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RESEARCH ARTICLE

Predicting antibody kinetics and duration of protection against SARS-CoV-2 following vaccination from sparse serological data

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Data availability statement: De-identified patient data are available upon request. We provide synthetic data representing the study cohort, and further provide the stan model code and scripts for model inference and evaluation on GitHub: https://github.com/juliadeichmann/sars-cov-2_ab-kinetic-model.

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Abstract

Vaccination against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) generates an antibody response that shows large inter-individual variability. This variability complicates the use of antibody levels as a correlate of protection and the evaluation of population- and individual-level infection risk without access to broad serological testing. Here, we applied a mathematical model of antibody kinetics to capture individual anti-SARS-CoV-2 IgG antibody trajectories and to identify factors driving the humoral immune response. Subsequently, we evaluated model predictions and inferred the corresponding duration of protection for new individuals based on a single antibody measurement, assuming sparse access to serological testing. We observe a reduced antibody response in older and in male individuals, and in individuals with autoimmune diseases, diabetes and immunosuppression, using data from a longitudinal cohort study conducted in healthcare workers at Sheba Medical Center, Israel, following primary vaccination with the BNT162b2 COVID-19 vaccine. Our results further suggest that model predictions of an individual's antibody response to vaccination can be used to predict the duration of protection when serological data is limited, highlighting the potential of our approach to estimate infection risk over time on both the population and individual level to support public health decision-making in future pandemics.

Author summary

Vaccination against SARS-CoV-2 has played a key role during the COVID-19 pandemic to lower transmission rates and reduce the number of severe cases. This is due to a vaccine-induced rise in antibody levels that provides protection against infection. However, antibody levels wane over time and exhibit high variability between individuals. In

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order to evaluate infection risk and develop effective vaccination strategies, it is therefore important to gain a better understanding of the individual-level antibody response to vaccination. In this work, we applied a mathematical model to describe antibody trajectories and to quantify the contributions of different characteristics to the antibody response. We show that the model can be used to predict individual antibody trajectories and the corresponding duration of protection, which may be used to monitor infection risk over time in individuals and across the population, identify populations most at risk and evaluate potential vaccination policies.

Introduction

The introduction of vaccines against SARS-CoV-2 in late 2020 has played a pivotal role in combatting the global spread of COVID-19. They provide protection against severe disease and death [1,2], and to a lower extent reduce the risk of infection and transmission [3,4]. However, vaccine effectiveness and humoral immunity show a progressive decline with time after vaccination [5].

Vaccination against SARS-CoV-2 elicits a complex cellular and humoral immune response. The humoral immune response is characterized by a rise in antibody levels against the spike protein of the virus, and it was shown in population- and individual-level studies that they can serve as a correlate of protection against COVID-19 infection [6–8]. Antibodies initially rise and then fall rapidly in the first three months after vaccination. This is followed by a period of slow waning over several months [9], resulting in a biphasic pattern typical for antibody kinetics [10]. The waning of antibody levels is associated with an increase in infection risk over time, warranting repeated vaccination to maintain antibody levels and prevent the loss of protection.

However, antibody levels display high inter-individual variability. They are not only associated with time since vaccination, but also depend on other factors like age, sex and coexisting conditions [11,12]. This makes it challenging to predict antibody levels to evaluate population- and individual-level infection risk, diminishing their predictive value as a correlate of protection without broad and ongoing serological testing. Mathematical models that take this heterogeneity into account could serve as a valuable tool to describe and predict antibody trajectories. Their predictions could then be used to evaluate how infection risk evolves over time, allowing to infer the vaccine-induced duration of protection and to identify individuals with an impaired immune response. This could further provide support in the development of boosting strategies, especially when determining the optimal timing of vaccination in subpopulations with an elevated infection risk and reduced duration of protection.

In this study, we present a framework to predict individual-level antibody trajectories and the corresponding duration of protection following vaccination based on limited serological data. We rely on a mathematical model of antibody kinetics previously developed for malaria [13], which has later been applied in the context of COVID-19 [9,14], and focus on the anti-SARS-CoV-2 response to primary vaccination. To quantify the effects of demographic characteristics and comorbidities on the antibody response, we calibrate the model using longitudinal IgG binding antibody data against the receptor-binding domain (RBD) of the SARS-CoV-2 spike protein. Data were collected in a cohort of healthcare workers at Sheba Medical Center, Israel, receiving two doses of the Bnt162b2 COVID-19 vaccine [15]. We then update the model to predict the antibody response of new individuals by providing a single serological measurement. We evaluate the effect of timing of serological sampling

on prediction accuracy and finally determine the resulting duration of protection induced by vaccination.

