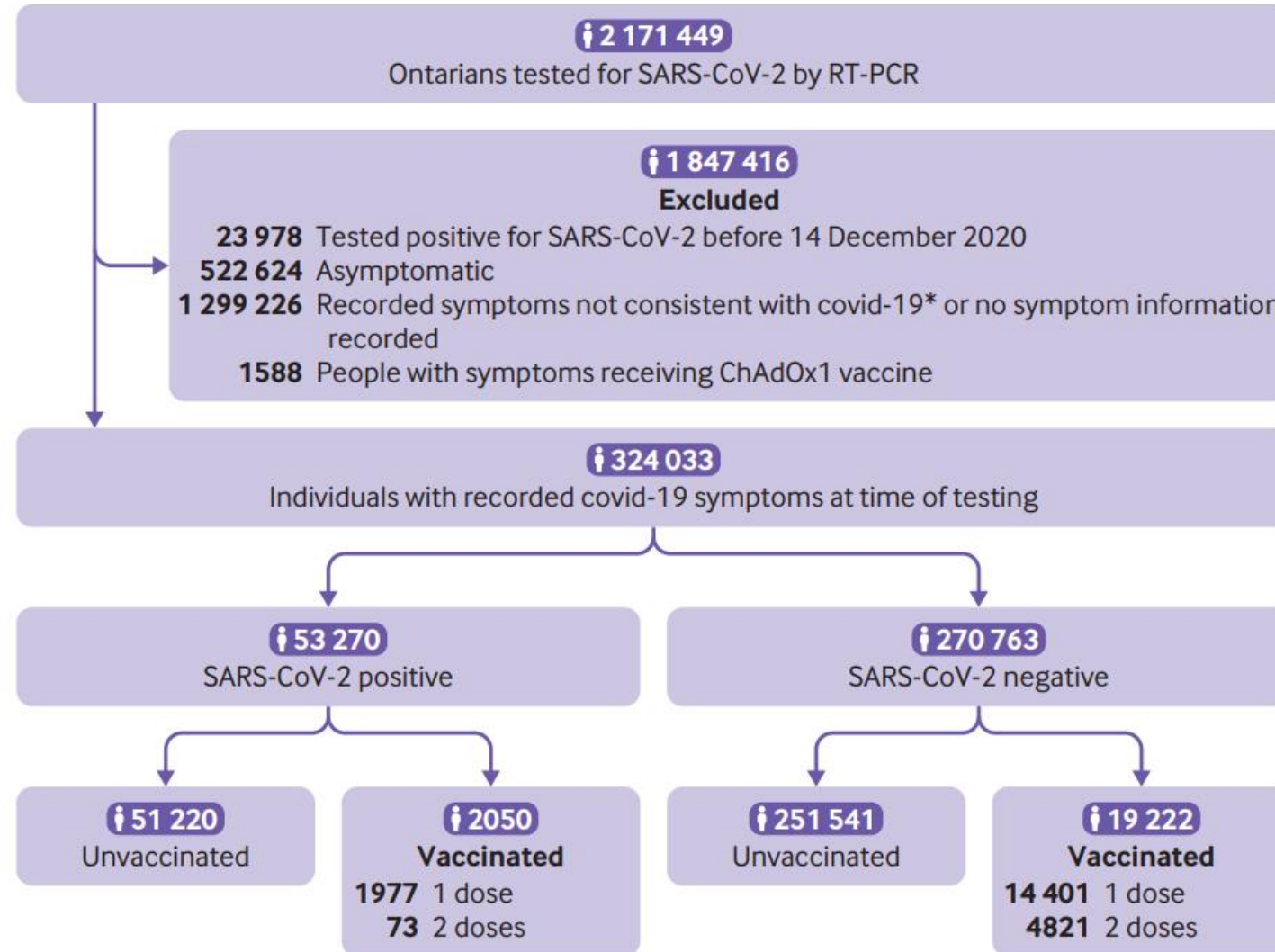World Health Organization

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

Paolo Eusebi

joint work with Niko Speybroeck, Sonja Hartnack, Jacob Stærk-Østergaard, Matthew J. Denwood & Polychronis Kostoulas

cost
EUROPEAN COOPERATION
IN SCIENCE & TECHNOLOGY

HARMONY
Novel tools for test evaluation and
disease prevalence estimation

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

2 171 449
Ontarians tested for SARS-CoV-2 by RT-PCR

1 847 416
Excluded

23 978 Tested positive for SARS-CoV-2 before 14 December 2020
522 624 Asymptomatic
1 299 226 Recorded symptoms not consistent with covid-19* or no symptom information recorded
1588 People with symptoms receiving ChAdOx1 vaccine

324 033
Individuals with recorded covid-19 symptoms at time of testing

53 270
SARS-CoV-2 positive

270 763
SARS-CoV-2 negative

51 220
Unvaccinated

2050
Vaccinated
1977 1 dose
73 2 doses

251 541
Unvaccinated

19 222
Vaccinated
14 401 1 dose
4821 2 doses

• Chung, Hannah, et al. "Effectiveness of BNT162b2 and mRNA-1273 covid-19 vaccines against symptomatic SARS-CoV-2 infection and severe covid-19 outcomes in Ontario, Canada: test negative design study." *Bmj* 374 (2021).

