H1N1 pandemic
Will vaccines solve the problem
and how will we know?

Monitoring vaccine effectiveness in EU
during seasonal and pandemic influenza

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I- MOVE: ECDC tender (FWC ECDC/07/015)
- ECDC
  - EISN
- Health Protection Surveillance Centre, Dublin, Ireland
- Instituto de Salud Carlos III, Madrid, Spain
- Institut de Veille Sanitaire, Paris, France
- National Center for Epidemiology, Budapest, Hungary
- National Institute of Research – Development for Microbiological and Immunology, Bucharest, Romania
- National Institute for Pubic Health and the Environment (RIVM), Bithoven, The Netherternlands
- Norwegian Institute of Public Health, Oslo, Norway
- National Public Health Institute, Helsinki, Finland
- Robert Koch Institute, Berlin, Germany
- Scientific Institute of Public Health, Brussels, Belgium
- Smittskidsinstitutet, Stockholm, Sweden
- Statens Serum Institut, Copenhagen, Denmark
- Scottish Centre for Infection and Environmental Health (CIEH)
- Istituto Superiore Di Sanita, Rome, Italy
- Slovenia, National Institute of Health
- Greece, National Institute of Health
- Royal College of General practitioners Brimingham Research Unit, UK
- Insituto Nacional de Saude Dr. Ricardo Jorge, Lisboa, Portugal.
Influenza vaccine effectiveness varies according to:

- **Outcomes**
  - Case definition
    - Laboratory methods
- **Matching** between vaccine & circulating strains
- **Population** (age & risk groups)
- **Vaccine** ascertainment
- **Study** designs
  - Biases
    - Health seeking behaviours
    - Confounding (+ & -)
- **Time** periods during seasons & pandemic
Which outcomes?

Different aspects of disease burden (programme impact)
Different questions

- Death
  (all causes, specific for pneumonia & influenza)
- Hospitalisation
  (all causes, pneumonia & influenza, CVD)
- Medically attended ARI, ILI

Se, Sp, VPP / N of case definitions varies with:
  Time (incidence, other viruses),
  Age
  Health seeking behaviours
Laboratory confirmation preferred

- **Culture, RT-PCR**
  - Time onset / consultation
    - varies by country, age groups, seasonal and **pandemic** flu
  - Specimen sampling (mode & timing < 8 days, < 4 days?)

- **Laboratory capacity**
  - Workload
  - Cost
  - Quality **assurance & control**
  - Validation sets
    - Systematic or random sample swabbing
How to ascertain vaccination status?

Sources
- Medical records
- Computerised medical records
- Registries
- Insurance data
- Patients interviews
- Vaccine coverage (administrative data, surveys)

In pandemics
- vaccination becomes a time dependant variable
- vaccine brand needed
- GPs no longer vaccinating?
Which confounding factors?

Vaccination → RR, OR → Outcome(s) → Confounder(s)

- **Negative confounding** underestimates VE
  - Confounding by indication
  - Individual with underlying chronic diseases more likely to be vaccinated

- **Positive confounding** overestimates VE
  - Healthier individuals more likely to request vaccination
  - Extremely frail individuals unlikely to be vaccinated

Strength of association depends upon chosen outcome
Difference between crude and adjusted VE against outcomes including deaths: cohort studies
Difference between crude and adjusted VE against laboratory confirmed Influenza: case control studies
Potential confounders

Negative

• Underlying chronic condition (ascertained through ICD codes or ad hoc questionnaires)
  - Asthma
  - Other pulmonary diseases
  - Heart diseases
  - Diabetes mellitus and other endocrine diseases
  - Renal diseases
  - Malignant disorders
  - Neurological diseases
  - Musculoskeletal and connective tissue diseases
  - Immunosuppression
  - Institutions

Positive

Data bases
- Reflect health care utilisation

Severity
- Medication prescribed & number of repeat prescriptions
- Length of hospital stay
- Number of hospital admissions and outpatients visits

Functional status
- Lifestyle factors
- Education level
- House heating

Potential confounders

Non Smoking

Former Influenza and Pneumococcal vaccination

Extreme frailty

High Socio economic status

Functional status

Physical activity

Health related behaviours

Education level

House heating

Data bases

- Reflect health care utilisation

Severity

- Medication prescribed & number of repeat prescriptions
- Length of hospital stay
- Number of hospital admissions and outpatients visits

Functional status

- Lifestyle factors
- Education level
- House heating
Adapted from Simonsen
Study design in seasons and during pandemics to enable:

- IVE for various outcomes
  - Laboratory confirmation preferred
- IVE by:
  - age and risk groups
  - vaccine brands
  - circulating strains
- Control for many + & - confounders
- Early and repeated measurements
- Acceptable (easy source of cases & reference groups)
- Vaccination = time dependant
- 3 potential designs
  - Cohort (data bases)
  - Case control
  - Screening method
Influenza VE studies in EU: 2009-10

Case control
- Spain
- Romania
- Hungary
- Portugal
- Ireland
- Italy
- France

Cohorts & Nested case control
- England, UK
- Scotland, UK
- Navarre, Spain
- The Netherlands