Results

Data

Of the 4 868 healthcare workers in the study cohort, we included 2 609 with complete demographic information and at least two serological samples in our analysis, providing a total of 14 853 serum samples. 3 863 (26%) of those samples fall above the antibody assay's upper limit of quantification. Participant characteristics are summarized in Table 1. The cohort consists of 2 003 (77%) female participants, with a median age of 47 years and BMI of 25 kg/m^2. Participants exhibit few comorbidities. The most common comorbidity is hypertension in 290 participants (11%), whereas immunosuppression only occurs in 36 participants (1%). No participants have a history of SARS-CoV-2 infection and all received two doses of the BNT162b2 COVID-19 vaccine.

We split the data into training and test data sets, which consist of 75% and 25% of study participants, respectively (S1 Appendix, Section S1). Characteristics of the two subgroups remain similar (Table 1).

Antibody trajectories

Anti-SARS-CoV-2 IgG antibody levels first increase and become detectable in week two after administration of the first vaccine dose (Fig 1A, green). This is followed by a steep increase after administration of the second dose, with peak antibody levels sometimes exceeding the upper quantification limit of the antibody assay used here. Antibody levels then slowly wane over the remaining study period.

To describe immunological processes involved in the antibody response after vaccination and quantify differences between individuals, we fit a model of antibody kinetics to the individual-level antibody trajectories of the training data set. The model includes the antibody boost generated through vaccination by short- and long-lived antibody-producing cells (APCs), the decay of those cells and the waning of antibodies. We followed a Bayesian approach for model calibration, with individual parameter values originating from population-level parameter distributions. The inferred anti-SARS-CoV-2 IgG antibody

Table 1. Characteristics of study participants overall and in the training and test groups.

	Total (n=2609)	**Training** (n=1957)	**Test** (n=652)
Sex (female)	2003 (76.8)	1487 (76.0)	516 (79.1)
Age (years)	47 [38–57]	47 [37–57]	47 [38–57]
BMI (kg/m^2)	24.8 [22.1–27.8]	24.8 [22.2–27.8]	24.7 [22.1–27.9]
Weight (kg)	69 [60–80]	69 [60–80]	68 [60–80]
Comorbidities			
Hypertension	290 (11.1)	219 (11.2)	71 (10.9)
Autoimmune disease	186 (7.1)	139 (7.1)	47 (7.2)
Dyslipidemia	177 (6.8)	135 (6.9)	42 (6.4)
Diabetes	134 (5.1)	111 (5.7)	23 (3.5)
Lung disease	93 (3.6)	64 (3.3)	29 (4.4)
Heart disease	68 (2.6)	53 (2.7)	15 (2.3)
Immunosuppression	36 (1.4)	29 (1.5)	7 (1.1)

Reported as *n* (%) or median [IQR].

