SARS-CoV-2 Vaccination and Attenuation of Breakthrough Infection Severity: A Systematic Review and Meta-analysis

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Background

COVID-19 vaccines have shown strong protection against severe outcomes, yet breakthrough infections still occur due to waning immunity and emerging variants. Vaccination may not fully prevent infection but can reduce disease severity. While clinical and hospital-based studies suggest attenuation in breakthrough cases, findings are limited by small sample sizes, potential selection bias, and inconsistent results [1, 2]. A comprehensive examination of existing evidence on vaccination's attenuation effect is needed to support public health decision-making.

Objectives

This study aims to synthesize global observational evidence to assess the extent to which COVID-19 vaccination attenuates disease severity among breakthrough cases. It also seeks to evaluate how this attenuation varies by vaccine type, SARS-CoV-2 variant, age group, and other study-level factors to inform more targeted vaccination strategies.

Methods

We conducted a systematic review and meta-analysis using vaccine effectiveness (VE) estimates from a WHO-led living systematic review of global observational studies. Eligible studies reported adjusted VE for completed primary vaccination against symptomatic infection and hospitalization in general populations. VE pairs—estimates for the two outcomes were matched by study characteristics. A random effects meta-analysis was used to estimate the relative difference in VE (rVE), representing vaccine-mediated attenuation. Meta-regression assessed the impact of study design, clinical outcome definition, age group, virus variant, vaccine type, and time since vaccination.

Results

A total of 167 VE pairs from 38 studies were identified, with rVE ranging from -235% to 96%. Among these, 148 pairs (89%) had a point estimate of rVE greater than 0, and 129 pairs (77%) had 95% confidence intervals for rVE excluding the null value. The overall pooled estimate of rVE from the random effects model was 45% (95% CI: 40%-50%).

