Addressing misclassification bias in vaccine effectiveness studies with an application to Covid-19

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joint work with Niko Speybroeck, Sonja Hartnack, Jacob Stærk-Østergaard, Matthew J. Denwood & Polychronis Kostoulas
A test-negative study for evaluating Covid-19 vaccine effectiveness

A test-negative study for evaluating Covid-19 vaccine effectiveness

• Cross-classification of subjects between vaccination status (2 doses of Covid-19 mRNA vaccines) and symptomatic SARS-CoV-2 infection (at least 7 days from the second dose)

<table>
<thead>
<tr>
<th>Covid-19 vaccine</th>
<th>SARS-CoV-2 RT-PCR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td>No</td>
<td>251,541</td>
</tr>
<tr>
<td>Yes</td>
<td>3,817</td>
</tr>
</tbody>
</table>

• Odds Ratio = \((57 \times 251,541)/(3,817 \times 51,220) = 0.073\)
• Vaccine Effectiveness = \((1-0.073) \times 100 = 93\%\)

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Previous calculations based on the assumption that SARS-CoV-2 RT-PCR is a perfect diagnostic assay for Covid-19

What if we can’t assume perfect sensitivity and specificity of the SARS-CoV-2 RT-PCR?

We can use available evidence on sensitivity and specificity of the SARS-CoV-2 RT-PCR as priors in a Bayesian model

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Perfect Classification
Sensitivity = 100%
Specificity = 100%

Stærk-Østergaard 2021
Sensitivity = 95.7% (92.8%-98.4%)
Specificity = 99.9% (99.9%-100.0%)

Kostoulas 2021
Sensitivity = 68.0% (63.0%-73.0%)
Specificity = 99.0% (98.0%-100.0%)

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• Test-negative design studies are vulnerable to misclassification bias.

• When the diagnostic tests used in the study are imperfect, vaccine effectiveness is mostly underestimated.

• Large bias in VE estimates is unlikely if specificity is equal to 1 and there is non-differential misclassification in sensitivity.

• The prior distributions of sensitivity and specificity need to be carefully specified according to the best available evidence.

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Abstract
Safe and effective vaccines are crucial for the control of Covid-19 and to protect individuals at higher risk of severe disease. The test-negative design is a popular option for evaluating the effectiveness of Covid-19 vaccines. However, the findings could be biased by several factors, including imperfect sensitivity and/or specificity of the test used for diagnosing the SARS-Cov-2 infection. We propose a simple Bayesian modeling approach for estimating vaccine effectiveness that is robust even when the diagnostic test is imperfect. We use simulation studies to demonstrate the robustness of our method to misclassification bias and illustrate the utility of our approach using real-world examples.

Keywords RT-PCR, Test-negative design, Sensitivity, Specificity, Covid-19