SARS-CoV-2 protective effectiveness of prior infection and hybrid immunity: a systematic review and meta-analysis

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Systematic review of the extent and duration of protection conferred by prior infection or hybrid immunity

Objectives

1) Systematic review of prior infection and hybrid immunity
2) Calculate pooled estimates (meta-analysis) of protection against reinfection; symptomatic disease; severe disease (hospital, ICU, death)
3) Determine changes in protection over time (meta-regression)

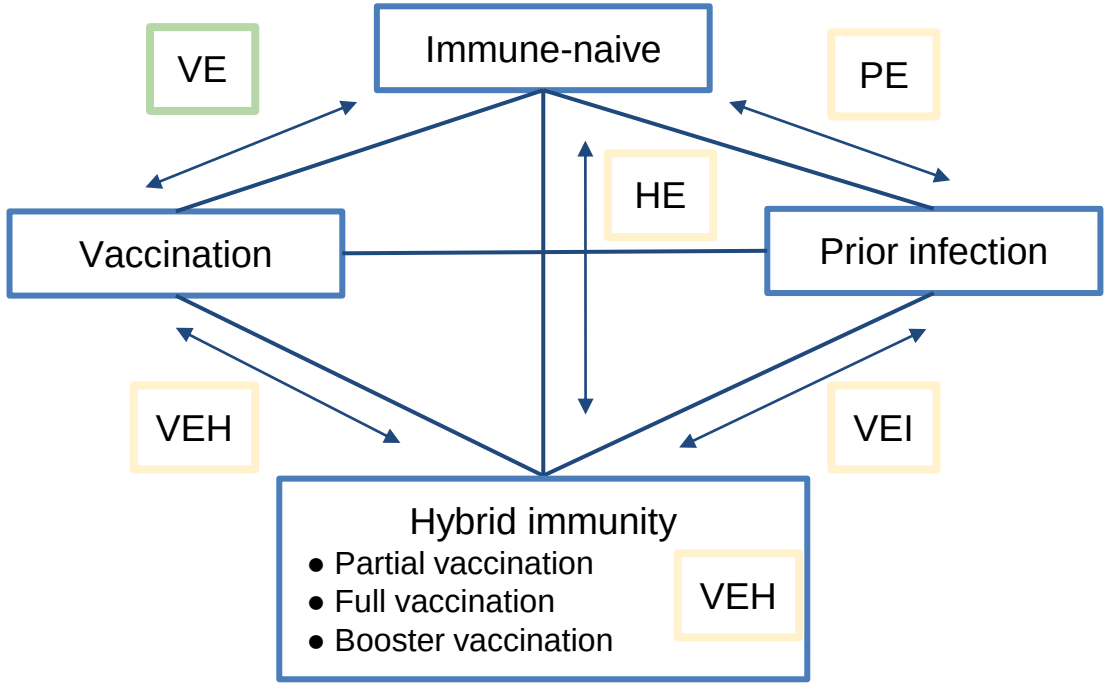
Methods

- Search dates: 1 Jan 2020 – 1 June 2022
- Sources: 6 databases, grey lit, expert recommendations
- Study design: Test-negative case-control, case-control, cross-sectional, cohort, RCTs, non-RCTs

*Results shown today

- Omicron reinfection
- Pre-omicron prior infection
- Up to 1st booster vaccine (insufficient data for 2nd booster hybrid)

Map of immunity status



Absolute effectiveness (benefit compared to immune naive)
VE: vaccine effectiveness
PE: protective effectiveness of prior infection
HE: protective effectiveness of hybrid immunity
Relative effectiveness (benefit added to existing protection)
VEI: vaccine effectiveness among those with prior infection
VEH: vaccine effectiveness amongst those with hybrid immunity or compared to hybrid immunity

