,
Vaccine Safety
Monitoring and investigating in Europe
Content

• Methods of safety monitoring
• General Safety
• Investigating Adverse Events Following Immunisations
• Guillain-Barré syndrome
• Narcolepsy
Methods of safety monitoring and investigation

Spontaneous Reporting by Clinicians and (increasingly) the public

National Systems

Feed into EMA System Eudravigilance


EU Vaccine Task Force


Rapid Evaluation Group – (PREG) -

Review by Committee on Human Medical Products

Formal requests for special studies when signal appears
Preliminary analyses from EudraVigilance: reporting proportion of Autoimmune disorders (MedDRA HLGT ‘Autoimmune disorders’) amongst all ADR reports, 1st October 2009 to 31st December 2010

2. Analysis restricted to Autoimmune Disorders with causality related (certain, probable, possible), time to onset 1→42 days for GBS and 1→30 days for other reactions and BC 1-3 (GBS), 1-2 (ITP), 1-3 (ADEM)

<table>
<thead>
<tr>
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<th>ADJUVANTED pandemic influenza vaccines “</th>
<th>NON-ADJUVANTED pandemic influenza vaccines **</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number ADRs with Autoimmune Disorders</td>
<td>126</td>
<td>12</td>
</tr>
<tr>
<td>Number ADRs total</td>
<td>49,236</td>
<td>4,048</td>
</tr>
<tr>
<td>%</td>
<td>0.26</td>
<td>0.30</td>
</tr>
<tr>
<td>CI 95 %</td>
<td>[0.21 - 0.30]</td>
<td>[0.13 - 0.46]</td>
</tr>
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* Arepanrix™, Celtura™, Fluval P™, Focetria™, Pandemrix™, Humenza™

** Cantgrip™, Celvapan™, Panenza™
Vaccine Safety Signal detection and assessment in Europe

- Routine reporting of adverse events following immunization
- Validation of safety concerns – case ascertainment
- Causal association studies

Post-licensure monitoring for AEFIs shared responsibility between manufacturers, Public Health Institutes/ECDC and National Regulatory Agencies/EMA

However, should a signal arise sustainable European infrastructure only now being built
VAESCO

- ECDC since 2008 funds and collaborates closely with a consortium of researchers in Denmark, Finland, France, Germany, Italy, Netherlands, Norway, Spain, Sweden, Switzerland, and UK:
  
  *Vaccine Adverse Event Surveillance & Communication*

- Coordination of the VAESCO consortium – Brighton Collaboration

- Central data analyses by Erasmus University

- Major component - data linkage of different health registries

- Rationale: For rare events populations of one country is too small

- Project was accelerated due to use of new pandemic vaccines – unprecedented effort - need for €€€ infusion
The European Vaccine Safety Data linkage system

Database in country 1
Jerboa vaccine module software

Database in country 2
Jerboa vaccine module software

Database in country..n
Jerboa vaccine module software

Country borders

EUROPEAN LEVEL
Pooling of national/regional **aggregated**
data at Erasmus university medical center

*this comes from the drug safety area where it is proven to work well and also in the US CDC Vaccine Safety Datalink system*
On-going and completed studies

- **Establishing Base-line for selected conditions** – undergoing validation

- **Assessment of GBS and pandemic vaccines** – € 1,1 million
  - TP and MMR – proof of concept, Vaccine 2011
  - CCS – accepted BMJ
  - SCCS – in manuscript

- **Assessment of narcolepsy and pandemic vaccines** – € 524,000
  - Case definition finalized together with European network of narcolepsy experts
  - Background incidence being developed
  - Case control study on-going
Results obtained from data linkage can be pooled from different countries using MMR vaccine and a known adverse event trombocytopenic purpura following MMR.

Table 3: Relative incidence of ITP after MMR vaccination in children aged 12-23 months using SCCS analysis of pooled data from Denmark and England and using meta-analysis of each countries individual SCCS RI estimates.

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Period after MMR (days)</th>
<th>RI (95% CI) [n]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-13</td>
<td>14-27</td>
</tr>
<tr>
<td>Pooled data with common age effect</td>
<td>1.38 (0.76-2.50)</td>
<td>3.09 (2.02-4.73)</td>
</tr>
<tr>
<td>Pooled data with country specific age effects</td>
<td>1.30 (0.71-2.38)</td>
<td>2.87 (1.85-4.46)</td>
</tr>
<tr>
<td>Meta-analysis</td>
<td>1.30 (0.71-2.38)</td>
<td>2.84 (1.82-4.43)</td>
</tr>
</tbody>
</table>

Andrews N et al Vaccine 2011
Background incidence results pooled
importance of age and sex standardisation

Sex specific GBS rate, pooled data

*Unpublished – validation on-going
Results GBS case control study*

We can exclude a relative risk increase beyond 2.7 based on the 95% confidence interval. Less than 3 attributable cases per 1,000,000 vaccinated persons

*Dieleman et al BMJ 2011 [http://www.bmj.com/cgi/doi/10.1136/bmj.d3908](http://www.bmj.com/cgi/doi/10.1136/bmj.d3908)
Conclusions

- Field vaccine effectiveness system can be established - need infrastructure and some expert capacity
- Don’t over-state effectiveness
- Vaccine safety again need infrastructure
- Simple signal reporting - need independent systems for rapid investigation – but its never fast
- Linked data-bases and registries are a way to go
- How to make the systems sustainable?
Acknowledgements

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Many many people in each of these
Thank you