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Comparative duration of neutralizing responses and protections of COVID-19 vaccination and correlates of protection

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The decline in neutralizing antibody (nAb) titers and vaccine efficacy /effectiveness (VE) for SARS-CoV-2 vaccines has been observed over time and when confronted with emerging variants, two factors that are hard to distinguish. Despite substantial drop in nAb titers against Omicron, VE remains high for severe cases and fatalities, raising questions about the utility of detected nAbs as a correlate of protection for COVID-19 vaccines for varying disease severity. Here, we conducted a systematic comparison of waning dynamics of nAb and VE over time and against variants with varying levels of disease severity. Using Bayesian linear regression models, we found that antigenically-shifted variants, like Omicron, could potentially lead to greater reductions in nAb titers and primary VE against mild infections than associated immunity waning observed over a 180-day period. By comparing model predicted nAb titers and VE on the same time scales, we found that VE against severe and fatal outcomes remained above 75% even when nAb titers reached the detectable limit of assays, despite strong correlations with nAb titers (spearman correlations ≥0.7) across variants over time. This finding suggested detectable nAb titers are not always sensitive enough to fully predict protection against severe disease and death from SARS-CoV-2.

As of April 2024, over 7 million COVID-19 deaths have been reported globally[1]. With increased population immunity from natural infections and vaccinations, COVID-19 has transitioned from a pandemic to an endemic disease. Neutralizing antibodies (nAb), produced after infections or vaccinations, are reported to mediate protection against asymptomatic, symptomatic and severe outcomes after SARS-CoV-2 infection[2–8]. However, nAb levels wane over time and the neutralizing capacity reduces when tested against antigenically-mutated viruses[9], which two factors often get mixed up when investigating nAb reductions. Understanding kinetics of nAb and associated protection over time, considering both time-related waning and mutation-leading reductions on neutralizing capacity, is crucial for informing booster strategies and developing new-generation vaccines.

Several studies have examined nAb as a correlate of protection (CoP) for COVID-19 vaccination[2–7,10]. However, most of these studies were conducted before the emergence of the Omicron variant, and were conducted primarily among individuals who received their priming series of COVID-19 vaccinations with limited follow-up[2,4–6]. In-vitro studies have reported significant reductions in nAb titers against variants of concerns, especially against the Omicron variant, which post-vaccination antibodies often fail to neutralize even at the lowest dilutions[11–14]. Nevertheless, empirical studies have demonstrated high vaccine-associated protection against severe outcomes and death

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after Omicron infections[15–19]. To date and to our knowledge, there has not yet been any comprehensive assessment of whether nAb serve as a consistent CoP for COVID-19 vaccines across variants, disease severities, vaccine types and doses over time.

Here, we systematically synthesized all available studies to separately estimate nAb kinetics and vaccine efficacy or effectiveness (VE) against different SARS-CoV-2 variants over time, taking into consideration disease severity, vaccine type and number of doses. This allowed us to dissect the contributions of time-related waning and variant mismatch to the observed reductions in nAb titers and VE, while controlling for other factors mentioned above. We then compared the predicted reductions in nAb titers and VE estimates, separately over the same time to assess nAb titers' potential as a CoP for COVID-19 vaccines against varied variants and disease severities.

Results

Data sources

To separately investigate the waning of nAb titers and VE after vaccinations, we systematically searched related studies (details in Tables S1-S3) and analyzed 49 nAb studies[9,11–14,18,20–62] and 44 VE studies[19,63–105] from 5,371 and 4,179 records retrieved from PubMed, respectively (details in Figures S1, S2, Supplementary data 1). Forty-nine studies reported nAb titers (Figures S3–S8) after various immunization types, including mRNA, inactivated, non-replicating viral vector, and heterologous vaccinations (i.e. not all doses entirely from the same vaccine platform) as well as infection convalescents, with 29 on primary immunization[9,11,13,14,18,20–26,28–36,44,45,51,52,54–57], 15 on booster immunization[37–42,47–50,58–62] and 5 on both[12,27,43,46,53]. Forty-four studies reported VE estimates (Figures S9-S12), with 36 studies on primary immunization[19,63–77,79–81,83,87–92,95–104], 2 on booster immunization[84,85] and 6 on both[78,82,86,93,94,105].

For included nAb studies, we extracted geometric mean nAb titers along with information including immunization types (i.e., natural infection or vaccine type and dose), time (in days) since complete immunization (i.e., time after 2nd dose or after infection for primary immunization, or time after booster dose for booster immunization), tested variants (i.e., ancestral, Alpha, Beta, Gamma, Delta and Omicron BA.1/1.1/2 subvariants (Omicron BA.1/1.1/2 after)), assay types (i.e., microneutralization assay (MNT), plaque-reduction neutralization assay (PRNT), focus-reduction neutralization assay (FRNT)) and age groups (i.e., adults, elderly only, all) (Table S4). All extracted nAb titers were obtained within six months of complete primary or booster immunization (Figures S3–S8).

For each extracted VE estimate, we also recorded information on time since complete immunization, immunization type and dose (i.e., primary or booster immunization), outcome severity (i.e., mild, severe or fatal COVID-19 disease), circulating variants (i.e., Alpha, Beta, Gamma, Delta, Omicron BA.1/1.1/2 and mixed variants) and age group at exposure (i.e., adults, elderly only, children and all) (Table S5). Extracted VE values were obtained within six months of complete primary immunization (Figures S9, S10) or within 140 days of complete booster immunization (Figures S11, S12). Among all included studies, 10 were randomized controlled trials and 83 were observational studies, including 52 cohort studies and 31 case-control studies. Most included randomized trials had overall low risk of biases, while observational studies were mostly assessed to have moderate risk of biases, with 5 nAb and 5 VE studies perceived to have serious risks (Tables S6, S7).