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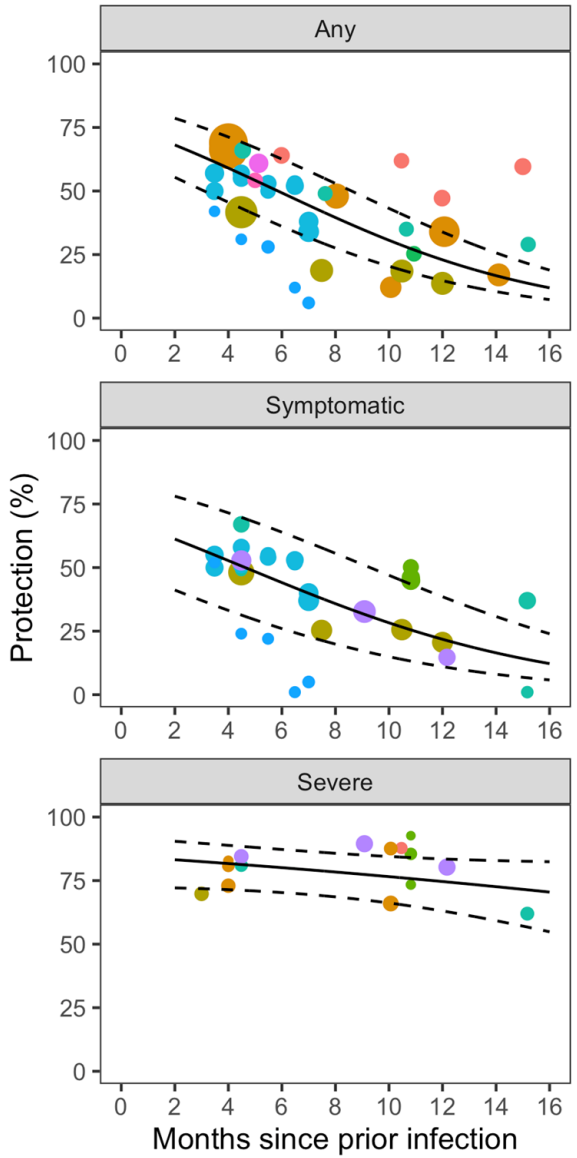
Absolute protection conferred by prior infection



Meta-regression of protection against Omicron reinfection after prior infection with a Pre-Omicron variant (n=10 studies)

Comparison	Severity of reinfection	Total number of studies	Protection after 3 months [95% CI]	Protection after 15 months [95% CI]
Prior infection vs naive	Any	10	63.7% [50.5-75.1%]	14.1% [8.7-22.1%]
Prior infection vs naive	Symptomatic	6	57.0% [37.1-74.9%]	14.2% [6.8-27.2%]
Prior infection vs naive	Severe	6	82.5% [71.8-89.7%]]	71.6% [57.1-82.6%]

- Protection against Omicron reinfection wanes by nearly 50 percentage pts after 15 months with the greatest loss in protection occurring rapidly between 3 and 10 months after initial infection
- Similar pattern of immunity waning for symptomatic disease
- Protection against severe disease wanes more slowly by 11 percentage pts after 15 months

