SHIVERS
Southern Hemisphere Influenza and Vaccine Effectiveness Research and Surveillance

Nikki Turner
Feb 2012
Aims

• Robust estimation of the protective effect of seasonal influenza vaccine in the prevention of:
  o Hospitalised influenza
  o Community influenza (presenting to General Practice)

• Investigate over 5 different seasons

• Investigate differential protective effects among subpopulations
  o Age
  o Co-morbidities
  o Ethnicity
Vaccine Effectiveness: Project Team

- **ESR: lead**
  - Sue Huang PI
- **University of Auckland**
- **University of Otago**

**VE Study team**
- Nikki Turner (UoA) PI.
- Nevil Pierse (UoO) and Ange Bissielo (ESR) bio-stats and analysis
- Heath Kelly (Australian epidemiologist, influenza VE expert) mentoring/advisory
- Epidemiology support: Don Bandaranayke (ESR), Michael Baker (UoO)
- CDC support: Marc-Alain Widdowson, Dianne Gross, David Shay
Tools: Two surveillance systems

• **Hospital-based surveillance**: enhanced, active, year-round (5 yrs), population based surveillance for hospital SARI (sudden acute respiratory) cases
  - Auckland and Middlemore Hospitals

• **Community-based surveillance**: enhanced, active, (4 yrs), population based surveillance for community ILI (Influenza-like illness) cases caused by influenza
  - Recruitment of 50 – 100 ‘sentinel’ General Practices in greater Auckland (200,000 – 400,000 patients)
Study One: Case Control

• Case-control study, test negative variant to estimate Vaccine Effectiveness (VE) in patients hospitalised for a febrile respiratory illness (SARI) due to laboratory confirmed influenza
Case-control

SARI Patients with the condition

Exposed to a factor (flu vaccination)

Not exposed to the factor

SARI Patients without the condition (‘test negative’)

Exposed to a factor (flu vaccination)

Not exposed to the factor
Study population

- All patients admitted to Auckland and Middlemore Hospital with a ‘SARI’

Sudden Acute Respiratory Illness (SARI)

- An acute respiratory illness with
  - A history of fever or measured fever $\geq 38^\circ C$
  - Cough AND
  - Onset within the past 7 or 10 days

NB modify the fever definition for elderly residential care patients
Case-control VE

SARI patients with Influenza (RT-PCR positive)
- Vaccinated
- Not vaccinated

SARI Patients without Influenza (RT-PCR negative)
- Vaccinated
- Not vaccinated
<table>
<thead>
<tr>
<th>VE Population</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Source population</td>
<td>All those residing in the Auckland metropolitan region</td>
</tr>
<tr>
<td>Study population</td>
<td>Patients from the source population admitted to any of the two Auckland hospitals with a diagnosis that is covered by the definition of SARI during the study period</td>
</tr>
<tr>
<td>Case</td>
<td>Any SARI patient from the study population who is influenza positive (RT-PCR)</td>
</tr>
<tr>
<td>Control</td>
<td>1. Any influenza negative (RT-PCR) patient from the study population</td>
</tr>
<tr>
<td></td>
<td>2. For children under 5 years: Any influenza negative (PCR) from the study population with evidence of another respiratory virus</td>
</tr>
<tr>
<td>Exposed</td>
<td>1. Received seasonal vaccine at least 14 days prior to onset of SARI</td>
</tr>
<tr>
<td></td>
<td>2. Children 6 months to ≤ 9 years: Received seasonal vaccine at least 14 days prior to onset of SARI and have had a previous vaccine in any year AND at least 28 days prior to the second dose</td>
</tr>
<tr>
<td>Unexposed</td>
<td>Not vaccinated with current seasonal vaccine or received vaccine less than 15 days prior to onset of SARI</td>
</tr>
</tbody>
</table>
Data collection

• Patient questionnaire and hospital data
  o Demographics
  o Medical history
  o Vaccination history

• GP PMS
  o Medical history
  o Vaccination record

• Occupational health flu vaccinators
  o Vaccination record
Analysis

• VE = 1-OR (odds ratio)
• OR = odds of being a vaccinated case divided by the odds of being a vaccinated control
• Multivariable conditional logistic regression model used
• Covariates to be included
  o Anything likely to be associated with the vaccine update
  o Anything likely to be association with catching flu
  o Anything likely to affect vaccine effectiveness
Study Two – Case Control

Test-negative design case-control to estimate influenza vaccine effectiveness in patients presenting to General Practice with a febrile respiratory illness (ILI)
Study population

• All patients enrolled with ‘sentinel’ General Practices

Cases obtained from nasopharyngeal swabbing of all presenting with Influenza-like illness (ILI)

• An acute respiratory illness with
  o A history of fever or measured fever $\geq 38^\circ C$
  o Cough AND
  o Onset within the past 7 or 10 days

NB modify the fever definition for elderly residential care patients
Study Three:  Case cohort

A prospective case cohort to estimate Vaccine Effectiveness in patients presenting to primary care in the greater Auckland region with a febrile respiratory illness due to laboratory confirmed influenza.
Conceptual illustration of the case-cohort design (Adapted from Ulithian et al, 2007)

Cohort  $N = 300\,000$

Eligible cohort
$Ne = 295\,000$

Subcohort (comparison group)
$N = 2000$

All cases $n = 600$

Cases in subcohort $n = 9$

Courtesy of Ange Bissielo, numbers for illustration only
<table>
<thead>
<tr>
<th>VE Population</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Source population</td>
<td>All those residing in the Auckland metropolitan region</td>
</tr>
<tr>
<td>Study population</td>
<td>All patients enrolled with the sentinel general practices</td>
</tr>
<tr>
<td>Case</td>
<td>Any of the study population who presents to the general practice in the time frame with an ILI which is influenza positive (RT-PCR)</td>
</tr>
<tr>
<td>Subcohort</td>
<td>A stratified random sample of patients from the same sentinel general practices</td>
</tr>
</tbody>
</table>
| Exposed             | 1. Received seasonal vaccine at least 14 days prior to onset of ILI  
                      | 2. Children 6m to < 9 years: Received seasonal vaccine at least 14 days prior to onset of ILI and have had a previous vaccine in any year and ≥ 28 days apart |
| Unexposed           | Not vaccinated with current seasonal vaccine or received vaccine < 15 days prior to onset of ILI |
Data collection

- **Patient questionnaire**
  - Medical history
  - Vaccination history

- **GP PMS**
  - Demographics
  - Medical history
  - Vaccination record

- **Occupational health flu vaccinators**
  - Vaccination record
Analysis

- Cohort sampled at start of the flu season
- Exposure compared between cases and the cluster random sample from the cohort with adjustment for significant covariates in a logistic regression model
- Analysis takes into account the cluster sampling and stratification used for control sampling

- Controls selected through a random cluster sampling frame

- \( \text{VE} = 1 - \text{OR} \) (odds ratio)
  The OR for a case-cohort study is an estimate of the risk ratio from the cohort
Limitations: examples

• VE measures very specific and limited:
  • Not a full measure of VE against all influenza illness in the community

• Potential biases – some examples
  o Incomplete data collection - Flu vaccination history, obesity measurements
  o Accuracy of sample collection
    • Are all hospitalised flu cases identified by the SARI definition e.g. elderly without a fever
  o Accuracy of the control group
    • e.g. SARI positive but PCR negative ?had flu earlier
  o Have we considered all covariates that are potential confounders
    • e.g. Vaccination bias – are we less likely to vaccinated frail elderly

• Sample size for subpopulations likely to be inadequate for differential VE measurements