Introducing the Flu and Other Respiratory Viruses Research (FOREVER) Cohort, a laboratory partnership for data sharing

JEFF KWONG
PHO GRAND ROUNDS
JULY 25, 2017
Financial disclosures

No financial conflicts of interest to disclose
Study team

Jonathan Gubbay
Aaron Campigotto
Tim Karnauchow
Kevin Katz
Allison McGeer
Dayre McNally
David Richardson
Susan Richardson
Andrew Simor
Marek Smieja
George Zahariadis
Hannah Chung
Michael Campitelli
Sarah Buchan
Kevin Schwartz
Natasha Crowcroft
Laura Rosella
Michael Jackson
Dennis Ko

Funding: Canadian Institutes of Health Research (MOP 130568)
Learning objectives

After the session, participants will be able to:

• Describe the creation of the FOREVER Cohort
• Appreciate the use of routinely collected laboratory and health administrative data for evaluating influenza vaccine effectiveness
• Discuss some other applications of these data
Annual burden of illness from influenza in Canada

- 3,500 deaths
- 12,000 hospitalizations
- 160,000 emergency department visits
- 900,000 physician office visits
- 2,300,000 work absences
- 3,500,000 symptomatic infections
Health burden of respiratory viruses

Exhibit 4.27: Years of life lost due to premature mortality (YLL), year-equivalents of reduced functioning (YERF) and health-adjusted life years (HALYs) for viral respiratory infections.

Protecting yourself and others from influenza and other respiratory viruses

- Hand hygiene
- Respiratory etiquette
- Social distancing
- Masks/respirators
- Influenza vaccination
Influenza vaccine coverage in Canada, 2013-14

<table>
<thead>
<tr>
<th>Region</th>
<th>Coverage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yukon</td>
<td>30%</td>
</tr>
<tr>
<td>Northwest Territories</td>
<td>34%</td>
</tr>
<tr>
<td>Nunavut Territory</td>
<td>35%</td>
</tr>
<tr>
<td>British Columbia</td>
<td>32%</td>
</tr>
<tr>
<td>Alberta</td>
<td>31%</td>
</tr>
<tr>
<td>Saskatchewan</td>
<td>30%</td>
</tr>
<tr>
<td>Manitoba</td>
<td>30%</td>
</tr>
<tr>
<td>Ontario</td>
<td>33%</td>
</tr>
<tr>
<td>Quebec</td>
<td>24%</td>
</tr>
<tr>
<td>New Brunswick</td>
<td>27%</td>
</tr>
<tr>
<td>Newfoundland</td>
<td>35%</td>
</tr>
<tr>
<td>Prince Edward Island</td>
<td>37%</td>
</tr>
<tr>
<td>Nova Scotia</td>
<td>45%</td>
</tr>
</tbody>
</table>

Overall: 31% (>11 million Canadians)

Creating the Flu and Other Respiratory Viruses Research (FOREVER) Cohort

• Linked respiratory virus testing data for the period May 2009 to May 2014 from 11 PHO and 8 academic hospital labs:
  • Children’s Hospital of Eastern Ontario
  • Hospital for Sick Children
  • Mount Sinai Hospital
  • North York General Hospital
  • St Joseph’s Healthcare Hamilton
  • Sunnybrook Health Sciences Centre
  • University Health Network
  • William Osler Health System
  • (London Health Sciences Centre)

Overall linkage proportion: 97.5%
Laboratories contributing to the FOREVER Cohort

Red = PHO lab
Blue = hospital lab
Respiratory viruses tested for

- Influenza A
- Influenza B
- Respiratory syncytial virus (RSV)
- Adenovirus
- Coronavirus
- Enterovirus/rhinovirus
- Parainfluenza virus
- Human metapneumovirus
- Bocavirus
Reason for testing and laboratory testing methods

• Reason for testing:
  • Routine clinical care
  • Outbreak investigations
  • Research
• Laboratory testing methods:
  • Polymerase chain reaction (PCR) (monoplex & multiplex)
  • Direct fluorescent antibody staining (DFA)
  • Viral culture
  • Enzyme immunoassay (EIA) rapid antigen tests
### Participating labs, viruses tested, methods used

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Testing Methods</th>
<th>Influenza A</th>
<th>Influenza B</th>
<th>Respiratory Syncytial Virus (RSV)</th>
<th>Human Metapneumovirus (HMPV)</th>
<th>Parainfluenza</th>
<th>Adenovirus</th>
<th>Enterovirus/Rhinovirus</th>
<th>Bocavirus</th>
<th>Coronavirus</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHO</td>
<td>Culture</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td>PCR</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>NYGH</td>
<td>EIA</td>
<td>✓</td>
<td>✓</td>
<td>✗</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PCR</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>HSC</td>
<td>DFA</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Culture</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PCR</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>SHSC</td>
<td>DFA</td>
<td>✓</td>
<td>✓</td>
<td>✗</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Culture</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PCR</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>UHN &amp; MSH</td>
<td>PCR</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>WOHS</td>
<td>EIA</td>
<td>✓</td>
<td>✓</td>
<td>✗</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PCR</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>CHEO</td>
<td>EIA</td>
<td>✓</td>
<td>✓</td>
<td>✗</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DFA</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Culture</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PCR</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>SJHH</td>
<td>DFA</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Culture</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PCR</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>

"*Test only includes parainfluenza types 1, 2, and 3"
Using ICES data to assign healthcare setting