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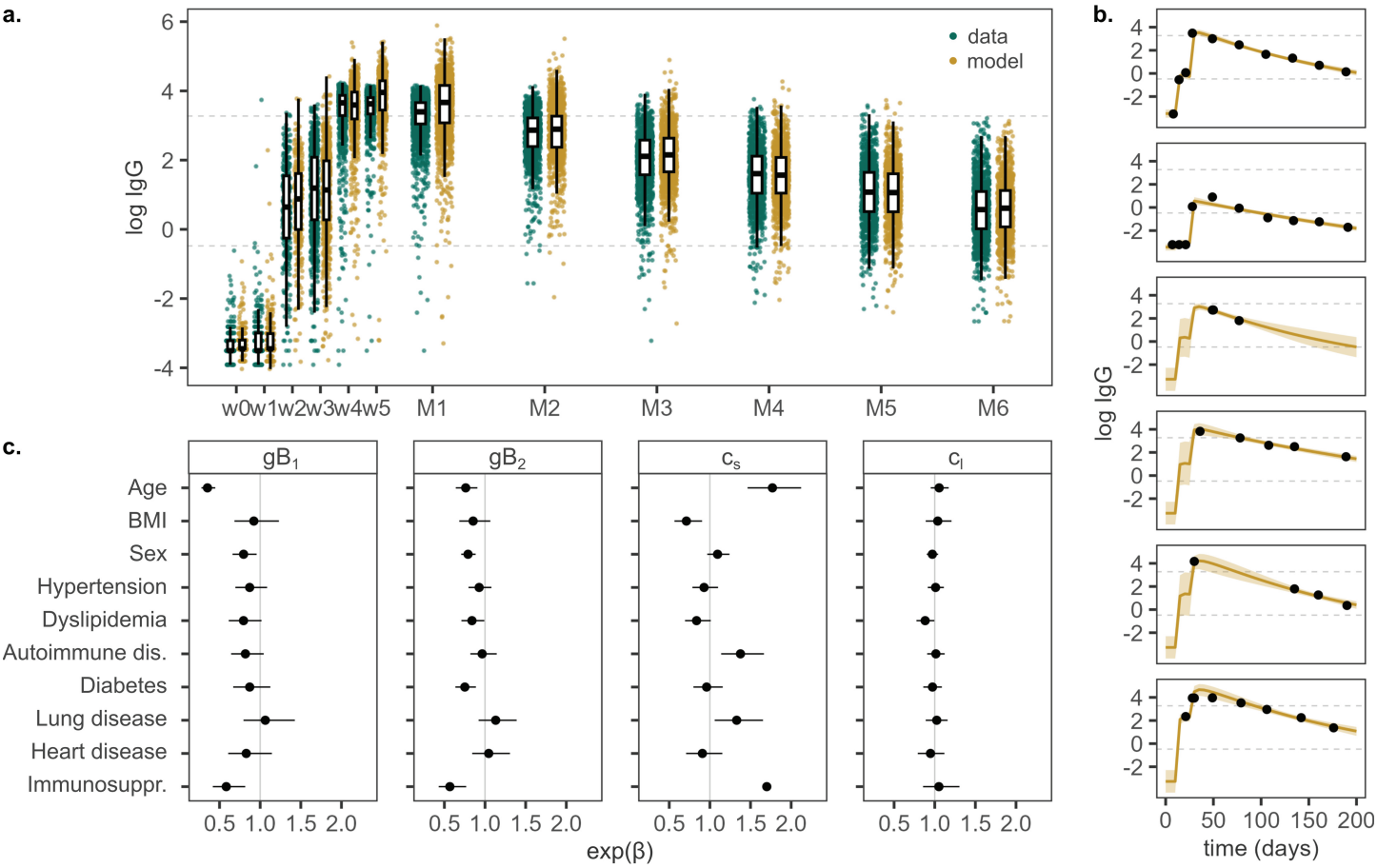

Fig 1. Model fit on the training data set. (**a**) Observed (green) and predicted (yellow) anti-SARS-CoV-2 IgG antibody levels following vaccination. Dose 1 is administered in week 0 (w0), dose 2 in week 3 (w3). Serum samples were taken weekly following dose 1 for five weeks (w1–w5), then monthly up to six months after dose 2 (M1–M6). The boxplots represent median and interquartile range (IQR) of the observed or modeled data points, with whiskers extending from the hinges to the largest value that is not further than 1.5 · IQR from the respective hinge. The lower detection and upper quantification limits of the antibody assay are shown as dashed lines. Measurements above the lower detection limit imply seroconversion and measurements above the upper quantification limit fall outside the antibody assay's linear range. (**b**) Observed and predicted antibody levels for six example individuals with different antibody response and sampling frequency. The solid line represents the geometric mean prediction, shaded areas indicate the 90% posterior predictive interval. (**c**) Estimated effects of covariates on antibody boost (gB_1 and gB_2) and decay rate of short- and long-lived antibody-producing cells (c_s and c_l), shown as median and 95% posterior interval estimates.

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levels capture the observed immune dynamics across the full training population and for individual study participants (Figs 1A and 1B). A root mean squared log error (RMSLE) of 6.9% (median, interquartile range [IQR]: 3.5–10.9%) on the training data set indicates excellent agreement between data and model, and posterior distributions of the population-level parameters are normally distributed (S1 Fig). We observe moderate positive correlations between parameter components related to the antibody boost after administration of the second vaccine dose and the waning rate of short-lived APCs. Furthermore, the proportion of short-lived APCs exhibits a moderate negative correlation with the waning rates of antibodies and long-lived APCs (S1 Table). Peak antibody levels are reached 36 days (IQR: 34–37 days) after vaccination, and the estimated half-life of the overall immune response when antibody levels drop below 50% of their peak level is 69 days (IQR: 65–73 days), both showing little variation among individuals in the study population.

Analysis of modeled antibody response. We further analyzed the modeled antibody trajectories and variability arising due to differences in demographics and comorbidities. In particular, we examined the amplitude of the immune response and the duration for which vaccination provides protective antibody levels (Figs 2 and 3).