Waning of nAb

To estimate the nAb titer waning dynamics, we fitted a Bayesian linear regression model to log-transformed geometric mean nAb titers (original data shown in Figures S3-S8) over time. For each immunization status, the best-fitting models were determined by the greatest significant expected log predictive density (*elpd*) values (Table S8; details in methods). Suggested best-fitting models were adjusted for immunization type, variant, assay type, and age group, and treated study heterogeneity as a random effect (Table S8).

For primary immunization, the best-fitting model suggested an interaction between immunization type and time since immunization completion, indicating that nAb titers wane at different rates depending on the vaccine platform (Figure S13A). For example, after peaking at 14 days post-primary immunization, titers from heterologous primary series declined 3.4-fold (95% CrI 2.5 to 4.7-fold) every 90 days due to time-related waning, whereas titers from viral vector vaccines dropped 1.4-fold (95% CrI 1.1 to 1.9-fold) in the same interval (Fig. 1a, Table S9). In contrast, for booster immunization, the best-fitting model suggested no significant differences between waning rates across vaccine platforms (Table S10, Figure S13 B). Notably, we found peak nAb titers varied by immunization type at both immunization statuses (Fig. 1, Tables S9, S10). After the primary vaccination, nAb titers elicited by inactivated and viral vector vaccines were 8.2-fold (95% CrI 4.0 to 16.8-fold) and 5.6-fold (95% CrI 3.4 to 9.4-fold) lower than the peak titers elicited by mRNA, respectively (Table S9).

While the best-fitting model suggested that both time and variant factors contributed to nAb reductions, model comparisons consistently indicated that antigenically-shifted variant differences between pre-Omicron and Omicron BA.1/1.1/2 (antigenically-shifted variant differences hereafter) explained more variability (Bayesian R^2) and provided better predictions (*elpd*) than time since immunization (Table S11). For primary immunization, the variant-only model yielded a Bayesian R^2 value of 0.76 (95% CrI 0.74 to 0.79), higher than 0.70 (95% CrI 0.67 to 0.73) for the time-only model. Similar results were found after booster immunization, with a Bayesian R^2 of 0.84 (95% CrI 0.81 to 0.86) for the variant-only model, compared to 0.76 (95% CrI 0.71 to 0.79) for the time-only model. Moreover, time-only models had lower *elpd* values than variant-only models (e.g., −35.7, SE 17.8 for primary and −30.0, SE 9.4 for booster immunization). Using the best-fitting model, we estimated that nAb levels against the ancestral virus dropped 2.3-fold (95% CrI 2.0 to 2.6-fold) at 3 months and 6.2-fold (95% CrI 4.6 to 8.3-fold) at 6 months post−2-dose mRNA vaccination, respectively, compared to the 14-day level (Fig. 1a, Table S9). In contrast, nAb levels against Omicron BA.1/1.1/2 at 14 days was already 14.5-fold lower (95% CrI 10.9 to 19.1-fold) than ancestral levels at the same time, before significant waning had occurred. This reduction was also greater than the decrease observed at either 3 or 6 months of waning for the ancestral virus. Furthermore, 3 and 6 months post−2-dose mRNA vaccination, nAb titers against Omicron BA.1/1.1/2 were 33.3-fold lower (95% CrI 24.3 to 45.0-fold) and 89.5-fold lower (95% CrI 59.3 to 133.2-fold) than ancestral titers at 14 days, respectively (Fig. 1a).

We found consistent results from sensitivity analyzes after transforming model outcomes to log-transformed fold changes and after including subsequently circulating Omicron variants (i.e., BA.4/5, BQ.1.1 and XBB.1.5) to analyzes (Tables S8, S11-S13; details in Methods).

Waning of VE

To estimate VE waning dynamics, we fitted a Bayesian linear model to the log-transformed risk ratio derived from VE values against various severity outcomes, with time as a predictor, considering separate effects of immunization type, circulating variant, age group and random effects of study heterogeneity, suggested as the best-fitting model (Table S14). Fourteen days after the second dose, mRNA vaccines achieved 91% VE (95% CrI 88 to 93%) against mild Delta infections, while viral vector vaccines provided 80% VE (95% CrI 75 to 85%) (Fig. 2a, Table S15). Three months post-2-dose, VE against the same endpoint of mild Delta infections decreased to 84% (95% CrI 80 to 88%) for mRNA vaccines and to 66% (95% CrI 57 to 74%) for viral vector vaccines (Fig. 2a, Table S15).

Model comparisons indicated that both antigenically-shifted Omicron variants and time-related waning contributed to VE