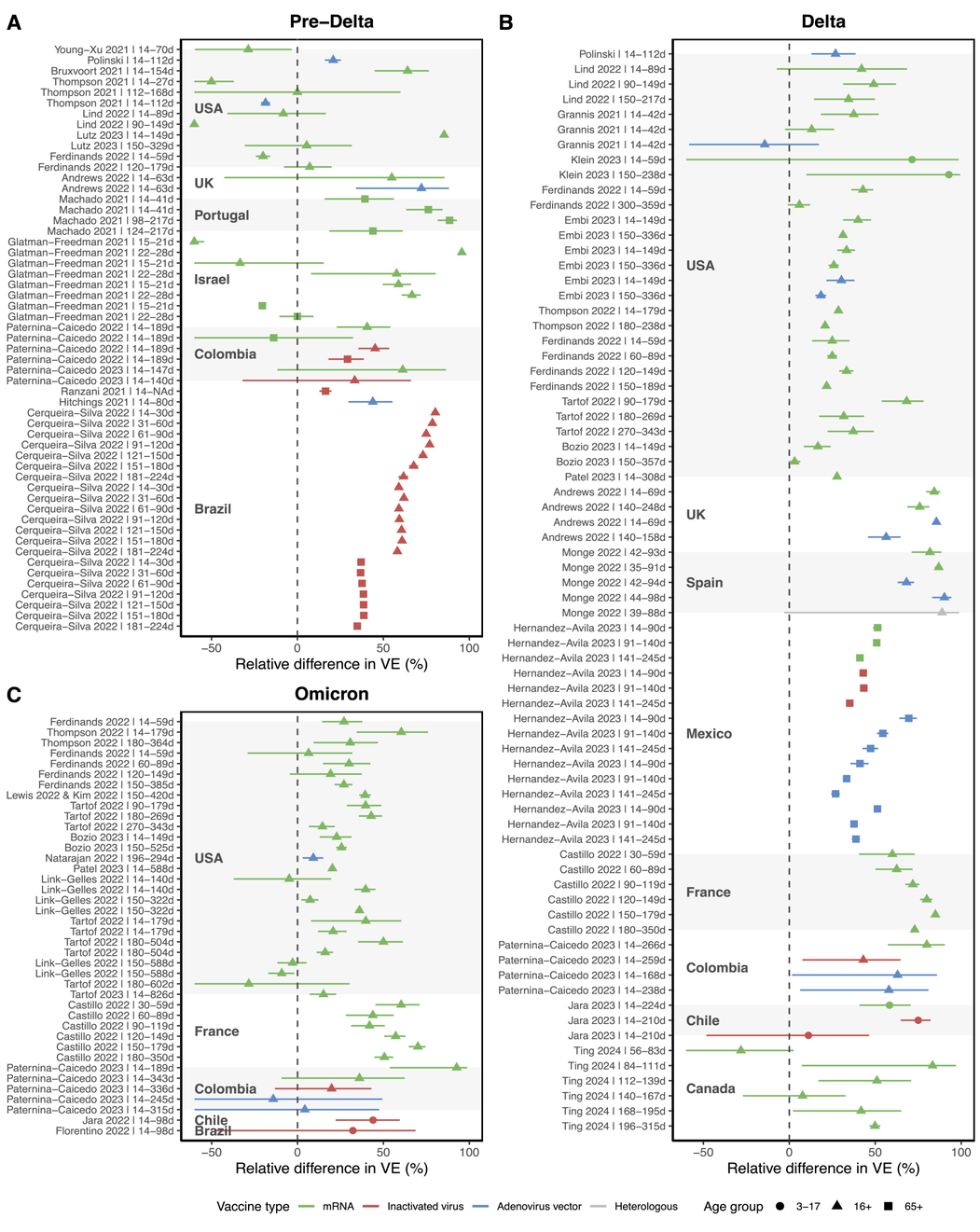

Figure 1. Relative difference in vaccine effectiveness (rVE) between hospitalization and symptomatic infection based on identified VE pairs. The 95% confidence intervals (CIs) were calculated by bootstrapping.

Significant differences in rVE were observed by symptomatic infection endpoint and predominant variant. The rVE was lower when symptomatic infection was restricted to medically attended cases and was slightly higher during the Delta period compared to the pre-Delta and Omicron periods.

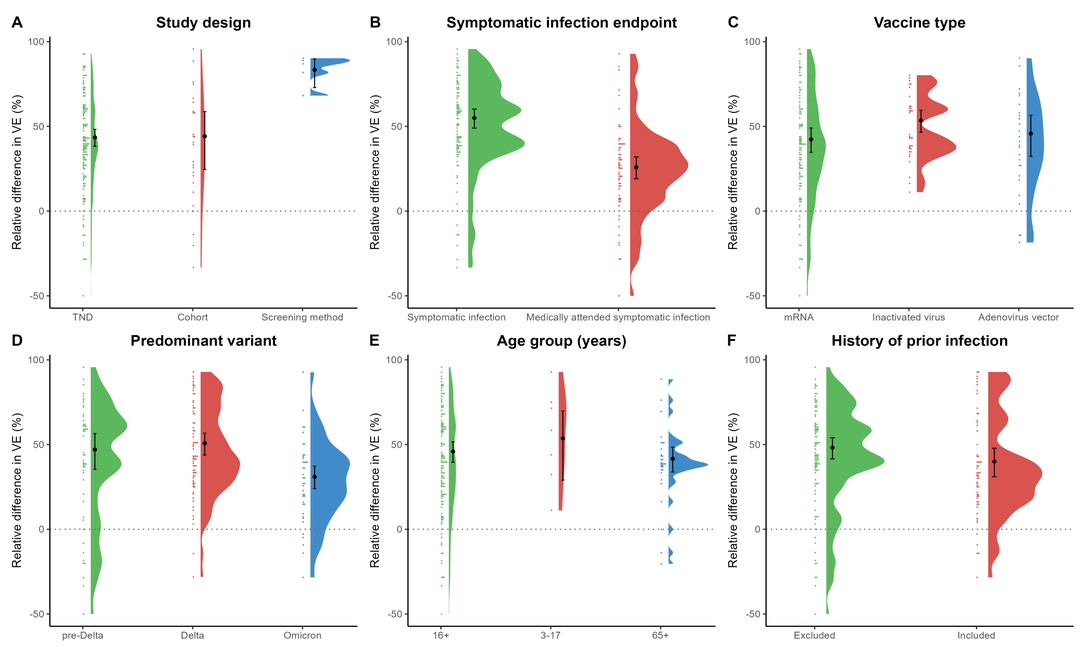

Figure 2. Relative difference in vaccine effectiveness (rVE) from subgroup meta-analyses, grouped by study design, symptomatic infection endpoint, vaccine type, predominant variant, age group, and prior infection history. Black points and lines show pooled rVE estimates with 95% CIs. Shaded areas represent the smoothed density of individual rVE values.

Meta-regression showed that rVE remained relatively stable over time. Compared to mRNA vaccines, rVE was lower for adenovirus vector vaccines but similar for inactivated vaccines. rVE was highest during the Delta period and lowest among individuals aged ≥65 years.