Antibody levels are lower for older individuals over the whole study period. This is also reflected in a decrease in maximum IgG levels with age, with a drop of 55% (95% confidence interval [CI]: 48–60%, Figs 2 and 3) for participants over 60 years compared to participants younger than 30 years of age. This drop for individuals over 60 is markedly more pronounced than for other age groups. While BMI does not affect the humoral immune response significantly, antibody levels are lower in male compared to female participants (ratio of means in peak IgG: 0.73 [95% CI: 0.68–0.79]). Additionally, antibody levels are generally lower when coexisting conditions are present, in particular for autoimmune disease and diabetes. There are 29 individuals in the training data set with immunosuppression, displaying the lowest antibody response to vaccination across the study population, with a decrease in peak antibody levels by 73% (95% CI: 65–79%).

Vaccination induces a rise in antibody levels that provides protection against SARS-CoV-2 infection. However, the modeled duration of protection, defined as antibody levels over 500 BAU/mL [16] corresponding to a sample-to-cutoff ratio of 11.6 in our data [17], varies strongly between individuals (IQR: 75–115 days). In accordance with lower overall antibody levels, duration of protection decreases with age, where participants up to 30 years of age exhibit protective antibody levels for distinctively longer time periods than other age groups (Figs 2 and 3). Similarly, the duration of protection is reduced in male compared to female individuals. Additionally, 78 out of 1957 (4%) individuals remain unprotected over the full study period. This unprotected subpopulation consists mostly of older individuals and individuals with autoimmune diseases, diabetes and immunosuppression.

Covariate effects on model parameters: antibody boost and APC decay. The variability in antibody response between individuals is captured in individual values for model parameters, which are associated with different processes involved in the humoral immune response. Here, we examined the effects of individual characteristics on the modeled antibody boost initiated by the first and second vaccine dose, represented by parameters gB_1 and gB_2, respectively, and the modeled decay of short-lived, c_s, and long-lived antibody-producing cells, c_l (Fig 1C).

The antibody boost decreases with age and is drastically reduced in older individuals following the first dose in particular, with a reduction by 52% (95% credible interval [CrI]: 43–59%) from age 30 to age 60. In addition, we observe a lower antibody boost in male compared to female participants (factor $exp(\beta)$, 0.80 [95% CrI: 0.66–0.96] after dose one and 0.79 [95% CrI: 0.71–0.88] after dose two) and in participants with dyslipidemia (0.80 [95% CrI: 0.61–1.02] and 0.84 [95% CrI: 0.71–0.99]) or immunosuppression (0.58 [95% CrI: 0.42–0.82] and 0.57 [95% CrI: 0.43–0.77]) after both vaccination events, and in people with diabetes after the second dose (0.75 [95% CrI: 0.64–0.89]).

The decay rate of short-lived APCs increases with age (factor 1.49 [95% CrI: 1.30–1.68] between age 30 and 60) and for individuals with autoimmune disease (1.38 [95% CrI: 1.14–1.67]), lung disease (1.33 [95% CrI: 1.06–1.65]) or immunosuppression (1.70 [95% CrI: 1.27–2.45]). Consequently, the modeled half-life of short-lived APCs is shorter in older individuals and in the presence of these comorbidities. A higher BMI is associated with a reduction in decay rate (factor 0.92 [95% CrI: 0.87–0.98] between a BMI of 22 kg/m^2 and 28 kg/m^2). In contrast, long-lived APCs remain unaffected by the examined covariates. Hence, the decay rate c_l and corresponding half-life are similar across the full study population.