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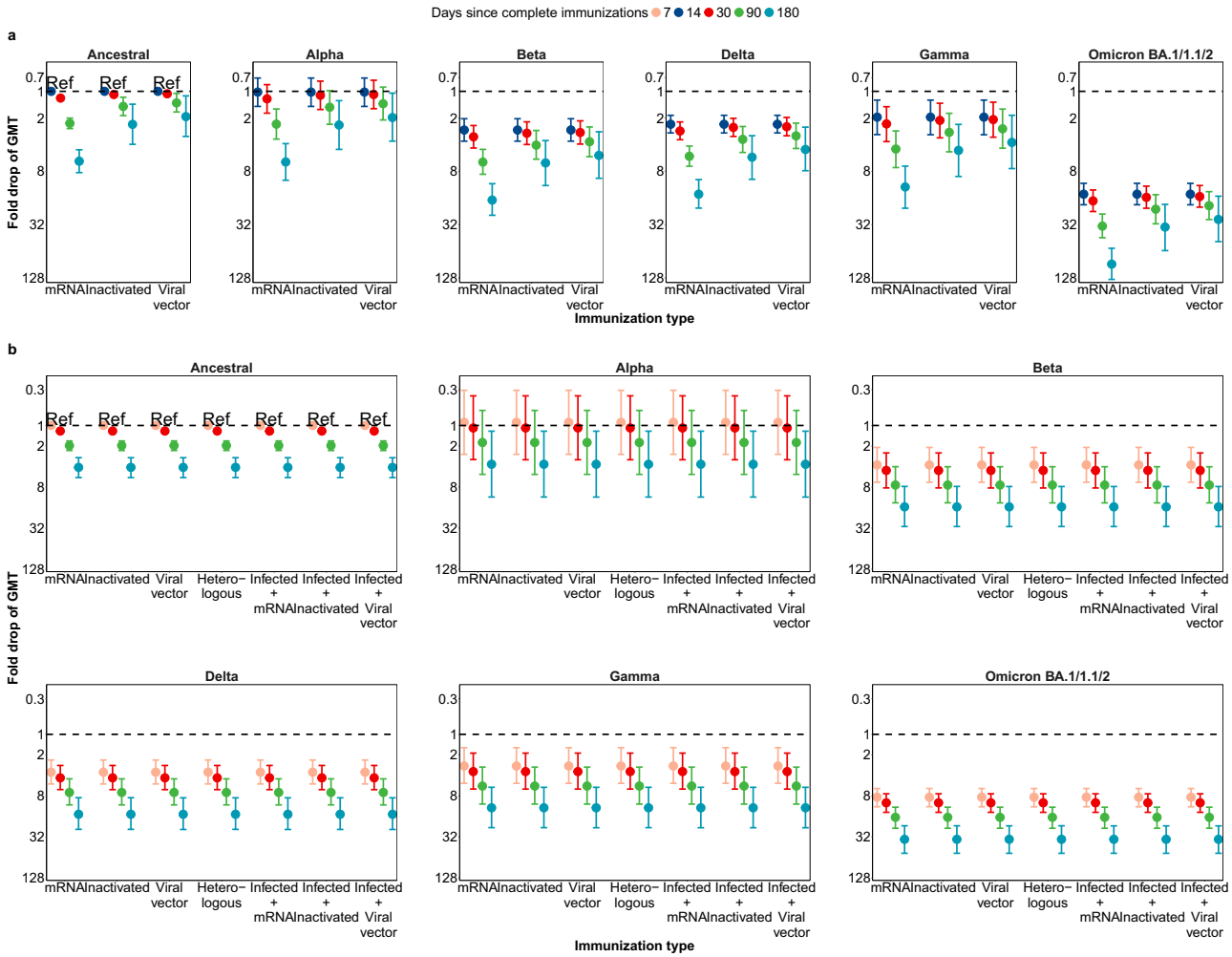

Fig. 1 | Estimated fold drops in geometric mean titer (GMT) with time after complete immunization across immunization types, stratified by tested variant and booster status. a Fold drops after primary immunization. **b** Fold drops after booster immunization. Fold drops were compared to the GMT against the ancestral virus on day 14 for primary immunization and on day 7 for booster immunization, with dots and error bars representing the mean and 95% credible interval of estimated fold drops from day 7 to 180. GMT were estimated assuming MNT50 were measured for sera from adults. Dashed line in each panel represented reference level of fold drop for each vaccine platform obtained at 14 days after primary immunization (**a**) and 7 days after booster immunization (**b**). ($n = 358$ for primary immunization in (**a**) and $n = 167$ for booster immunization in (**b**)).

reductions against mild and severe outcomes after both primary and booster immunizations (Table S16). However, for primary VE against mild infections, variant-only models explained more variability in observed VE variations (Bayesian R^2: 0.64. 95% CrI 0.60 to 0.67 vs. 0.53, 95%CrI 0.48 to 0.57) and yielded better predictive performance (direct comparison *elpd* -60.2, SE 16.7) than time-related waning only model (Table S16). Using the best-fitting model (Table S14), we estimated that VE against mild Delta infections was 91% (95% CrI 88 to 93%) at 14 days post−2-dose mRNA vaccination, decreasing to 84% (95% CrI 80 to 88%) at 3 months and to 70% (95%CrI 62 to 77%) at 6 months (Fig. 2a, Table S15). In contrast, VE against mild Omicron BA.1/1.1/2 infections was only 60% (95% CrI 48 to 69%) at 14 days after the same vaccine regimen (before significant time-related waning occurred), which was lower than Delta estimate at 3 months and similar to that at 6 months (Fig. 2a, Table S15). VE against mild BA.1/1.1/2 infections further declined to 31% (95% CrI 11 to 46%) at 3 months (Fig. 2a, Table S15).

For primary immunization, model comparison indicated that both antigenically-shifted variant differences and time-related waning contributed similarly to reductions in VE against severe and fatal outcomes. Variant-only and time-only models showed comparable Bayesian R^2 values (0.53, 95% CrI 0.46 to 0.59 vs. 0.54, 95% CrI 0.47 to 0.60) and non-significant *elpd* differences (− 3.8, SE 9.2) (Table S16). In contrast, for VE against severe outcomes after a booster, time-related waning played a larger role than antigenically-shifted variant differences, as evidenced by higher Bayesian R^2 values (0.70, 95% CrI 0.61 to 0.76) compared to the variant-only model (0.36, 95% CrI 0.20 to 0.49) and a larger *elpd* difference (− 27.3, SE 5.3) (Table S16). We observed similar results in VE estimates using the best-fitting model (Fig. 2b, c, d).

