Innovation and Research Week

שבוע חדשנות ומחקר

Correlates of protection for booster doses of the BNT162b2 vaccine

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Background

Variants of concern (VOC) of SARS-CoV2 and waning immunity pose a serious global problem. Overall, vaccination and prior infection appear to provide significant protection to most individuals, but some remain susceptible to infection and severe disease. Rigorously identifying a broad spectrum of correlates of protection (COP) is necessary to identify these susceptible populations. The extent to which additional booster doses provide protection is also poorly understood

Methods

To address this need, we conducted a multicenter prospective study assessing the association between serological profiles and the risk for SARS-CoV-2 infection, comparing those vaccinated with three to four doses of Pfizer BNT162b2 vaccine.

Results

Of 607 healthy adults that previously received three doses of the vaccine, 242 opted to receive a fourth dose. During the first 90 days of followup, 239 (39%) were infected, of whom 165/365 (45%) received three doses and 74/242 (30%) received four doses. We found that the additional dose elicited a significant rise in antibody binding and neutralizing titers against multiple variants, and reduced the risk of symptomatic infection by 37% [95% I, 15% - 54%]. We identified several parameters based on IgG and IgA binding that were COPs. The strongest association with infection risk was reduced IgG levels to RBD mutants and IgA levels to VOCs, a COP in the three-dose group (HR=6.34, p=0.008) and in the four-dose group (HR=8.14, p=0.018). A combination of IgG levels measured using two commercially available ELISA assays was also associated with protection in both groups (HR = 1.84, p = 0.002; HR = 2.01, p = 0.025, respectively).

Discussion and Conclusions

Our baseline markers and their combinations were validated as CoPs using a second clinical cohort of 46 healthy adults followed longitudinally across nine months. Most importantly, we identified a subset of individuals with low antibody levels after three doses of vaccine that responded with a significant boost in neutralizing antibody titers after a fourth dose but were still at significantly increased susceptibility to infection compared to those who had pre-existing high levels of binding antibodies. Thus, we identify a highly susceptible population that remains susceptible despite apparent responsiveness to vaccines.
Our data demonstrate that baseline binding antibody markers are significantly associated with infection risk and may be utilized to identify individuals most at risk from future exposures.

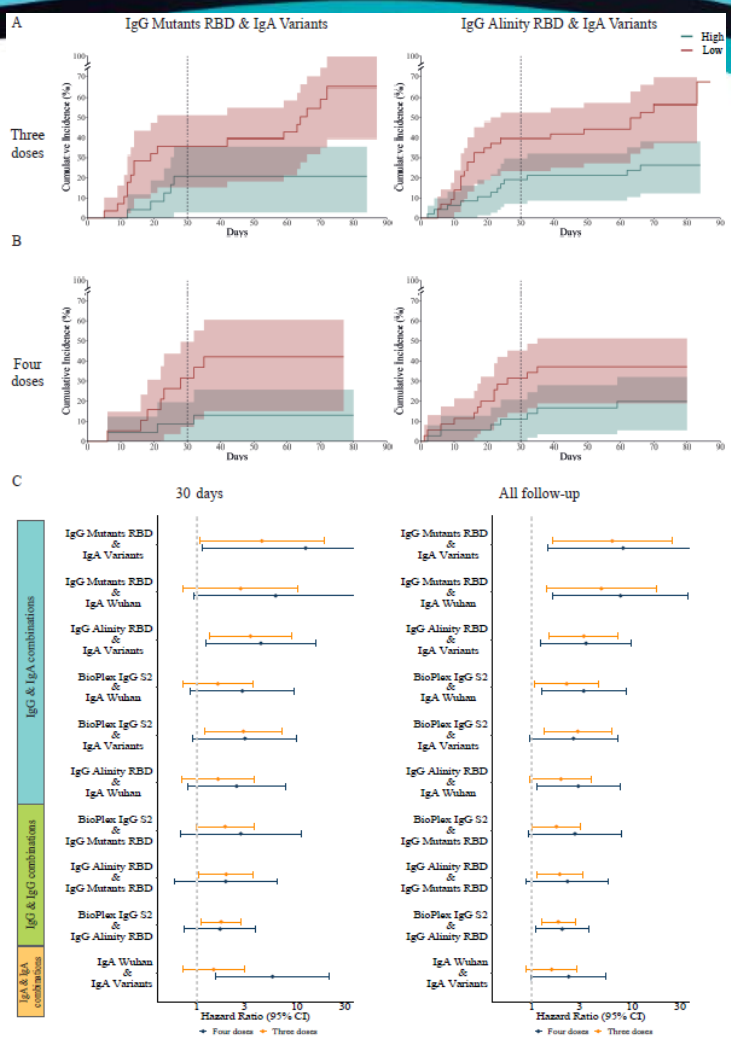
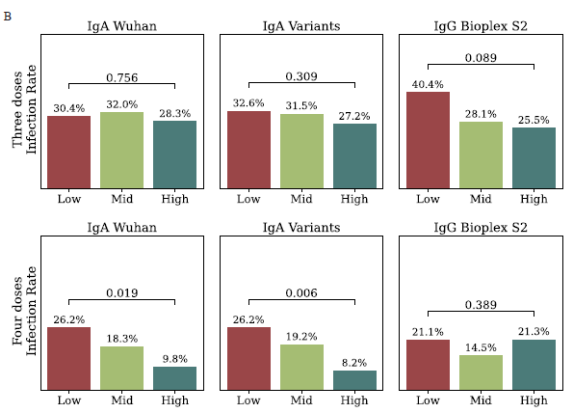