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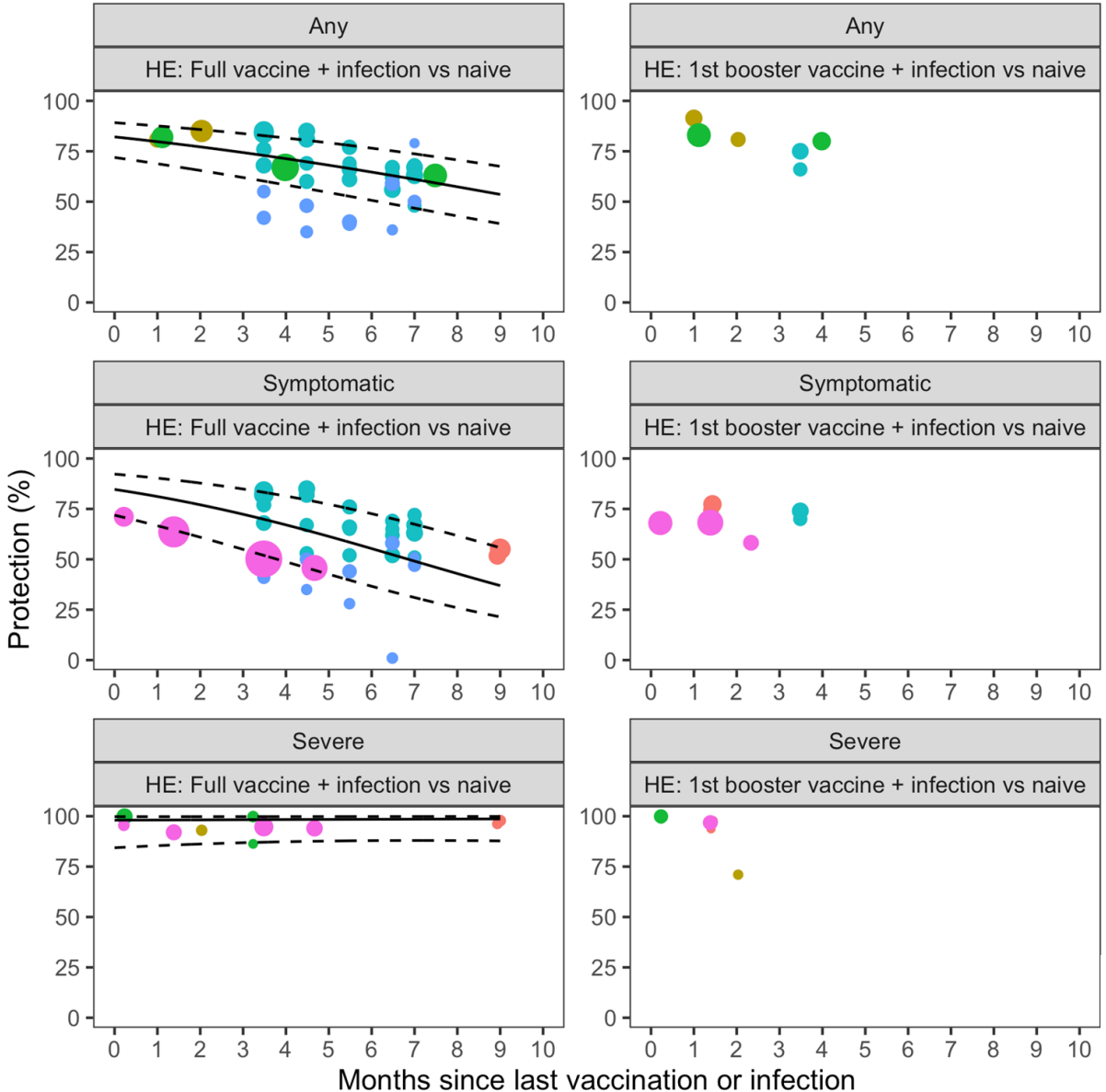
Absolute protection conferred by hybrid immunity (full, 1st booster)



Meta-regression of protection against reinfection over time stratified by severity of reinfection (n=6 studies)

Comparison	Severity of reinfection	Total number of studies	Protection after 1 month [95% CI]	Protection after 9 months [95% CI]
Full vaccine + infection vs naive	Any	6	79.8% [68.8-87.6%]	53.6% [39.1-67.5%]
Full vaccine + infection vs naive	Symptomatic	4	81.2% [66.6-90.3%]	36.9% [21.4-55.7%]
Full vaccine + infection vs naive	Severe	4	98.1% [85.4-99.8%]	98.6% [87.7-99.9%]

- Protection against reinfection wanes by 26 percentage pts over 9 months after full series + prior infection
- Similar pattern of immunity waning for symptomatic disease
- Protection against severe disease remains stable at 98% up to 9 months (limited data after 5 months)
- Wane in protection after 1st booster cannot yet be modelled as data limited, but trends appear similar