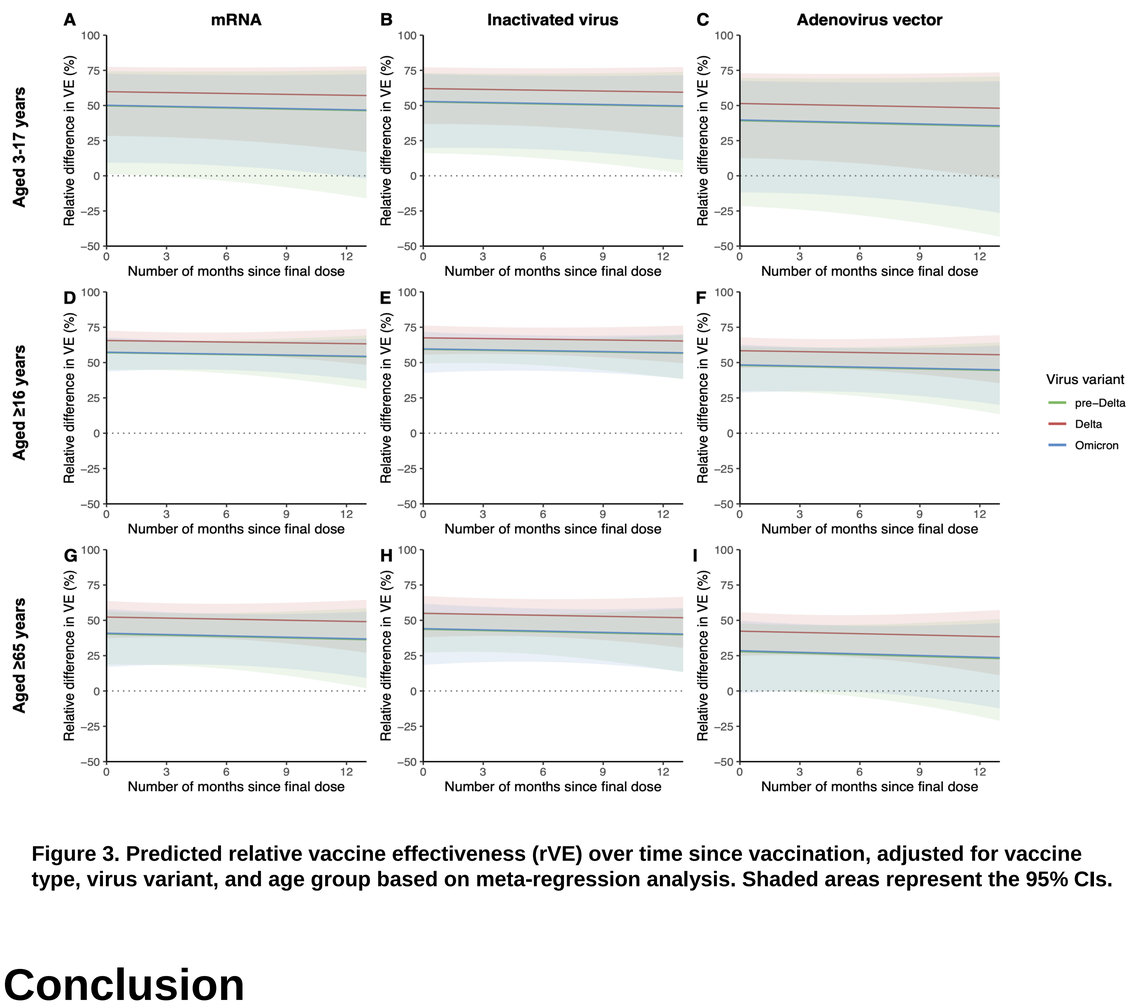

Figure 3. Predicted relative vaccine effectiveness (rVE) over time since vaccination, adjusted for vaccine type, virus variant, and age group based on meta-regression analysis. Shaded areas represent the 95% CIs.

Conclusion

- COVID-19 vaccination significantly attenuates disease severity, regardless of vaccine type and regardless of virus variant.
- This attenuation is sustained over time, suggesting persistent protection against disease progression despite waning immunity to infection.
- The effect is more pronounced for the Delta variant and weaker among older adults and medically attended symptomatic infections.

References

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[2] Mielke N, Johnson S, Bahl A. Boosters reduce in-hospital mortality in patients with COVID-19: An observational cohort analysis. Lancet Reg Health Am. 2022;8:100227.

Acknowledgements

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