- ICU: 14%
- Ward: 45%
- ED: 20%
- MD office: 6%
- LTCF: 6%
- Missing: 9%
Using the FOREVER Cohort to assess influenza vaccine effectiveness
Background

- Annual influenza vaccination recommended for older adults
- Systematic review of 35 test-negative design studies in community-dwelling adults aged ≥60 years:
  - Vaccine match: VE=52% (95%CI, 41%-61%)
  - Vaccine mismatch: VE=36% (95%CI, 22%-48%)
- But evidence that influenza vaccines reduce laboratory-confirmed serious outcomes in older adults is relatively sparse

Test-negative design

- Has become the preferred method for assessing influenza VE (when RCTs not possible)
- Estimates VE against medically-attended laboratory-confirmed influenza
- Like a nested case-control study: among those who seek medical care for ARI/ILI, those who test positive for influenza are “cases” and those who test negative are “controls”
- Removes confounding from health-seeking behaviour
Typical test-negative design studies

- Case definition for ILI/ARI
- Symptom onset ≤7 days
- Tested by PCR

Recommendations for VE studies using the TND

• “VE analyses based on a convenience sample of clinical diagnostic tests could be biased and should be avoided”

Confirming the appropriateness and validity of using the FOREVER Cohort to estimate influenza VE

1. Test assumptions of the TND
2. Estimate VE under various conditions
3. Compare FOREVER VE estimates with the literature
Assumption 1: Influenza vaccination and non-influenza viruses

• Influenza vaccination should not be associated with infections by non-influenza viruses
• Vaccine coverage should be similar between the control group (i.e., influenza-negative individuals) and the source population (i.e., all tested individuals)


Assumption 1: Influenza vaccination and non-influenza viruses

Source population

Tested for influenza

Should have similar vaccine coverage

Cases

Influenza-positive

Influenza-negative

Controls

Other virus-positive

Pan-negative
Assumption 1: Influenza vaccination and non-influenza viruses

- Restricted to community-dwelling adults aged >65 years tested by multiplex PCR (panel of influenza + ≥5 other viruses)
- Healthcare settings:
  - Hospitals
  - Emergency departments
  - Physician offices
- Diagnostic codes:
  - ARI-coded (substitute for case definition)
  - Non-ARI-coded
Assumption 2:
Influenza vaccination and testing for influenza

• Testing for influenza should not be influenced by vaccination status


Assumption 2: Influenza vaccination and testing for influenza

• Restricted to community-dwelling adults aged >65 years
• Extracted healthcare encounters during influenza season
• Healthcare settings:
  • Hospitals
  • Emergency departments
  • Physician offices
• Diagnostic codes:
  • ARI-coded (substitute for case definition)
  • Non-ARI-coded
Estimating VE under various conditions

- Restricted to community-dwelling adults aged >65 years
- VE = (1 – aOR) x100%, adjusted for age, sex, calendar month of test, presence of any comorbidity
- Healthcare setting:
  - Outpatients and inpatients combined
  - Outpatients
  - Inpatients
- Laboratory testing methods:
  - Tested by any laboratory method
  - Tested by PCR
VE in inpatients vs. outpatients

- Compared 25 pairs of estimates
- Pooled difference = −2% (95% CI −12%, 10%)

Including specimens tested by non-PCR methods

- Impact of test sensitivity on VE is far less than test specificity
- Other available testing methods are not as sensitive as PCR, but have comparable specificity

Estimating VE under various conditions

• Applying restrictions to simulate typical TND studies
  A. Inpatients (no restrictions)
  B. ARI-coded hospitalizations
  C. Non-outbreak-related specimens
  D. Documented symptom onset ≤7 days
  E. ARI-coded + non-outbreak
  F. ARI-coded + non-outbreak + symptom onset ≤7 days
  G. Correcting for exposure misclassification


Additional influenza VE studies (in progress/future)

- Influenza VE in:
  - Young children (6-59 months)
  - Pregnant women
  - Older adults with:
    - COPD
    - Asthma
    - Cancer
    - Diabetes
    - Cardiovascular disease
    - Chronic kidney disease
- VE of LAIV vs. IIV in children aged 2-17 years (Alberta)
- Impact of repeated vaccination on VE in young children (6-59 months)
- Intraseason waning of VE
- Impact of statins on VE
Risk of acute myocardial infarction after laboratory-confirmed influenza infection
Background

• Coronary artery disease remains number one cause of mortality globally
• Long-recognized temporal associations between influenza epidemics and CV mortality, supported by epidemiological studies of association between ARI/ILI and acute CV events
• Pathophysiological mechanisms: systemic inflammation, vasoconstriction, platelet activation, endothelial dysfunction, increased metabolic demand
• Only 1 study (case-control) has examined association between laboratory-confirmed influenza infection (using serology) and AMI
Self-controlled case-series design
Protecting yourself and others from influenza and other respiratory viruses ... to reduce the risk of AMI

- Hand hygiene
- Respiratory etiquette
- Social distancing
- Masks/respirators
- Influenza vaccination
Take-home messages

• Linking laboratory data to health administrative data represents a relatively inexpensive and efficient way to create a large cohort of individuals tested for an infectious agent
• Use of routinely collected data for TND studies is likely appropriate and produces estimates similar to typical TND studies
• Efforts to reduce the burden of AMI should include measures to prevent respiratory infections
• Data linkage opens up a plethora of opportunities for infectious diseases research
Questions?

jeff.kwong@utoronto.ca