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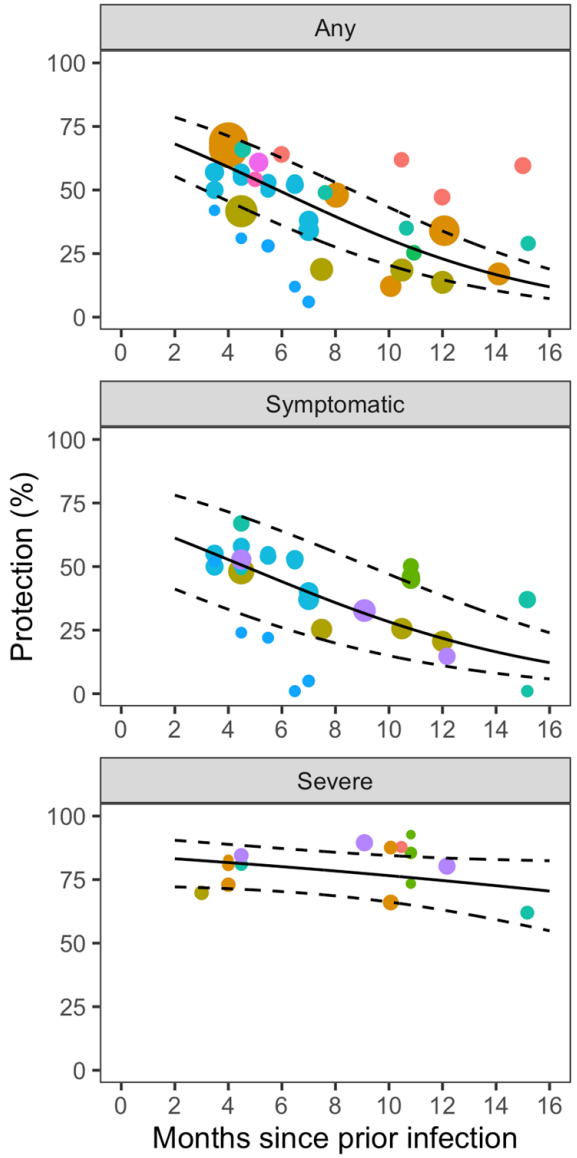
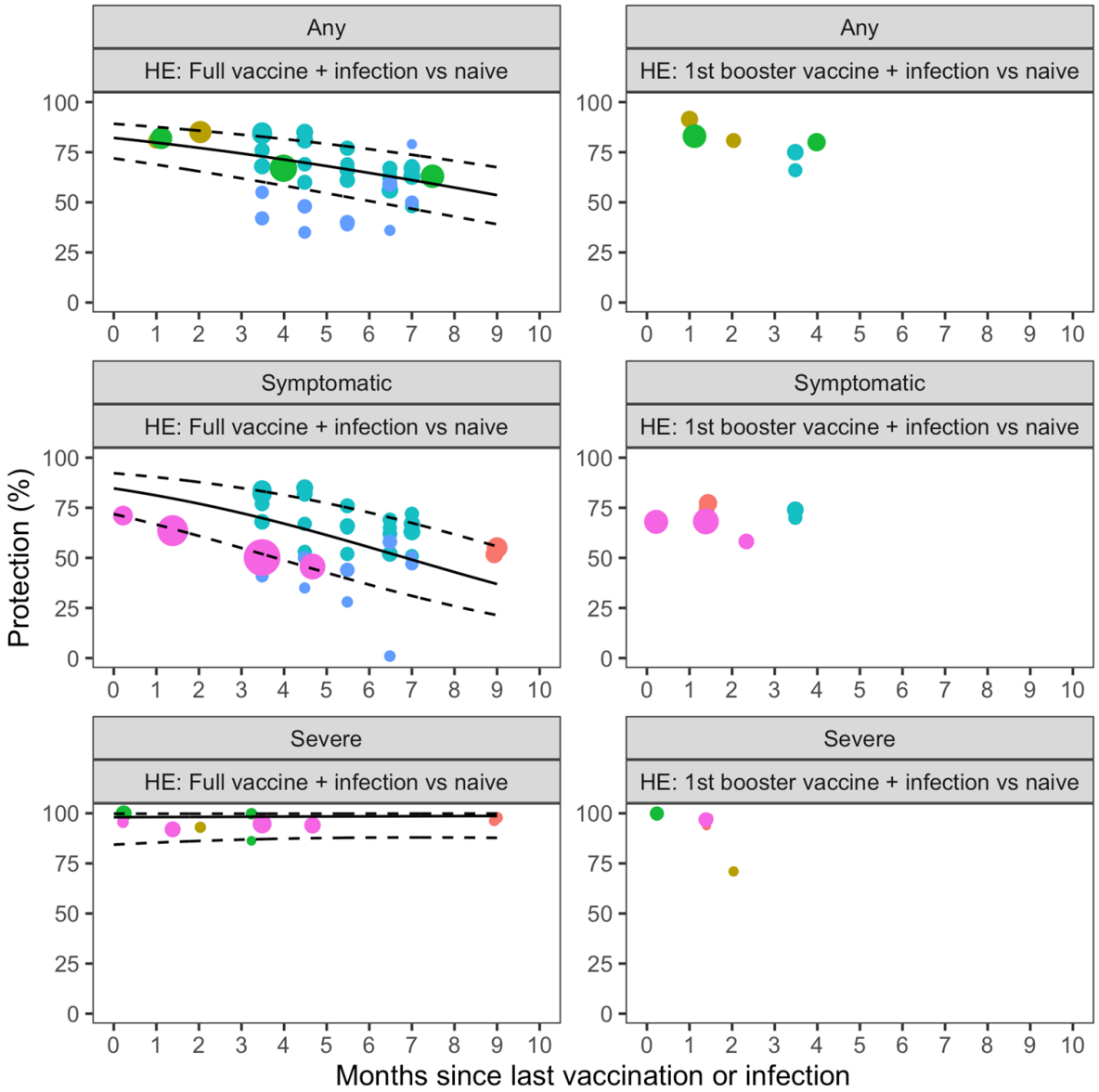
Absolute protection appears more durable with hybrid immunity than prior infection

