Predictors of Breakthough COVID-19 infection from the STOPCoV cohort

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BACKGROUND

The degree of protection conferred by COVID-19 vaccines against infection and transmission especially with emerging variants cannot be quantified. We aimed to determine predictors of breakthrough COVID infections.

METHODS

The STOPCoV (Safety and efficacy of Preventative COVID-19 vaccines) is an ongoing decentralized study with the primary aim of a longitudinal assessment of antibody levels to COVID-19 vaccines and infection comparing those > 70 years of age to a cohort aged 30-50 years. Participants submit dried blood spots for the determination of antibody levels to Receptor Binding Protein (RBD) and NucleoProtein (NP) by ELISA every 3 months (12 weeks) and monthly report electronically on vaccine doses, brands and COVID-19 infections and outcomes. Survival analysis with time-dependent covariates was used.

Antibody levels based on the ancestral COVID-19 vaccine strain cannot be used to predict the risk of breakthrough infection or the need for booster doses.

Receipt of a vaccine booster that matches the circulating COVID variant is strongly associated with protection against breakthrough infection.

Table 1 *Hazard Ratios (and 95% Confidence Intervals) of Receptor Binding Domain antibody quintiles and age groups in association with breakthrough infection after index date.*

Characteristics	Univariable	Multivariable
Log_e(RBD.BAU) quintiles		
All waves		
< 4.92	Ref.	
4.92-6.03	0.851 [0.576, 1.256]	0.823 [0.557, 1.216]
6.03-7.13	0.795 [0.549, 1.152]	0.77 [0.53, 1.118]
7.13-8.13	0.861 [0.602, 1.233]	0.872 [0.608, 1.252]
> 8.13	0.688 [0.475, 0.996]	0.689 [0.474, 1]
Delta + BA.1 wave (15 December 2021 – 28 February 2022)		
< 4.92	Ref.	
4.92-6.03	0.974 [0.521, 1.818]	0.885 [0.47, 1.666]
6.03-7.13	0.955 [0.487, 1.875]	0.88 [0.443, 1.748]
7.13-8.13	0.292 [0.114, 0.747]	0.302 [0.117, 0.776]
> 8.13	0.198 [0.08, 0.486]	0.205 [0.082, 0.508]
BA.2 wave (22 March 2022–18 June 2022)		
< 4.92	Ref.	
4.92-6.03	0.846 [0.35, 2.044]	0.674 [0.276, 1.646]
6.03-7.13	0.755 [0.332, 1.718]	0.645 [0.282, 1.476]
7.13-8.13	0.96 [0.448, 2.058]	0.746 [0.344, 1.616]
> 8.13	1.192 [0.563, 2.523]	0.894 [0.417, 1.918]
BA.4/5 wave (19 June 2022–25 March 2023)		
< 4.92	Ref.	
4.92-6.03	1.243 [0.615, 2.511]	1.226 [0.603, 2.489]
6.03-7.13	1.291 [0.661, 2.522]	1.256 [0.638, 2.472]
7.13-8.13	1.508 [0.782, 2.908]	1.562 [0.805, 3.033]
> 8.13	0.977 [0.495, 1.929]	1.012 [0.509, 2.012]
XBB wave (26 March 2023–present)		
< 4.92		
4.92-6.03	---	---
6.03-7.13	0.349 [0.102, 1.192]	0.414 [0.101, 1.7]
7.13-8.13	0.475 [0.151, 1.492]	0.618 [0.163, 2.35]
> 8.13	0.404 [0.108, 1.503]	0.57 [0.132, 2.464]

RESULTS

Out of the 1286 enrolled participants, 983 were eligible for exploring the correlates of breakthrough infection. A first breakthrough infection occurred in 477 participants over the study period.

Figure 1- Cumulative Incidence of the first COVID-19 infection by age cohort

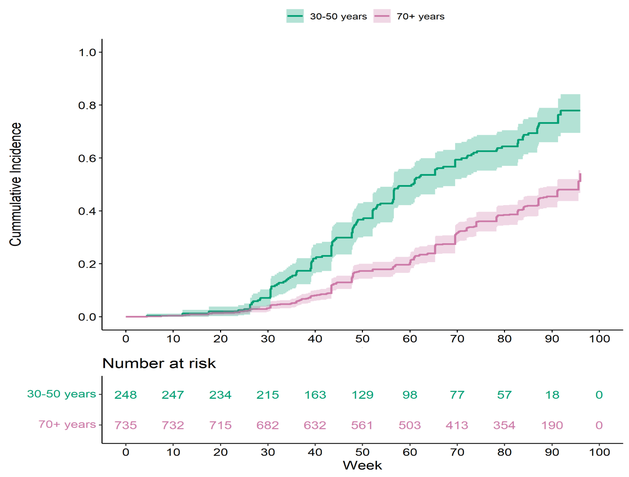
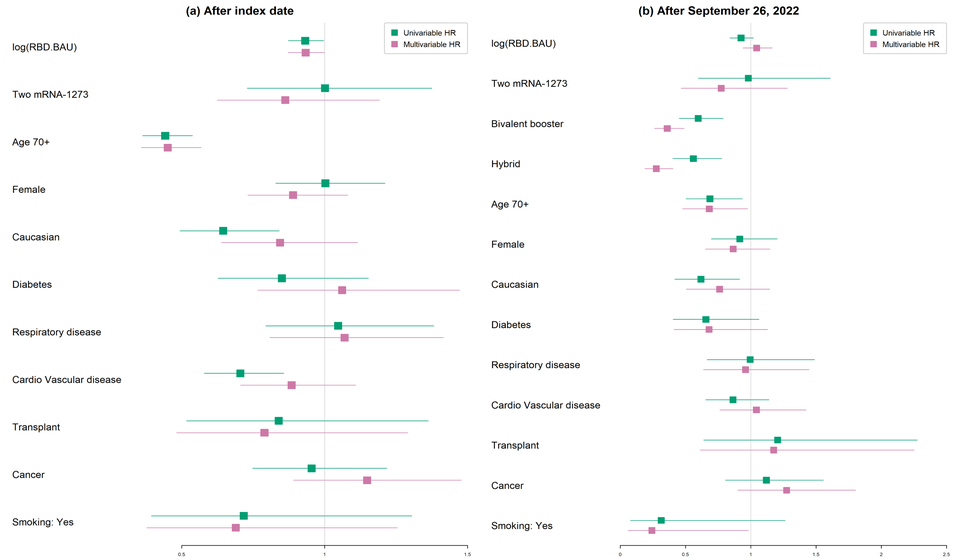


Figure 2: Hazard ratios of predictors in association date of second vaccine dose) and b) After September 26, 2022, when the Original/Omicron BA.4/5 bivalent booster were available. For b), participants with infection prior to September 26, 2022, were classified as having hybrid immunity.
with COVID-19 breakthrough infection: a) After index date



CONCLUSIONS

1. Antibody levels based on the ancestral strain *cannot be reliably* used to determine the necessity or timing of booster dosing.
2. The association between higher antibody levels and lack of breakthrough infection during the early waves decreased over time and with the emergence of variant strains.
3. An association between receipt of a bivalent vaccine booster and lack of a breakthrough infection during the Omicron BA.4/5 waves suggests that receipt of vaccines matching the circulating variants may provide the most effective protection.
4. Hybrid immunity was associated with protection against subsequent infections

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