

# Protective effectiveness of prior SARS-CoV-2 infection and hybrid immunity against Omicron infection and severe disease: a systematic review and meta-regression

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## Introduction

How much protection do I have against COVID-19, if I've been infected? Infected and vaccinated?	Estimates of protective effectiveness
	Prior infection vs. Immune naïve
	Hybrid immunity vs. Immune naïve
If I've been infected is there still benefit to getting vaccinated?	Estimates of comparative protective effectiveness
	Hybrid immunity vs. Prior infection
	Hybrid immunity vs. Vaccination
If I have hybrid immunity, do I need to get vaccinated again?	Hybrid immunity vs. Hybrid immunity with fewer vaccine doses

## Objective

We systematically reviewed the magnitude and duration of the protective effectiveness of previous SARS-CoV-2 infection and hybrid immunity against infection and severe disease caused by the omicron variant. We compared our estimates to previous estimates of the magnitude and durability of vaccine effectiveness<sup>1,2</sup>

## Methods

### Search strategy:

Search dates: 1 Jan 2020 – 1 June 2022. Sources: MEDLINE, Embase, Web of Science, ClinicalTrials.gov, Cochrane Central Register of Controlled Trials, WHO COVID-19 database, and Europe PMC. Grey literature, expert recommendations. Study design: Controlled observational studies. Risk of bias assessment: ROBINS-I tool<sup>3</sup>

### Modeling approach:

We used log-odds meta-regression to bound protection between 0% and 100% to model waning protection over time. A random intercept was included for each study. Risk ratios or hazard ratios were converted to the odds ratios. We regressed the log-odds of protection on months since the last immunological challenge (i.e., last vaccine dose or infection).

### Outcomes:

Estimates of protective effectiveness against 1) COVID-19 hospitalization or severe disease and 2) any Omicron infection at discrete time points.

## Results

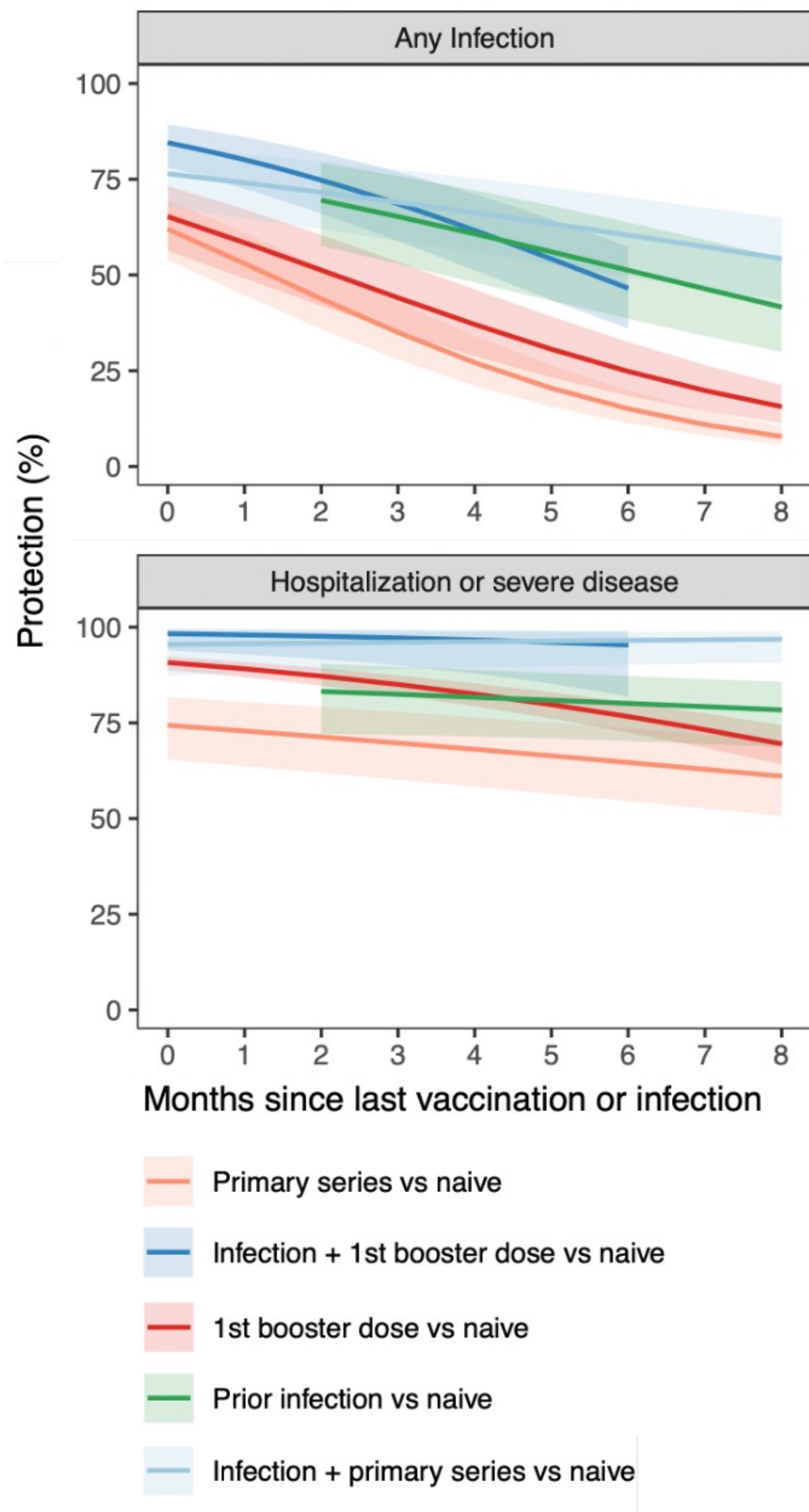
We analyzed 11 studies of prior infection and 15 studies of hybrid immunity. **Table 1.** Study characteristics