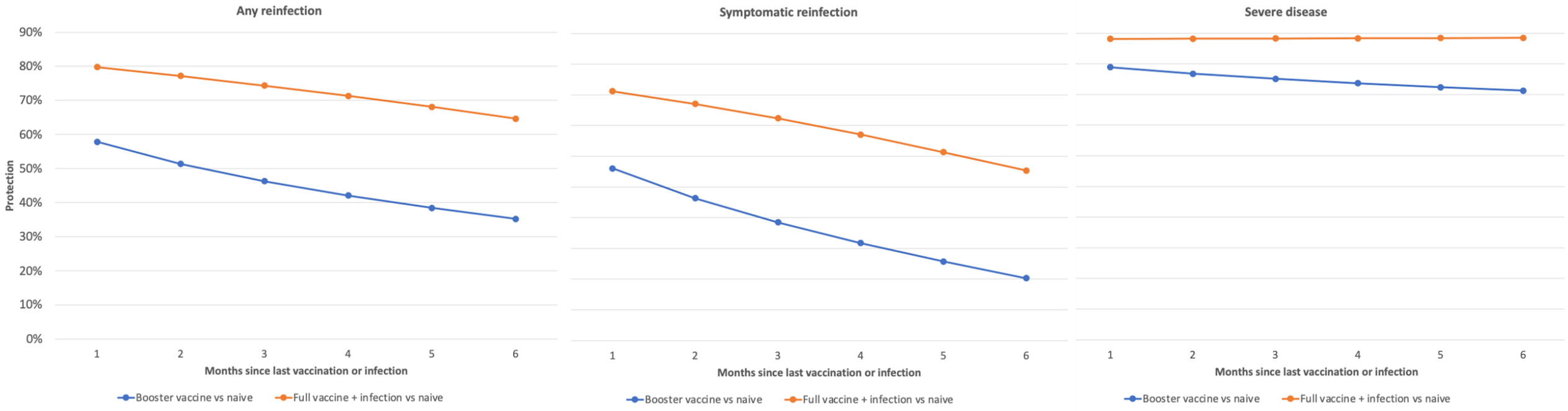




Absolute protection is greater with hybrid immunity (full vaccine) than the 1st booster vaccine alone

Meta-regression of protection against reinfection over time stratified by severity of reinfection

- Protection 6 months after last immunologic challenge for persons with prior infection + full vaccine is equivalent to peak 1st booster protection (and no prior infection), with no wane in protection against severe disease