Comparing waning of nAb and VE and correlate of protection

To simultaneously compare the waning of nAb titers and VE over time, we plotted model-predicted nAb titers and VE estimates on the same time scales after primary or booster immunization, stratified by disease severity and adjusted for immunization type, variants and age group (Fig. 3, and Figures S14, S15). Predicted nAb GMTs against Delta decreased from 101.0 (95%CrI, 48.4 to 190.4) at two weeks to 17.0 (95% CrI 8.8 to 33.0) after 6 months for primary mRNA vaccine immunization, corresponding to a 6.0-fold (95%CrI, 2.3 to 15.2-fold) decrease in predicted titers (Fig. 3a, and Figure S14). By comparison, VE against mild Delta infections decreased from 91% (95%CrI 89 to 93%) at two weeks to 71% (95%CrI 63 to 77%) 6 months after two mRNA doses, corresponding to a 3.2-fold (95%CrI 2.2 to 4.4-fold) increase in relative

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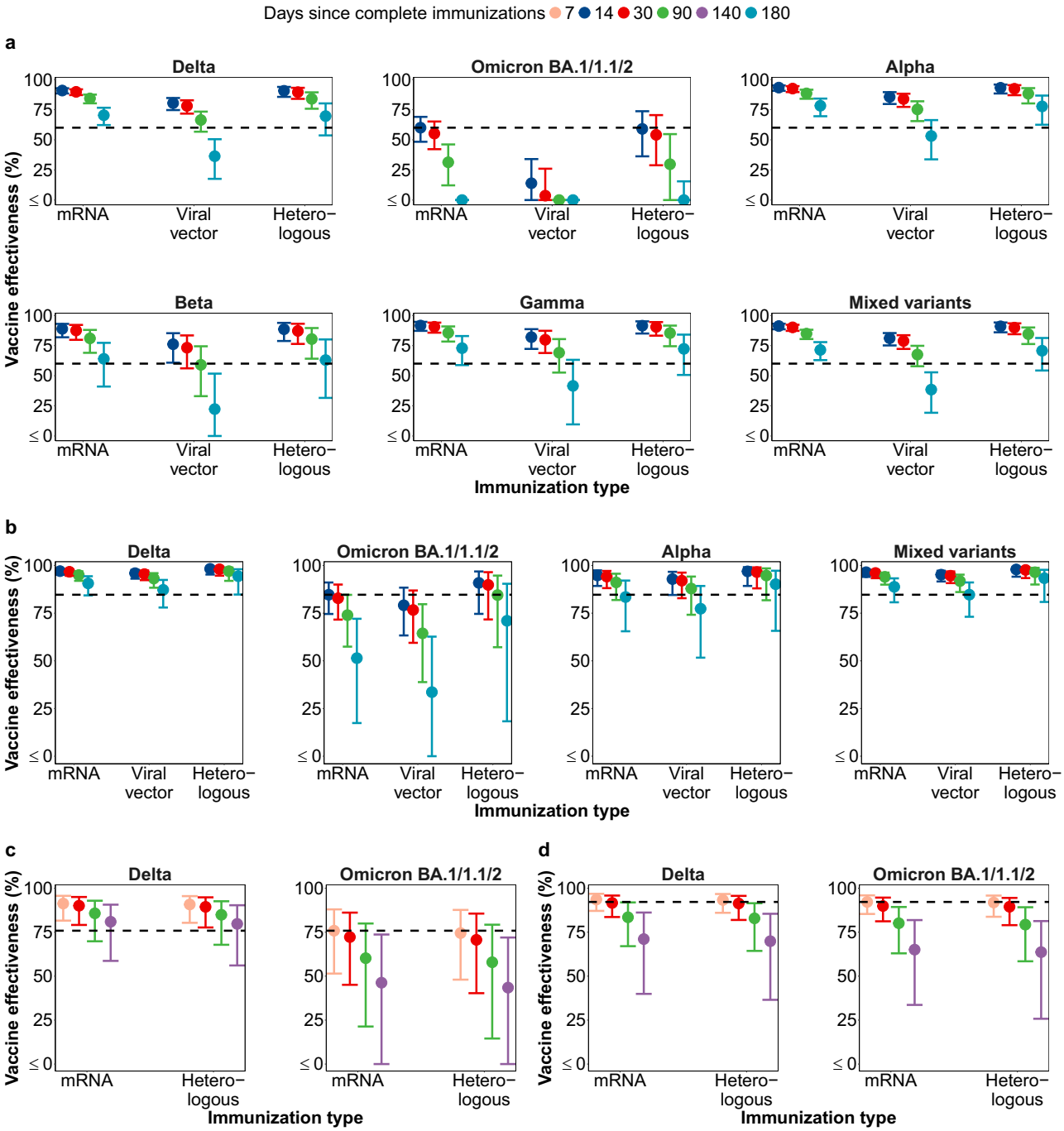

Fig. 2 | Estimated vaccine effectiveness (VE) with time after complete immunization across disease severities and immunization types, stratified by circulating variant and booster status. a Primary-immunized VE against mild infections. **b** Primary-immunized VE against severe/fatal infections. **c** Booster-immunized VE against mild infections. **d** Booster-immunized VE against severe infections. Dots and error bars represented the mean and 95% credible interval of estimated VE from day 7 to 180. VE was estimated for adult group. Dashed line in each panel represented mean estimated VE values against Omicron BA.1/1.1/2 14 days after primary-series mRNA vaccination (**a**, **b**) or 7 days after mRNA vaccination (**c**, **d**) (n = 485 and 243 for mild infections and severe/fatal infections for primary immunization in (**a**) and (**b**); n = 98 and 69 for mild infections and severe infections for booster immunization in (**c**) and (**d**)).

risk (Fig. 3A, and Figure S14). Similar results were found against Omicron BA.1/1.1/2 variant and after boosters across different disease severities (Fig. 3b, c, d, and Figure S15).

Next, we investigated the correlation between nAb levels and VE, assessing whether changes in nAb could reflect changes in VE across different disease severities. For each variant, we generated random time points within six months after vaccination, and used the fitted models to predict nAb titers (measured by MNT_{50}) and VE following primary-series mRNA vaccinations in adults. We compared the model-predicted nAb levels and VE estimates for the same time points, stratified by varying disease outcomes (Fig. 4). We found strong correlations between predicted nAb titers and VE across variants and severity levels (Spearman correlation, 0.700 – 0.878). A titer of 40 for nAb was associated with VE of 82% (95%CrI, 71 to 88%) against mild disease, 92% (95%CrI, 69 to 97%) against severe disease or death. At a titer of 10, protection decreased to VE of 44% (95%CrI, 29 to 56%) against mild diseases, but remained high at 79% (95%CrI, 65 to 87%) against severe diseases or death (Fig. 4).