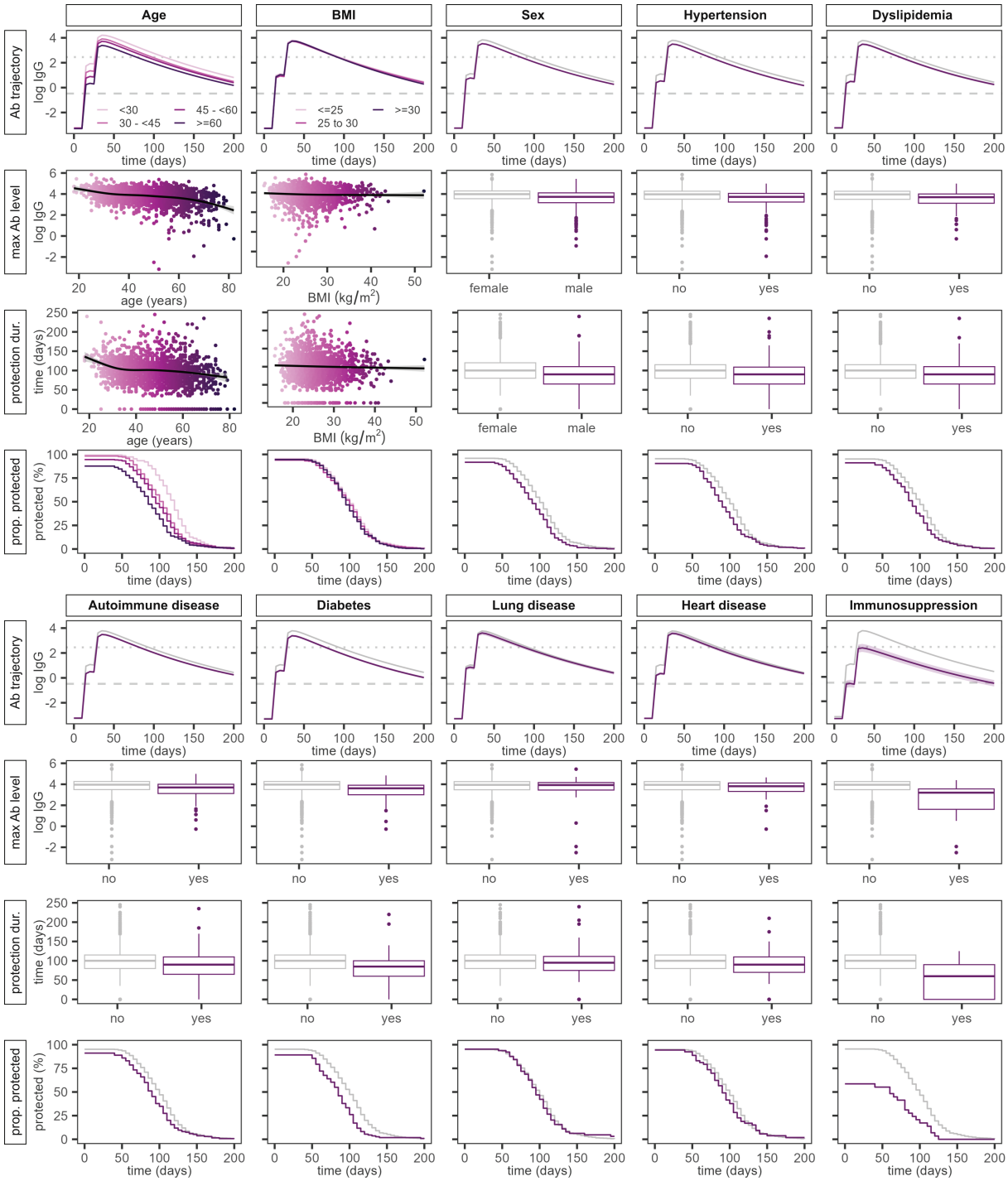

Fig 2. Evaluation of the modeled antibody response stratified by covariates considered in the antibody kinetics model. Predicted antibody trajectories are shown in the upper panels, represented by the estimate of the geometric mean antibody concentration (solid lines) and the standard error of the mean (shaded areas). Dashed lines indicate the lower detection limit and dotted lines the protective antibody threshold. The maximum antibody level and duration of protection inferred from the modeled antibody trajectories are displayed in the second and third row, respectively. Smoothing lines based on a generalized additive model are overlaid for the continuous covariates age and BMI. Boxplots are used for categorical covariates. The lower panels show the proportion of protected individuals over time determined from the predicted duration of protection.

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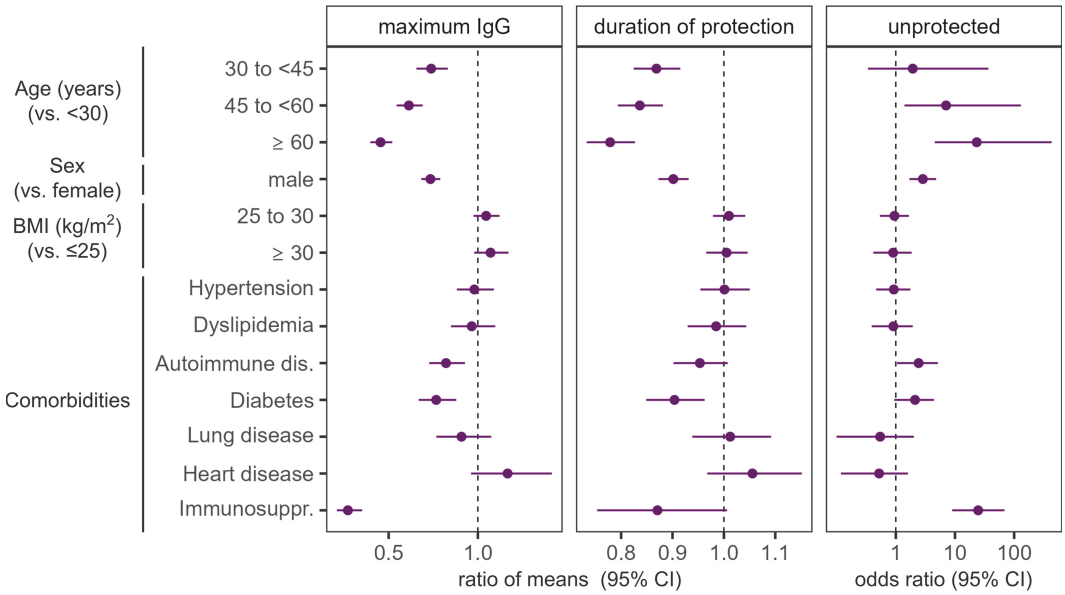