Relative protection conferred by hybrid immunity vs. prior infection

Meta-analysis of protection conferred by hybrid immunity against Omicron reinfection compared to people with prior infection (n=7 studies)

Outcome	Exposure	Comparator	No. estimates	Pooled protection [95% CI]
Any reinfection	Infection + Full vaccine	vs infection	4	40.6% [23.9-59.8%]
	Infection + 1st Booster vaccine	vs infection	4	43.1% [16.4-74.5%]
Severe disease	Infection + Full vaccine	vs infection	4	57.7% [28.6-82.2%]
	Infection + 1st Booster vaccine	vs infection	4	69.6% [23.4-94.5%]

- Hybrid immunity with full vaccination and 1st booster vaccination confers a relative gain in protection compared to only prior infection
- Greatest gain in protection is against severe disease.

Relative protection conferred by hybrid immunity vs. hybrid immunity

Meta-analysis of protection conferred by additional vaccination against Omicron reinfection among people hybrid immunity (n=4 studies)

Outcome	Exposure	Comparator	No. estimates	Pooled protection [95% CI]
Any reinfection	Infection + Full vaccine	vs Infection + Partial vaccine	1	16.3% [11.1-21.2%]
	Infection + 1st Booster vaccine	vs Infection + Full vaccine	3	40.8% [22.0-62.7%]
Severe disease	Infection + Full vaccine	vs Infection + Partial vaccine	2	49.6% [19.9-79.7%]
	Infection + 1st Booster vaccine	vs Infection + Full vaccine	2	37.0% [6.2-83.9%]

- Providing another vaccination among people with hybrid immunity confers a relative gain in protection against infection and severe disease.

It is unclear if there are age-based differences in protection conferred by prior infection or hybrid immunity

Prior infection

- **It is unclear whether protection from prior infection varies by age group**
  - Significant reduction in protection in adults (18 to 59) vs. children (<18) (Netherlands, n=317,110)[1]
  - Generally similar protection in adults and older adults (18 to ≥70) vs. children (<18) (Canada, n=696,439)[2]

Hybrid immunity

- **It is unclear whether protection from hybrid immunity varies by age group**
  - Higher protection in older adults ≥60 years vs. younger adults (<60) (Netherlands, n=317,110)[1]
  - Generally similar protection among adult and the elderly (18 to ≥70) compared to children (<18) (Canada, n=696,439)[2]

Adjusted estimates of protection conferred by prior infection and hybrid immunity compared to immune naive persons

	Prior infection	Infection + 1 dose	Infection + 2 doses	Infection + 3 doses
	Adjusted effectiveness[a] (95% CI)	Adjusted effectiveness[a] (95% CI)	Adjusted effectiveness[a] (95% CI)	Adjusted effectiveness[a] (95% CI)
Global	44% (38, 48)	65% (63, 67)	68% (67, 70)	83% (81, 84)
Age (years)				
12-17	57% (36, 71)	78% (70, 83)	79% (74, 93)	96% (65, 99)
18-49	44% (29, 43)	62% (60, 65)	67% (65, 68)	79% (77, 81)
50-69	51% (38, 60)	71% (66, 75)	72% (69, 74)	86% (83, 88)
≥70	46% (16, 65)	79% (65, 87)	67% (60, 73)	81% (75, 86)

Carazo et al. 2022.

Gap in data

Few high quality studies report age-stratified data. Investigators should be encouraged to pursue these analysis and publicly report these findings.

1) Carazo et al. 2022. Protection against Omicron re-infection conferred by prior heterologous SARS-CoV-2 infection, with and without mRNA vaccination. 2) Andeweg et al. Protection of COVID-19 vaccination and previous infection against Omicron BA.1, BA.2 and Delta SARS-CoV-2 infections.