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- 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)

Covid-19 vaccine	SARS-CoV-2 RT-PCR	
	Negative	Positive
No	251,541	51,220
Yes	3,817	57

- **Odds Ratio = (57×251,541)/(3,817×51,220)=0.073**

- **Vaccine Effectiveness = (1-0.073) ×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
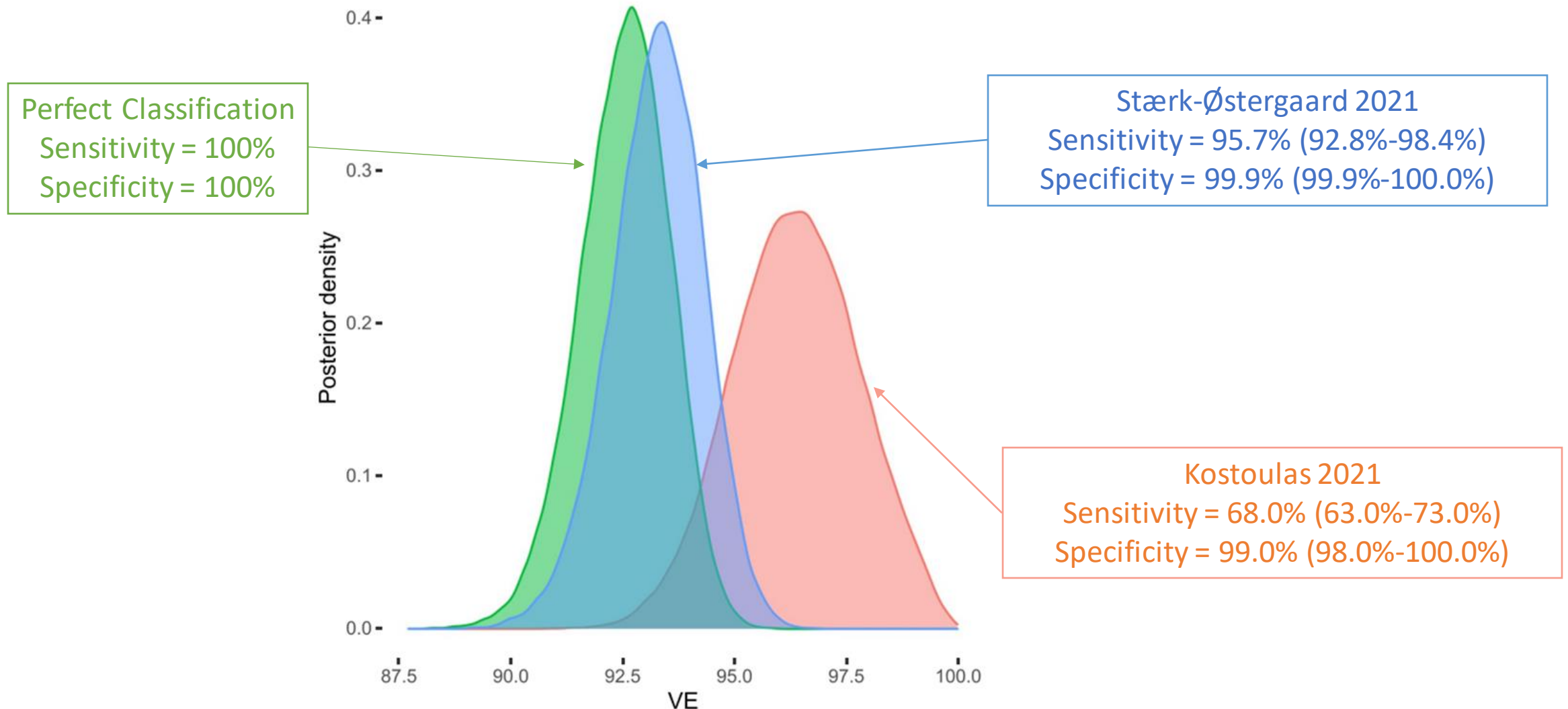
What if we can't assume perfect sensitivity and specificity of the SARS-CoV-2 RT-PCR?

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

- Eusebi, Paolo, et al. "Addressing misclassification bias in vaccine effectiveness studies with an application to Covid-19." BMC Medical Research Methodology 23.1 (2023): 55.
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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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Addressing misclassification bias in vaccine effectiveness studies with an application to Covid-19

Paolo Eusebi[1,2]*, Niko Speybroeck[3], Sonja Hartnack[4], Jacob Stærk-Østergaard[5], Matthew J. Denwood[5] and Polychronis Kostoulas[6]

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