Fig 3. Analysis of maximum IgG levels and duration of protection from modeled antibody trajectories. We show the ratio of means between the examined covariates and their reference level, and the odds ratio of remaining unprotected following vaccination.

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Prediction of antibody levels

For model validation, we predicted the antibody responses of individuals in the test data set. We provided one anti-SARS-CoV-2 IgG measurement per individual to adjust the model's random effect estimates, assuming limited availability of serological testing. We evaluated both how well the model captures the full antibody trajectory as well as the accuracy of forward predictions from the time of testing. Moreover, we repeated this analysis with serological sampling being carried out at different times after vaccination to analyze the effect of timing on prediction accuracy.

We show predicted antibody trajectories for one example individual and residuals across the full test population in Fig 4 and S2 Fig, where IgG measurements are provided between month one (M1) and month six (M6) following vaccination. Overall, providing a single data point for model adjustment leads to an improved geometric mean prediction and refined posterior prediction interval compared to predictions made without model adjustment (S3 Fig). For serological testing of the individual participant during M1 and M2, antibody levels during waning are slightly overestimated (Fig 4). For the remaining sampling times, we observe good agreement between model predictions and measured IgG antibody levels, including narrower posterior prediction intervals. Similarly, residuals across the population are smaller for serological sampling performed during M3 or later compared to sampling performed during the first two months following vaccination, with the RMSLE between data and model predictions after administration of the second vaccine dose decreasing from 26.6% (IQR: 13.7–49.0%) for M1 to 18.0% (IQR: 11.4–26.2%) for M3 across the test population (Fig 4 and S2 Fig). Afterwards, the RMSLE is stable for the remaining study period. Moreover, we quantified the accuracy of forward predictions from the time of serological testing in monthly increments using the RMSLE (Table 2). The antibody predictions one month ahead (diagonal, Table 2) are the most precise and comparable for all sampling times, with a median RMSLE