	Prior infection studies	Hybrid immunity studies			
	Prior infection vs. immune-naïve	Hybrid immunity vs. immune-naïve	Hybrid immunity vs. prior infection	Hybrid immunity vs. hybrid immunity with fewer vaccine doses	Hybrid immunity vs. vaccination
Number of studies	n=11	n=9	n=7	n=4	n=1
Median sample size (IQR)	294,900 (83,251, 1,142,605)	317,110 (50,576, 696,439)	130,073 (14,625, 470,984)	75,643 (17,919, 271,664)	38
Number of estimates	97	153	86	6	1
Estimated Risk of Bias					
Moderate risk of bias	27 (28%)	78 (51%)	48 (56%)	1 (17%)	-
Serious risk of bias	70 (72%)	75 (49%)	38 (44%)	5 (83%)	1 (100%)

**Table 2.** Protection conferred by 1) a prior infection, 2) hybrid immunity with a primary series, 3) hybrid immunity with a first booster

Comparison	Outcome	Total number of studies	Protection after 3 months [95% CI]	Protection after 6 months [95% CI]	Protection after 12 months [95% CI]	Percentage point change in protection from 3 to 12 months [95% CI]
<b>Prior infection</b>						
Prior infection vs naïve	Any infection	11	65·2% [52·9-75·9%]	51·2% [38·6-63·7%]	24·7% [16·4-35·5%]	<b>-40·5</b> [-33·9 to -51·9]
Prior infection vs naïve	Hospital or Severe	6	82·5% [71·8-89·7%]	80·1% [70·3-87·2%]	74·6% [63·1-83·5%]	<b>-7·8</b> [-20·9 to +12·1]
Prior infection vs naïve	Severe	3	80·2% [42·6-95·7%]	82·3% [62·6-92·8%]	85·9% [70·5-94%]	<b>-7·8</b> [-12·1 to +20·9]
<b>Hybrid immunity with a primary series of vaccines</b>						
Full vaccine + infection vs naïve	Any infection	7	69·0% [58·9-77·5%]	60·4% [49·6-70·3%]	41·8% [31·5-52·8%]	<b>-27·2</b> [-6·4 to -53·2]
Full vaccine + infection vs naïve	Hospital or Severe	5	96·0% [89·0-98·6%]	96·5% [90·2-98·8%]	97·4% [91·4-99·2%]	<b>+1·3</b> [-4·3 to +7·4]
Full vaccine + infection vs naïve	Severe	3	97% [76-99·7%]	96·5% [90·2-98·8%]	97·4% [91·4-99·2%]	<b>-6·6</b> [-20·9 to +17·8]
*Model extrapolation from 11 months.						
<b>Hybrid immunity with a first booster</b>						
Full vaccine + infection vs naïve	Any infection	8	68·6% [58·9-76·9%]	46·6% [36·1-57·4%]	-	<b>-22·0</b> [-4·3 to -38·8]
Full vaccine + infection vs naïve	Hospital or Severe	5	97·2% [90·0-99·3%]	95·3% [81·9-98·9%]	-	<b>-1·8</b> [-10·3 to +0·77]
*Model extrapolation from 4 months.						

**Figure 1.** Meta-regression plotting protection conferred by vaccination (VE), prior infection (PE), and hybrid immunity (HE)



## Findings

- Prior infection and hybrid immunity both provided greater and more sustained protection against Omicron than vaccination alone.
- Protection remains high for hospitalization or severe disease but wanes quickly against infection
- Individuals with hybrid immunity had the highest and most and durability protection

## Recommendations

People should get vaccinated even if they have had a prior infection. But do not purposely get infected to obtain hybrid immunity. A 6-month delay in booster may be justified after the last infection or vaccination for individuals with a known prior infection and full primary series vaccination. A longer delay (12 months) could be justified without losing protection against severe disease for the general population. Given the waning protection for both infection-and vaccine induced immunity against infection, mass vaccination could be timed for roll-out prior to periods of expected increased incidence, such as the winter season.

## References

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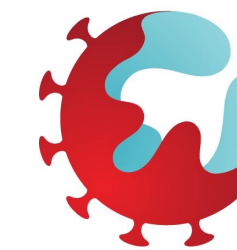
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