Protection conferred by hybrid immunity with partial vaccination

Meta-analysis of protection conferred by hybrid immunity with partial vaccination against Omicron reinfection compared to immune naive persons (n=6 studies)

Outcome	Exposure	Comparator	No. estimates	Pooled protection [95% CI]
Any reinfection	Infection + Partial vaccine	vs naive	2	41.8% [10.1-82.2%]
Symptomatic disease	Infection + Partial vaccine	vs naive	1	71.0% [63.3-77.1%]
Severe disease	Infection + Partial vaccine	vs naive	6	89.8% [23.1-99.6%]

- Hybrid immunity with one dose of vaccination confers an absolute gain in protection against Omicron compared to persons that are immune naive.

Meta-analysis of protection conferred by hybrid immunity with partial vaccination against Omicron reinfection compared to people with prior infection (n=3 studies)

Outcome	Exposure	Comparator	No. estimates	Pooled protection [95% CI]
Any reinfection	Infection + Partial vaccine	vs infection	1	59.0% [46.8-68.3%]
Severe disease	Infection + Partial vaccine	vs infection	3	28.9% [14.4-49.6%]

- Hybrid immunity with one dose of vaccination confers a relative gain in protection against Omicron compared to persons with prior infection only.

Summary of key findings about the protection from prior infection and hybrid immunity against Omicron

- **Delaying 1st booster by 6-9 months may be reasonable** among people with a full series and prior infection:
  - **At 6 months**: protection from full series+prior infection is still equal to or better than peak 1st booster (~60%).
  - **At 9 months**: full series+prior infection shows >95% absolute protection against severe disease.
  - Results may provide insight into the timing of **2nd booster** for people with **1st booster and a prior infection.**

- **Vaccination provides added protection for people with prior infection:**
  - **Protection from prior infection alone wanes rapidly** by 15 months against reinfection (14%) and symptomatic disease (14%), although protection against severe disease wanes more slowly (72%).
  - **Hybrid immunity confers a relative gain** in the magnitude of protection compared to prior infection alone
  - **Hybrid immunity appears to have more durable** protection than prior infection alone.

- **It is unclear if there are age-based differences in protection from prior infection or hybrid immunity:**
  - Investigators should be encouraged to report age-stratified data.

Thank you to the team making this work possible

Thank you to the investigators and supporting institutions

- Harriet Ware, Zihan Li, Xiaomeng Ma, Christian Cao, Anabel Selemon, Reza Hosseini, Mairead Whelan, Vanessa Piechotta, Annika Falman, Wiebe Kulper-Schiek, Antonio Pilic, Iris Thielemann, Thomas Harder, Zahra Premji, Hanane Issa, Brianna Cheng, Isabel Bergeri, Anthony Nardone, Mercedes Yanes Lane, David Buckeridge, Maria Van Kerkhove, Melissa Higdon, Rahul Arora, Daniel Feikin, Annelies Wilder-Smith, Minal Patel, Lorenzo Subissi

- World Health Organization, SeroTracker, University of Toronto, University of Calgary, Johns Hopkins, Mcgill University

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Appendix

Absolute protection conferred by hybrid immunity

Meta-analysis of protection conferred by hybrid immunity against Omicron reinfection compared to people that are immune naive.

Outcome	Exposure	Comparator	No. estimates	Pooled protection [95% CI]
Any reinfection	Infection + Partial vaccine	vs naive	2	41.8% [10.1-82.2%]
	Infection + Full vaccine	vs naive	11	73.4% [60-83.6%]
	Infection + 1st Booster vaccine	vs naive	7	83.9% [76.4-89.4%]
Symptomatic disease	Infection + Partial vaccine	vs naive	1	71.0% [63.3-77.1%]
	Infection + Full vaccine	vs naive	12	66.8% [53.6-77.9%]
	Infection + 1st Booster vaccine	vs naive	9	73% [68.2-77.3%]
Severe disease	Infection + Partial vaccine	vs naive	6	89.8% [23.1-99.6%]
	Infection + Full vaccine	vs naive	16	96% [89.2-98.6%]
	Infection + 1st Booster vaccine	vs naive	9	98.2% [90.9-99.7%]