Screening method
- Italy
- France
- Spain
- Portugal
EU: 4 Cohort studies

- Large data sets
  - Health insurance schemes
  - GP networks with computerised medical records
  - National linked data bases

- Various outcomes (ILI, Hospitalisation, Deaths)

- Data validation?
  - ICD codes
  - Severity?
  - Functional status?
  - Early estimates?
  - Laboratory confirmation?
    - Validation sets
  - Vaccine brand?
Weekly mortality in the cohort of ≥65 years by vaccine status, Navarra, Spain, 2008-9

Wednesday Late breaker

Early estimates of 2008-9 seasonal influenza vaccine effectiveness against A(H1N1)v outcomes, results from a computerized medical records cohort in Navarra (Spain)

Jesús Castilla, Marta Valenciano
Sources of controls for case control studies with FLU + cases identified at GP practice

Potential controls
1 - ILI FLU test negative
2 - Random sample of Non-ILI GP patients or of all GP patients
3 - Random sample from source population
Wednesday 11 05: New methods in public health

I-MOVE, towards monitoring seasonal and pandemic influenza vaccine effectiveness in Europe: pooled analysis of 5 countries case-control studies in the 2008-9 pilot phase

Esther Kissling
Sources of controls for case control studies with severe cases identified at hospital level

Controls:
1 - Test negative SARI or random sample of hospitalised patients
2 - Random sample at GP practice
3 - Random sample of source population (screening method)

Screening method

Based on Carrat et al. & Legrand et al. method
H1N1 pandemic
Will vaccines solve the problem and how will we know?

- Biases are here to stay?
- Efforts ++ to control for confounding
- Canadian data (not to be rejected so far)

- No decision with a single study
- Improve our mode of funding!
Study design

- **Experimental**
  - RCT
  - GRT

- **Observational**
  - Cohort studies
    - Risk (%)
    - Rate (person time)
  - Case control studies
    - Traditional (Odds Ratio)
    - Density (Rate Ratio)
    - Case cohorts (Risk Ratio)
  - Screening method

- Meta analyses
- Modelling
Why measuring Influenza VE?

- Recommendations for use of vaccine
- Complementary or alternative public health measures (e.g. antivirals)
- Estimates of impact of vaccination on various disease burden measures
- Further investigations on seasonal and pandemic vaccines (improve composition, use of adjuvants, need for booster doses)
- Better respond to reports of vaccine failures

IVE point estimates? or above acceptable threshold?
Vaccination coverage estimates by year and influenza status using systematic and ad hoc sampling, 15-64 y. old
GROG network, 2006/7-2008/9

<table>
<thead>
<tr>
<th>Year</th>
<th>Influenza positive</th>
<th>Test negative</th>
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<tr>
<td>2006/7</td>
<td>13.7</td>
<td>16.5</td>
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<tr>
<td>2007/8</td>
<td>7.1</td>
<td>8.4</td>
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<tr>
<td>2008/9</td>
<td>7.6</td>
<td>9.7</td>
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Carrat. Quantifying influenza vaccine efficacy and antigenic distance
Vaccine 2006;24(18):3881–8

Vaccine efficacy for years when A/H3N2 was the predominant influenza virus

Years are coloured to represent the degree of vaccine/circulating strain match as determined using P epitope. P epitope defines the degree of antigenic drift. Gupta V, Earl DJ, Deem MW.
VE estimates in cohort and case control studies in elderly (> 59 years) with outcome including hospitalisation

Authors, year

Cohort

Case control

VE (%)
Adjusted Flu VE estimates from literature review, all outcomes, all age & risk groups, all study designs, all seasons

We cannot summarise Flu VE with a single value
VE estimates in cohort studies in children by outcome and age group
VE estimates in institutionalised elderly
VE estimates in screening and cohort studies by outcome, age group 15-64 years
VE estimates in case control and cohort studies in elderly (> 59 years): Outcome including death

Authors, year

Cohort studies

Case control studies
Overall and component specific age-chronic adjusted VE estimates among > 8y. old, Canada, Skowronsky 2006-2007
VE estimates by outcomes in case control and cohort studies in high risk groups

Authors, year

Voordouw BC 2003
Looijmans-Van den Akker

Voordouw BC 2003
Voordouw BC 2006

Voordouw BC 2006
Hara M 2006
Hara M 2006
Voordouw BC 2003

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Davis JW 2001
Davis JW 2001
Nichol KL 1998

Voordouw BC 2006
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Nichol KL 1998
Davis JW 2001
Land 2006
Nichol KL 1998
Shapiro U 2003
Nichol KL 1998
Herrera
Nichol KL 1998
Hara M 2006
Looijmans-Van den Akker
Hak 2005

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Jackson L 2002
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Jackson L 2002

Hara M 2006
Voordouw BC 2003
Nichol KL 1998
Looijmans-Van den Akker
Nichol KL 1998
Shapiro U 2003
Hak 2005
Fleming DM 1995
Ferguson
Herrera

Any event/complication
Pneum/IL/Influenza
ARD/CVD
GP visit
Hospitalisations
Hosp or death
Cardio deaths
Death
Lab
Overall and component specific age adjusted, chronic adjusted and age-chronic adjusted VE estimates by age group, Skowronsky 2006-2007