Introduction

• Influenza vaccination is required each year due to
  • Changes in the influenza virus (antigenic drift)
  • Waning immunity from vaccination
  • A new influenza vaccine is produced and vaccine effectiveness (VE) must be estimated annually.
  • Placebo-controlled randomized clinical trials (RCT) can no longer be used to assess influenza VE in the USA and many other populations.
  • Observational studies are used to obtain annual VE estimates.

Objective

Compare bias of influenza VE estimates from test-negative (TN) and traditional case-control (TCC) studies.

Outcomes of Interest

• Symptomatic influenza (SI) – influenza infection resulting in an ARI
• Medically-attended influenza (MAI) – influenza infection resulting in an ARI for which a person seeks medical care
• TN cases/controls are individuals with acute respiratory illness (ARI) who seek medical care and test positive/negative for influenza.
• TCC cases are the same as in a TN study, while controls are individuals who never developed an ARI.

Aims

1. Develop a dynamic probability model that incorporates:
   • Two covariates (health status and health awareness)
   • A time component (measured in weeks) to allow the VE's effectiveness to change over time
   • Possibility of developing more than one ARI during the study
   • Use the model to compare biases of VE estimates against two outcomes of interest from two case-control study designs

Assumptions

a) A person may only be vaccinated prior to the study and vaccination is determined without error.
   b) A person can only have one ARI during the season.
   c) A person can have at most one TN per week.
   d) The probabilities of MAI and TN do not depend on a person's health awareness or health status.
   e) Every person who seeks medical care for ARI is tested for influenza infection. Test has 100% specificity and sensitivity.

The model consists of five steps

Step 1: Covariates
We assume people within the population studied can be classified with respect to:
• Health status (Xj = “healthy” (XH) or “frail” (XF))
• Health awareness (Uj = “high” (UH) or “low” (UL))

Step 2: Vaccination
We consider the vaccination scenario where everyone who is vaccinated (V=1) becomes effectively vaccinated prior to the study.

Step 3: Influenza and non-influenza ARI
During the study:
• A person may become infected with influenza and develop
   FARI and/or develop one or more MAIs.
   • Yj is the illness/status in week j, where
     • No ARI in week j (Yj = 0)
     • FARI in week j (Yj = 1)
   • Mj = 1 for a person who sought care for ARI in week j.

Step 4: Seeking medical care for ARI
A person with ARI in week j may seek care (Mj):
• Mj = 1 for a person who sought care for ARI in week j.

Step 5: Testing for influenza infection
A person who seeks medical care for ARI in week j is tested for influenza infection (Yj):
• Yj = 1 for influenza positive test result.

Model (continued)

Figure 1. Directed acyclic graph (DAG) of our model

Model

Sources of Bias

<table>
<thead>
<tr>
<th>Source of Bias</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>B1</td>
<td>Healthy persons have a lower probability of influenza ARI</td>
</tr>
<tr>
<td>B2</td>
<td>Healthy persons have a higher probability of influenza ARI</td>
</tr>
<tr>
<td>B3</td>
<td>Healthy persons have a lower probability of influenza and non-influenza ARI</td>
</tr>
<tr>
<td>B4</td>
<td>Healthy persons have a higher probability of influenza and non-influenza ARI</td>
</tr>
<tr>
<td>C</td>
<td>Cervical cancers in patients with high health awareness have a higher probability of seeking medical care</td>
</tr>
</tbody>
</table>

Probability Ratios Corresponding to Sources of Bias

<table>
<thead>
<tr>
<th>Source of Bias</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>Probability ratio, V= Vaccinated, U=Unvaccinated, FARI=Influenza ARI, MAI=Non-Influenza ARI, HA=Health awareness, SM=Seeking medical care</td>
</tr>
</tbody>
</table>

Results

<table>
<thead>
<tr>
<th>Source of Bias</th>
<th>Test-Negative Range of Bias</th>
<th>Traditional Case-Control Range of Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>(0.00, 0.00)</td>
<td>(0.02, 0.02)</td>
</tr>
<tr>
<td>A</td>
<td>(0.56, 0.29)</td>
<td>(0.27, 0.15)</td>
</tr>
<tr>
<td>B1</td>
<td>(0.00, 0.02)</td>
<td>(0.01, 0.02)</td>
</tr>
<tr>
<td>B2</td>
<td>(0.00, 0.02)</td>
<td>(0.05, 0.05)</td>
</tr>
<tr>
<td>B3</td>
<td>(0.00, 0.02)</td>
<td>(0.06, 0.08)</td>
</tr>
<tr>
<td>B4</td>
<td>(0.00, 0.02)</td>
<td>(0.06, 0.10)</td>
</tr>
<tr>
<td>B5</td>
<td>(0.00, 0.02)</td>
<td>(0.06, 0.15)</td>
</tr>
<tr>
<td>C (VE against SI)</td>
<td>(0.00, 0.29)</td>
<td>(0.02, 0.29)</td>
</tr>
<tr>
<td>C (VE against MAI)</td>
<td>(0.00, 0.10)</td>
<td>(0.01, 0.02)</td>
</tr>
</tbody>
</table>

Interpretation

• A: VE estimates from both studies may be severely biased.
• B1: TN-based estimate is equal to the true VE.
• B2: VE estimates from both studies designs have a small bias.
• B3: TN-based estimate has a little or no bias.
• C: Estimates of VE against MAI may have little or no bias, but estimates of VE against SI may suffer from severe bias. True VE and bias depend on outcome of interest.
• D: TN-based estimate is less biased than TCC-based estimate.

Conclusions

• Estimates of influenza VE from case-control studies may suffer from severe bias, especially when the outcome of interest is SI.
• Bias of estimates may depend on the outcome of interest.
• When the outcome of interest is MAI then the TN study provides valid estimates of VE if:
  a) Vaccination does not affect the probability of MAI
  b) Confounding variables have the same effect on the probabilities of FARI and MAI
• When the outcome of interest is SI then the TN study provides valid estimates of VE if (a), (b), and the additional assumption (c) hold:
  • Vaccination does not affect the probability of seeking care for FARI
  • If vaccination affects the probability of MAI then the TN should be preferred over the TN.

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Conflicts of Interest

The authors report no conflicts of interest.