Figure 5: Combinations of IgG and IgA baseline markers are improved baseline correlates of protection. Pairs of baseline markers were used for ranking individuals using the intersection between the low and high groups of each baseline marker separately. Comparisons were conducted for 3rd and 4th dose recipients separately.(**A-B**) Cumulative incidence plots of individuals in the low and high- baseline response groups as measured using: (**A**) IgG RBD mutants and IgA SARS-CoV-2 VOCs (four doses n=42, three doses n=52); and (**B**) IgG Alinity and IgA SARS-CoV-2 VOCs (four doses n=71, three doses n=90). (**C**) Hazard ratios comparing low to high baseline response groups using pairwise combinations of baseline binding antibody markers for individuals vaccinated with three doses (orange) or four doses (blue). Error bars denote the 95% confidence intervals. Hazard ratios were computed using a cox proportional hazard model adjusted for age, occupation, medical center, and time from the third vaccination.



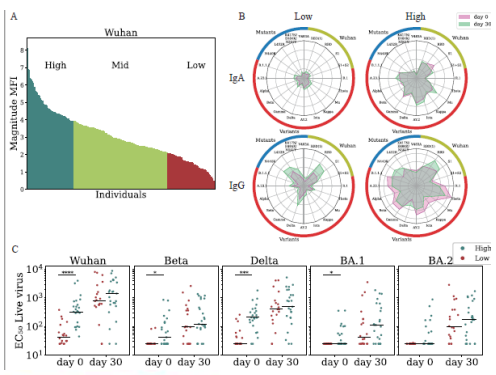


Figure 3: identifying baseline correlates of protection following three or four doses of the Pfizer-BioNTech vaccine. (A) Antibody levels of uninfected (green) and infected (red) individuals against Wuhan, RBD mutants and VOCs measured at enrollment. (**B**) Day 30 infection rates in low- mid- and high-baseline response groups ranked by baseline binding antibodies. Comparisons were conducted for three dose (top) and four dose (bottom) recipients separately. Individuals were ranked by IgA magnitude to Wuhan (Left), IgA to SARS-CoV-2 variants (Center), and by IgG S2 Bioplex (Right) (**D**) P-values were computed using a cox proportional hazard model, adjusted for age, occupation, medical center, and time from the third vaccination. * $p < 0.05$; ** $p < 0.001$; *** $p < 0.0001$; **** $p < 0.00001$.