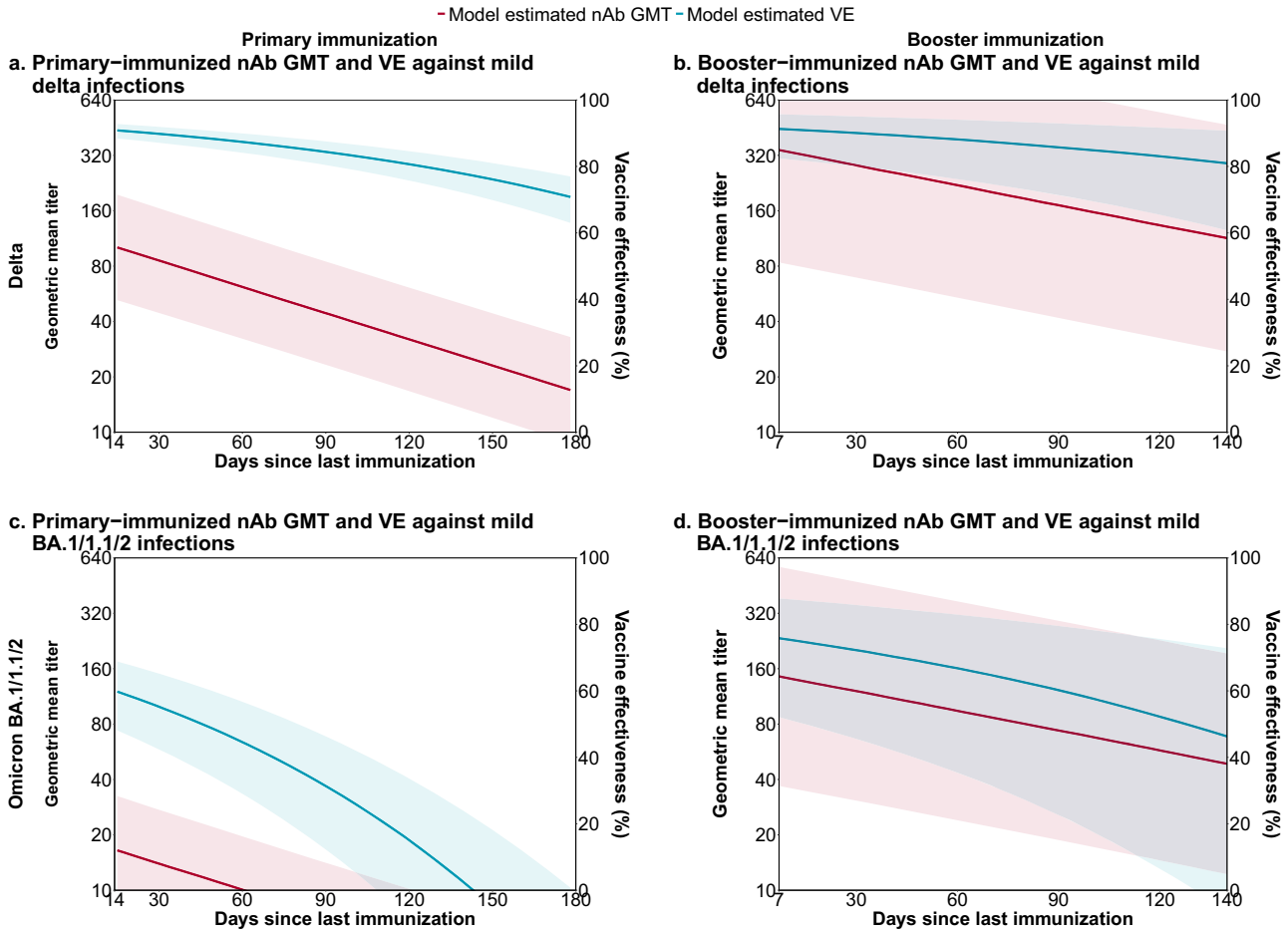

Fig. 3 | Comparative waning in neutralizing antibody (nAb) and vaccine efficacy or effectiveness (VE) over time for two and three doses mRNA vaccine. a nAb and VE against mild Delta infection after primary immunization. **b** nAb and VE against mild Delta infection after booster immunization. **c** nAb and VE against mild Omicron BA.1/1.1/2 infection after primary immunization. **d** nAb and VE against mild Omicron BA.1/1.1/2 infection after booster immunization. GMT were assumed to be measured by MNT_{50} for sera from adults. VE was estimated for adult group.

We found significant differences in nAb titers when tested by $PRNT_{50}$ at primary immunization status (Table S9, and Figure S16) and in VE estimates among different age groups (Figures S17, S18). Including subsequently circulating Omicron variants (i.e. BA.4/5, BQ.1.1 and XBB.1.5) into VE analyzes also returned similar results as original analyzes (Tables S17, S18). Additionally, we observed no significant difference in predicted nAb titers across age groups (Tables S9, S10).

Discussion

Our study demonstrated a systematical evaluation framework for the literature on nAb titers and VE against various SARS-CoV-2 variants over time, considering different vaccine types, doses, and disease severities. This enabled us to estimate the correlation between predicted nAb titers and VE across variants and disease severities. Our results suggested that VE against severe and fatal outcomes was insensitive to changes in nAb titers within detectable ranges (i.e., 1:10 dilution and above for 50% neutralization in most cases[106,107]). Using data up to 6 months after primary immunization and 140 days after booster immunization, the best-fitting model suggested while both factors contributed to reductions in nAb and VE, antigenically-shifted variant differences play a larger role in reduced nAb titers and primary VE against mild infections, with no such impact observed for severe or fatal infections. Our results, together with previous findings[8,17,46,108–110], suggest that protection from pre-existing SARS-CoV-2 immunity may involve factors beyond nAb, warranting further investigations into other potential biomarkers or improved assays, especially for more severe outcomes.