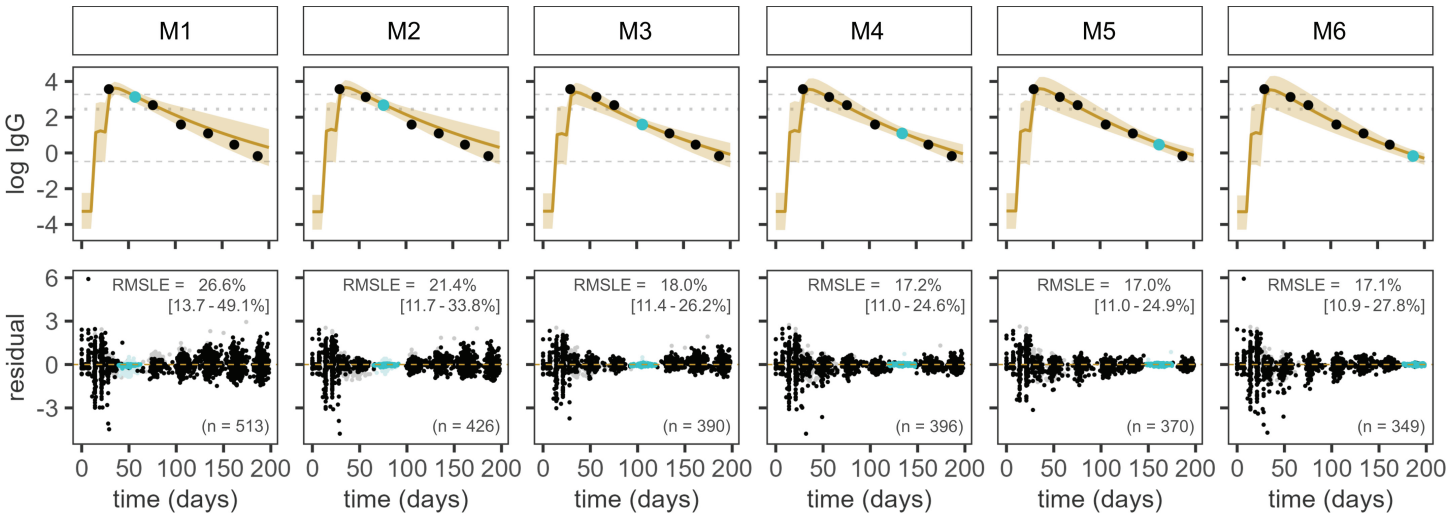

Fig 4. Prediction of antibody response on the test data set. Predicted IgG antibody trajectories (yellow) for one example individual from the test data set. One measurement is provided between months one (M1) and six (M6) for model adjustment (light blue), the remaining data points (black) are unknown to the model. The solid line represents the geometric mean prediction, shaded areas indicate the 90% posterior predictive interval. Dashed lines indicate the lower detection and upper quantification limit and dotted lines indicate the protective antibody threshold. Residuals and the RMSLE for antibody levels after receipt of the second vaccine dose (median, IQR) are shown in the lower panels for the full test population, where lighter shades are used for measurements above the limit of quantification. Individuals are included in the analysis if an antibody measurement was available for the corresponding month.

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between 14.5% and 17.9%. The RMSLE increases for predictions further into the future. Predictions one and two months ahead have a lower accuracy for sampling during M3, when the immune response transitions from short- to long-lived processes, compared to the surrounding months. Additionally, the variation in RMSLE among participants is higher for earlier sampling times and with increasing distance from the time of testing.

Finally, we evaluated whether we can predict the time at which an individual's antibody levels drop below the protective threshold for the different sampling times, where we considered individuals that are protected at the time of testing. Predictions align with the duration of protection determined for individuals in the training data set (IQR: 75 – 115 days). We further validated our predictions against the duration of protection inferred from the measured anti-SARS-CoV-2 IgG antibody levels of the test individuals (Table 3). In the majority of cases, we

Table 2. RMSLE between model predictions and test data for the months following serological sampling between month one (M1) and month five (M5).

	Prediction				
Sample time	**M2**	**M3**	**M4**	**M5**	**M6**
M1	17.9%	31.5%	36.9%	36.8%	37.4%
	[8.5–31.9]	[18.3–53.7]	[15.0–57.1]	[10.9–73.0]	[19.8–68.2]
M2	–	14.5%	23.7%	34.0%	30.4%
	–	[4.5–31.7]	[12.9–37.9]	[15.3–48.3]	[14.5–53.9]
M3	–	–	16.1%	31.2%	23.7%
	–	–	[9.0–28.5]	[11.5–40.1]	[12.9–41.3]
M4	–	–	–	15.8%	17.5%
	–	–	–	[8.4–26.5]	[9.9–33.6]
M5	–	–	–	–	16.0%
	–	–	–	–	[7.2–22.3]

Median [IQR].

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Table 3. Validation of protection status and duration by sampling time between month one (M1) and month 5 (M5). We compare the number of unprotected (U) and protected (P) individuals between data and model prediction, and determine the proportion of protected whose duration of protection (t_{prot}) is also predicted accurately. In this summary, individuals are excluded if the measured IgG antibody level for model calibration falls above the limit of quantification for the given month, and if the time window to extract the duration of protection from the data exceeds 45 days.

		M1 (n=145)			M2 (n=173)			M3 (n=104)			M4 (n=38)			M5 (n=8)		
		Prediction			Prediction			Prediction			Prediction			Prediction		
		U	P	(t_{prot})	U	P	(t_{prot})	U	P	(t_{prot})	U	P	(t_{prot})	U	P	(t_{prot})
Data	U	13	3		6	0		6	0		2	0		1	0	
	P	2	127	(71%)	2	165	(82%)	1	97	(64%)	1	35	(86%)	0	7	(100%)

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categorize individuals correctly into protected or unprotected. Furthermore, we are able to predict the time window when participants lose protection, where we achieve slightly higher accuracy when serological sampling is performed at later time points following vaccination.

Discussion

IgG binding antibody levels against SARS-CoV-2 have been used as a correlate of protection for COVID-19 infection. However, this relies on access to broad serological testing, since large inter-individual variability in the humoral immune response to vaccination or infection makes it difficult to predict antibody levels and evaluate the population- and individual-level infection risk. In this study, we used a model of antibody kinetics to capture the antibody response to vaccination and identify factors that lead to differences between individuals. We then evaluated the prediction accuracy of the model and its capability to predict the time until a threshold IgG level is reached.

We followed a Bayesian approach to infer model parameters using antibody data collected in healthcare workers after primary vaccination. We quantified the effects of individual characteristics on parameters describing the vaccine-induced antibody boost and the decay rate of short- and long-lived antibody-producing cells, which govern the amplitude and duration of the antibody response. The model accurately describes individual antibody trajectories in the training data set. While the half-life of the overall response is similar across the full study population, we observe differences in amplitude and the duration of protection.