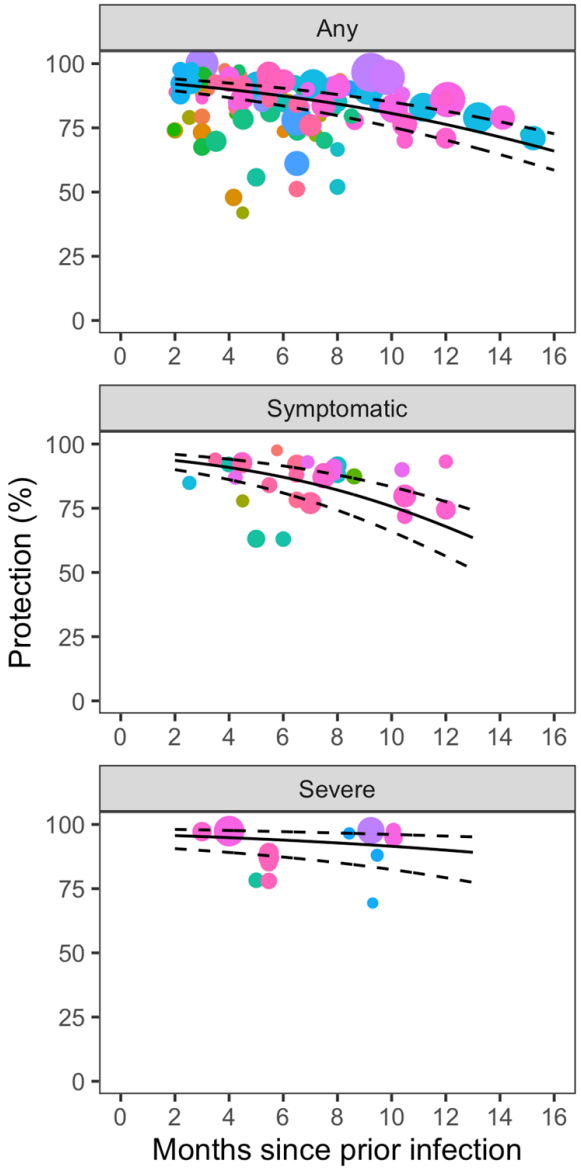
- Hybrid immunity with partial, full, or 1st booster vaccination confers an absolute gain in protection compared to people that are immune naive.
- Greatest level of protection is against severe disease.

Absolute protection conferred by prior infection against pre-Omicron variants

Meta-regression of protection against reinfection over time stratified by severity of reinfection (n=61 studies)

Comparison	Severity of reinfection	Total number of studies	Protection at 2 months [95% CI]	Protection at 12 months [95% CI]
Prior infection vs naive	Any	56	92.0% [89.4-94.0%]	76.3% [70.2-81.5%]
Prior infection vs naive	Symptomatic	12	93.6% [90.0-96.0%]	67.9% [56.4-77.6%]
Prior infection vs naive	Severe disease	9	95.6% [90.6-98.1%]	90.0% [79.3-95.5%]

- >90% initial protection against pre-Omicron variants for all outcomes
- Protection against pre-Omicron infection gradually wanes by 16 percentage pts over 10 months from 92.0% to 76.3%
- Steeper pattern of wane against symptomatic disease
- Protection against severe disease remains steady over a period of 10 months



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Age-based differences in protection conferred by prior infection against pre-Omicron variants

Meta-regression of protection against <u>any reinfection</u> by age group (n=16 studies)

Comparison	Age group	Number of estimates	Protection at 2 months [95% CI]	Protection at 8 months [95% CI]
Prior infection vs naive	Adults (18-64 years)	30	97.7% [94.2-99.1%]	77.1% [63.6-86.6%]
Prior infection vs naive	Seniors (65+ years)	10	88.9% [68.6-96.7%]	72.6% [50.1-87.5%]
Prior infection vs naive	Children and youth (0-17 years)	15	91.5% [69.4-98.1%	68.4% [38.7-88.1%]

- Between study differences - estimates from studies using different age cutoffs (not meta-analysis of sub-group data).
- Caution required as differences in studies may account for differences in estimates.
- On average, prior infection appears to provide slightly higher protection against reinfection to adults than to children or seniors.
- Similar pattern of waning immunity over 8 months.

Meta-regression of protection against <u>any reinfection</u> over time stratified by age group