We found a strong correlation between nAb and VE across different disease severities, after accounting for variants, vaccine types and doses. This finding is consistent with previous studies on different variants[2,5,6,111,112] and might be explained by the ability of nAb in transmission blockade against infection and disease attenuation through Fc-effector function for virus clearance after infection[113]. However, the sensitivity of VE to changes in nAb titers varied by disease severity. We estimated limited changes in VE within detectable nAb ranges for severe and fatal outcomes and could not model the association for nAb levels below detectable dilution thresholds. We estimated over 70% effectiveness against severe infections, consistent with findings that individuals who received two inactivated vaccines maintained over 90% protection against fatal outcomes during the Omicron BA.1/2 surges[108,114], despite generally having no detectable nAb against Omicron BA.1/2 after vaccinations[110,115].

Our results align with studies reporting short-term protection against mild and severe infections[17,108,109] in the absence of detectable nAb against Omicron[46,110]. This, along with evidence that serum nAbs alone may not fully explain pre-existing SARS-CoV-2 immunity[8], implied a potential role for other immune mechanisms, like pre-existing T cell immunity[8,108]. Indeed, higher pre-exposure T cell levels were found to correlate with protection from infection[116], whereas lower levels of cross-reactive $CD4^+$ T cells from seasonal coronaviruses may increase susceptibility to severe COVID-19[117]. T cells, especially

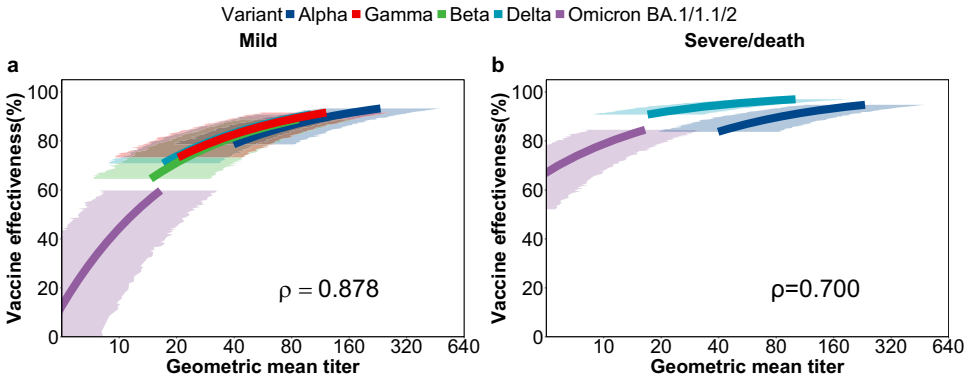

Fig. 4 | Estimated correlate of protection against varying disease outcomes after two doses mRNA vaccine, stratified by circulating variant. Neutralizing antibody geometric mean titers (GMT) and vaccine effectiveness (VE) were estimated against mild (**a**) and severe/fatal (**b**) outcomes at different time since primary immunization completion, against various variants separately. Colored lines indicate the median of GMT and VE at each time point against the corresponding variant. Shaded areas indicate 95% credible interval from 1000 bootstrapped GMT and VE estimates against the corresponding variant at each time point. GMT was assumed to be measured by MNT50. Both nAb and VE were estimated for adult group.

$CD8^+$ T cells, directly contact and kill infected cells to control viral replication, mitigating disease progression[118]. Notably, vaccine-induced T cells recognize both ancestral and Omicron variants, regardless of vaccination time[22], which might explain sustained protection against severe COVID-19 despite decreased nAb responses. Non-neutralizing binding antibodies have also been implicated to reduce COVID-19 disease severity by maintaining Fc-effector function even against mutated variants[113]. These antibodies bind to a broad range of epitopes on the virus rather than to specific sites like the receptor-binding domain, which most neutralizing antibodies target and are prone to mutations[113,119]. Collectively, various immune mechanisms may all contribute to protections, and further research to correlates of protection with additional immune markers is warranted.

Our findings indicate that antigenically-shifted differences in Omicron variants caused more significant reductions in nAb and primary VE against mild infections than time-related waning or vaccine types within 180 days after immunization. When comparing nAb titers and VE for mild infections contemporaneously, we observed greater decreases against antigenically distinct variants, such as pre-Omicron (e.g., ancestral, Delta variants) and Omicron variants[120], compared to against the same variant over time for both primary and booster immunizations.

For VE against severe outcomes, the antigenically-shifted Omicron BA.1/1.1/2 variant had a similar impact as time-related waning within 180 days after primary immunization, while after a booster dose, the antigenically-shifted Omicron BA.1/1.1/2 variant explained fewer variances than the time-related waning. These observations are likely due to high VE against severe COVID-19 across variants and reduced sensitivity of VE against severe outcomes to changes in nAb. Our findings suggested variant mismatch may have a great effect on mild infections and population susceptibility than time since immunization, implying the potential benefits of variant-adapted vaccines over booster with mismatched compositions, similar to how vaccines are developed for antigenically variable pathogens like seasonal influenza[121].

Our findings on nAb and VE waning are consistent with previous studies[122–129] that examined these factors separately. Additionally, by calculating absolute VE, the percent drop in VE against symptomatic infections is greater than VE against severe diseases, consistent with previous findings that VE against severe disease declines more slowly than VE against mild infection[19,63,67,69].

