Disease and exposure misclassification in studies of vaccine effectiveness: a simulation tool


CONFLICT OF INTEREST STATEMENT
The simulation tool was developed within the ADVANCE project. The research leading to this tool received support from the Innovative Medicines Joint Undertaking under ADVANCE grant agreement Nr: 115557

REFERENCES

BACKGROUND

• ADVANCE is a public-private consortium whose aim is to develop the blueprint of a European framework for the assessment of benefits and risks of vaccines.
• To be useful for regulators and public health decision-makers, vaccine effectiveness (VE) studies should:
  • be performed rapidly,
  • provide accurate estimates,
  • have sufficient power to analyze effects also in specific subpopulations
• Thus, the need for using observational databases. Nonetheless, such databases are subject to misclassification.
• The magnitude and direction of bias in VE studies are difficult to predict, especially in the presence of differential and multi-source bias

• Example scenarios were pertussis and influenza, given expected differences in disease attack rates and vaccination coverage.

<table>
<thead>
<tr>
<th>Assumptions</th>
<th>VE Vaccination</th>
<th>VPD attack rate</th>
<th>Non-VPD (similar disease, non-vaccine pathogens) attack rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Childhood pertussis</td>
<td>80%</td>
<td>95%</td>
<td>15%</td>
</tr>
<tr>
<td>Pediatric influenza</td>
<td>70%</td>
<td>10%</td>
<td>15%</td>
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</tbody>
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For each disease example, 1,000 simulations of a population of 50,000 were generated. Sensitivities and specificities of disease and exposure misclassification were allowed to vary.

Observations:
• The magnitude and direction of bias are scenario dependent
• The different impacts of sensitivity and specificity parameters are more noticeable than between study designs
• Specificity of exposure classification (poorer identification of non-vaccinees) has greatest impact for influenza VE estimation
• Sensitivity of exposure classification (poorer identification of vaccinees) has greatest impact for pertussis
• Simulations of non-differential misclassification lead to underestimation of VE, whereas certain configurations of differential misclassification lead to overestimation

Our tool:
• allows users to estimate the impact of different misclassification parameters on multiple observational study designs
• enhances the feasibility assessment of VE studies, and help determine whether corrective measures (e.g. validation studies) are needed
• could also facilitate the correct interpretation of study results

METHODS

• We developed a simulation tool dwelling upon the simulation studies by Orenstein et al. to quantify the potential (joint) impact of
  • Disease and exposure misclassification,
  • Differential and non-differential misclassification.
We used cohort, case-control, test negative case-control, and screening method designs
• The tool considered a total of 13 parameters:
  • VE
  • Vaccination coverage
  • Population size
  • Vaccine preventable disease (VPD) attack rate & non-VPD (similar disease, non-vaccine pathogens) attack rate
  • 9 misclassification parameters.
• We did not consider other sources of bias and confounding.

Figure 1. Web-application

• The user can modify the parameter settings to run simulations for a selected VPD.
• The web application then plots the VE estimates generated from the simulations.
• The simulation model was developed using R version 3.3.1. and the Shiny package, for the web application.

Figure 2. Example using test negative case-control design

RESULTS

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