Our study has several limitations, primarily related to the studies and data used in our analysis. First, no study has simultaneously examined long-term waning of nAb titer and VE. Our COP estimate was based on separate assessments of nAb and VE kinetics and linking them on the same timescale for similar vaccination and variant conditions. Second, few studies have examined VE against ancestral viruses beyond 3 months, therefore our models were primarily informed by VE against Delta and Omicron BA.1/1.1/2 variants. Third, VE studies used varying designs and estimation techniques, including both clinical trials and observational studies, and we addressed this heterogeneity with a random-effect term. Forth, the compiled data varied in terms of vaccine types, doses and prior infections. To address data sparsity, we grouped data by vaccine platforms (rather than specific brands) and booster status. Fifth, to estimate CoP, we focused on primary and first-booster immunization data, which may not fully represent the current population's immune landscape and should not be directly used for vaccination recommendations. Sixth, we could not identify a single timeframe where variants consistently outweighed waning across all vaccines and variants due to the interaction between waning and vaccine regimen. Nevertheless, our primary goal was to clarify the relative contributions of these factors rather than define a universal timeframe for comparison. Finally, most studies used in our analyzes were observational studies, which may be subject to varying biases, especially due to confounding. Stronger data, like data from randomized clinical trials, are needed to better quantify the relationship between nAb levels and VE.

In conclusion, our findings suggest that while both variant and time-related waning contribute to reductions in nAb titers and primary VE against mild COVID-19, antigenically-shifted differences in variants, like Omicron, could have a greater impact than time-related waning over a 6-month period. We observed correlations between nAb titers and VE across variants and disease severities. However, as VE against severe and fatal outcomes remained high even when nAb levels fall to the limit of detection, using nAb titer changes as a COP for severe diseases within detectable ranges may be limited and challenging. Future research into additional CoPs against severe outcomes or more appropriate nAb assays is warranted.

Methods

Search strategy and selection criteria

We conducted a systematic search in PubMed on March 18th, 2024, for peer-reviewed studies on the waning of neutralizing antibodies (nAb) and vaccine efficacy or effectiveness (VE) against SARS-CoV-2 variants infections and diseases. We used terms of ("SARS-CoV-2" OR "COVID-19") AND "variant", and excluded study topics such as cost-effectiveness, meta-analysis and animal studies although we reviewed their reference lists for relevant original studies. For nAb studies, we included "antibody" OR "antibodies" in the search term. For VE studies, we included terms "vaccin*" or "immune*" combined with "effectiveness",

"efficacy" or "effective" in title and abstract. We provided detailed search strategies in Tables S1 and S2.

We included randomized controlled trials, cohort, and case-control studies that measured nAb using live-virus assays. These assays tested for 50% neutralization, employing either a plaque reduction neutralization test ($PRNT_{50}$), microneutralization test (MNT_{50}), or focus reduction neutralizing test ($FRNT_{50}$). We only included studies that recorded nAb titers at two time points or more, with the final time point exceeding three months post-immunization (i.e., vaccination or infection). We excluded studies that (1) investigated the monoclonal and therapeutic antibody efficacy against variants; (2) solely examined seroprevalence; (3) detected only non-neutralizing antibodies (4) reported biological features of specific mutations; (5) lacked precise collection times since exposure or had wide time intervals (i.e., >90 days); (6) were reviews or commentaries; and (7) used non-human sera or data from human with specific health conditions (i.e., cancer, organ transplantation or pregnancy).

We included randomized controlled trials for vaccine efficacy, and observational studies for vaccine effectiveness. We included studies reporting vaccine efficacy or effectiveness ("VE" hereafter) adjusted for relevant confounding factors or provided values transformable into VE (e.g., adjusted odds ratio, aOR; adjusted risk ratio, aRR; adjusted hazard ratio, aHR). Additionally, these studies needed to record values at discrete time points, with the latest one being more than three months after the final vaccine dose. We excluded studies that (1) only reported effectiveness of partial vaccination; (2) used a comparison group other than unvaccinated individuals; (3) did not use a test to confirm SARS-CoV-2 infection status (i.e., polymerase chain reaction (PCR) tests and rapid antigen tests (RAT)); (4) were reviews, commentaries, modeling, or transmission studies; (5) used an unvaccinated group that was restricted to persons with previous infection; and (6) did not report specific time intervals or had very wide time intervals for recorded VE values(i.e., >90 days).

To assess the quality of the included studies, the Cochrane risk of bias tool 2.0 was used for randomized controlled trials and the risk of bias in non-randomized studies-of interventions (ROBINS-I) tool was used for observational studies[130].

Data extraction and processing

Two reviewers (CL and BY) independently screened titles and full texts of studies based on the predetermined inclusion and exclusion criteria and extracted relevant information of included studies onto standardized forms. For nAb studies, the information about the study that was extracted included immunization types (i.e., natural infection or vaccine type and dose), time (days for unit) since complete immunization (i.e., time after 2nd dose or after infection for primary immunization or time after booster dose for booster immunization), types of neutralization assays used, SARS-CoV-2 antigens tested, age groups examined and number of subjects providing sera. Additionally, for each study j, we extracted the geometric mean nAb titers ($GMT_{j,g,t}$) and standard deviations ($\sigma_{j,g,t}$) for each immunized group g at time t. If not provided, we estimated the values of these variables using individual data points or using median, interquartile range (IQR) and sample sizes[131]. We recorded nAb titers only for study visits that allowed a sufficient number of days for the development of detectable antibodies (see Table S3 for the standards used). To account for the impact of primary and secondary immunizations, we categorized extracted nAb titer data into two groups: (1) primary immunization, including individuals who had received primary-series vaccination or who had tested positive for SARS-CoV-2; and (2) booster immunization, including individuals who received booster vaccination doses after completing their primary vaccination series or received vaccinations after recovery from SARS-CoV-2.

We recorded VE estimates with their corresponding 95% confidence interval (CI), adhering to the same time standards as for nAb titers. For each VE estimate, we also extracted information about vaccine type (e.g. mRNA, adenoviral vector, heterologous platforms), vaccination doses, the predominant circulating variants, severity of COVID-19 outcomes, time since complete immunization, age group and sample sizes for both vaccinated and unvaccinated subjects. When studies did not report a VE estimate, but did report an aOR, aRR, or aHR, we converted these values into VE percentages using VE = (1-value) *100. When the reported VE estimate was 100%, we deducted 0.5% from the VE estimate and from all other VE estimates measured at different time points in the same study-vaccine group, following Feikin's approach[122]. We then categorized the VE estimates into primary and booster immunization based on booster status. Within each status, we further categorized VE estimates by outcome severities.

Statistical analysis

Waning of nAb and VE after primary immunization. To estimate the association between nAb titer and time since immunization, we fitted Bayesian generalized linear models on log-transformed $GMT_{j,g,t}$ to time since complete immunization (T_t, in days; average time when only intervals were provided). The models adjusted for independent variables, including immunization type ($I_{j,g}$), assay type ($M_{j,g}$), tested variant ($V_{j,g}$) and age group ($A_{j,g}$) (details in Table S4). To eliminate the heterogeneity of different studies, we included a random intercept (b_j^{Ab}) to explain studies' variation. To further eliminate heterogeneities from different assay types and laboratories, we also standardized $GMT_{j,g,t}$ as fold change to nAb titers which was obtained using the earliest collected serum to test against ancestral variant, in each study and used log-transformed fold change as outcomes to perform model fitting. Additionally, we conducted sensitivity analyzes by including nAb data tested against subsequently circulating Omicron variants (i.e., BA.4/5, BQ.1.1 and XBB.1.5) to fit models.

VE estimates were also fitted with Bayesian linear models with structures listed in Table S14, where VE was transformed into a log-scale risk ratio ($RR_{j,g,t}$) and back transformed later, estimated by time since complete immunization (T_t). The models were adjusted for immunization type ($I_{j,g}$), circulating variant ($V_{j,g}$), age group at exposure ($A_{j,g}$) (details in Table S5) and random effects brought by studies (b_j^V). We also conducted sensitivity analyzes of including subsequently circulating Omicron variants to fit models with VE estimates.

For both nAb and VE fitted models, we applied weakly informative priors (N (0, 1000); details in Table S19) to time variables and intercepts. 95% credible intervals (CrI) were derived using Bayesian estimation to quantify uncertainty, with non-overlapping CrIs indicating substantial differences. Results for each model were obtained by running four Markov chains, with 2000 iterations, including 1000 burn-in iterations, for each chain. We set target acceptance rate to 0.95 for primary-immunization models and 0.99 for booster-immunization models. Maximum depth of the trees for No-U-Turn Sampler was set to 12 for all models. Model convergence is assessed with R hat (i.e. <1.01), effective sample size (i.e., >1000) and trace plots. We also examined the models that failed to converge, which consistently involved the interaction between time, immunization type and tested variant (Tables S8, S14), likely due to data insufficiency. As a result, these non-converged models were excluded from further analysis.

We selected the best-fitting model for nAb titer and VE separately, by comparing converged models based on prediction accuracy using expected log predictive density (*elpd*) values from "*loo_compare*" function in "*loo*" package[132]. For models with more than 90% of included data having Pareto-k values below 0.5, we compared models' *elpd* values (details in Table S8, S14) and preferred the ones with statistically-significant (i.e., absolute value of *elpd* difference is greater than twice of associated standard error) highest absolute *elpd* value[132,133]. If fewer than 90% of included data had Pareto-k values below 0.5, we applied a four-fold standard error criterion (i.e., absolute value of *elpd* difference is greater than four times of associated

standard error) to determine the significance (Table S8)[132,133]. Parameter estimates from all models are provided in Tables S20-S25. We also examined models that incorporated interaction terms between time since complete immunization with either immunization type or variant for both nAb and VE (details in Tables S8, S14).

Waning of nAb and VE after booster immunization. Using the same approach for primary immunizations, we fitted and selected the best-fitting models for predicting nAb titers and VE after booster doses (details in Tables S8, S14).

Comparing waning of nAb and VE. To compare the waning of nAb titers and VE over time, we plotted the model-predicted nAb titers and VE estimates after primary or booster immunization, against time since immunization completion, immunization type, variants and age group. We displayed fitted values for nAb and VE on the same time scale and under the same conditions for vaccine platform, dose, variant and age group.

To assess the CoP, we investigated the relationship between predicted nAb titers and VE against SARS-CoV-2 infection for various severity levels and different variants. We plotted model-predicted nAb values in relation to VE for each variant, separately, against mild, severe and fatal outcomes of infection. To account for uncertainty, we estimated standard errors for nAb and VE estimates respectively using 1000 bootstraps from their point estimates. We used Spearman's correlation to quantify the relationship between nAb titers and VE, stratified by disease severity.

All analyzes were performed in R (version 4.2.1 R Foundation for Statistical Computing), with Bayesian generalized linear models fitted by "*brm*" function using "*brms*" package.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

Integrated data used to reproduce the figures are available at Zenodo[134].

Code availability

Code used in the analysis and figures is available at Zenodo[134].

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Author contributions

All authors meet the ICMJE criteria for authorship. The study was conceived by BY and B.J.C. C.L. and B.Y. performed the literature review and screening, extracted data, and wrote the first draft of the manuscript. C.L. analyzed the data. B.Y. and T.K.T. contributed to analytical methods. T.K.T., S.G.S. and B.J.C. critically reviewed the manuscript. All authors read and approved the final version.

Competing interests

BJC consults for AstraZeneca, Fosun Pharma, GSK, Haleon, Moderna, Novavax, Pfizer, Roche, and Sanofi Pasteur. SGS reports consulting for GSK, Moderna, Novavax, Pfizer, Sanofi, CSL Seqirus and Evo Health. The authors report no other potential conflicts of interest.

Additional information

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