Many of the factors associated here with a lower vaccine-induced antibody boost and shorter half-life of APCs, yielding lower antibody levels, are known to impair the humoral immune response to vaccination and increase the risk of severe acute COVID-19 [11,12,18]. Older age is associated with a lower antibody response [19,20]. In our study, this is captured in a reduction in antibody boost, especially following the first vaccine dose. This finding is in agreement with a decreased likelihood of seropositivity in individuals 60 years of age and older before receiving the second dose of the BNT162b2 COVID-19 vaccine [21]. Moreover, the risk of severe disease increases exponentially with age [22]. Consistent with this relationship, we observe a pronounced decrease in antibody levels and consequently a shorter duration of protection for older age groups, caused by the lower antibody boost in combination with a shorter modeled half-life of short-lived APCs. Similar to other studies, we observe a stronger antibody response in female compared to male study participants [23], driven by a higher antibody boost after both vaccine doses. The modeled half-life of short-lived APCs increases with BMI. However, we do not detect significant differences in amplitude or duration of the resulting antibody response for different BMI categories. Although obesity has been linked to a higher rate of hospitalization and death from COVID-19 [24], IgG antibody levels were shown to be similar between individuals with severe obesity and a normal BMI. Instead, obesity was associated with a lower neutralizing capacity of these antibodies [25].

A lower antibody response is further associated with autoimmune disease and diabetes [11]. For both comorbidities, the duration of protection is reduced and the proportion of individuals that never reach protective antibody levels following the primary vaccination series is elevated. Finally, our results capture the impaired antibody response due to immunosuppression [11,26]. A significant reduction in antibody boosting following vaccination and the half-life of short-lived APCs leads to a drastic reduction in maximum IgG levels and a high proportion of unprotected individuals.

Next, we applied the model to participants in the test data set that was not used for model inference. It accurately predicts individual IgG antibody trajectories after updating the model based on a single serological sample to mimic limited access to serology. The highest prediction accuracy for the full antibody trajectory is achieved when testing is performed during antibody waning in month three following vaccination or later. Forward predictions perform well for all sampling times and the variability in prediction accuracy across the study population decreases for later sampling. Consequently, we are also able to predict the duration of protection of individuals who display protective antibody levels at the time of testing, suggesting that serological testing during month two following vaccination is most beneficial, when the majority of individuals display protective antibody levels and prediction accuracy is high. In contrast to previous studies, where antibody levels are projected forward following a longitudinal serology period used for model calibration [14,27], these individual-level predictions rely on minimal data. While they give insight into an individual's infection risk, this approach can also be leveraged on the population level to assess the duration of protection against infection across the full or different subpopulations. It could thus be used to inform public health decisions on booster vaccination, especially by supporting the design of prioritization strategies or the determination of booster frequency for highly vulnerable groups that remain unprotected or at high risk for infection following vaccination.

Higher antibody levels are generally associated with a lower risk of infection with COVID-19 [28]. In this study, we used an antibody threshold of 500 BAU/mL to define protection. However, we did not consider that infection risk follows a continuous dose-response relationship and is further influenced by other factors like age. Moreover, protective antibody thresholds vary for different variants of concern [29]. With the emergence of immune-escaping variants, as we have seen during the spread of Omicron, higher antibody levels may be required to protect against infection. To adapt our analysis and evaluate the duration of protection against different variants, variant-specific antibody thresholds could be utilized. We did not include this here, since antibody levels after two vaccine doses are typically not high enough to protect against later variants and future studies will require careful assessment of model performance when applying different thresholds. Alternatively, we could extend our model to link antibody kinetics and neutralizing capacity, for example by assuming a dose- and variant-dependent proportional relationship between antibody levels and neutralization [27]. In this case, the duration of protection could be inferred directly from the predicted neutralizing capacity based on a common neutralization threshold.

There are several limitations to this study. We used data from the Sheba healthcare worker cohort study, which consists of adults between 18 and 82 years of age. While a wide age range is covered and common comorbidities are represented, the proportion of older individuals and individuals with comorbidities in the cohort is lower compared to the general population. As a result, some combinations of comorbidities only occur once in the whole data set, making it difficult to extract systematic differences in the antibody response and potentially leading to lower model performance for those individuals. In addition, study participants all received the vaccine at the same time, with similar timing between doses and no prior COVID-19 infection, warranting care when transferring our results to a general, more

heterogeneous population. After administration of the second vaccine dose, measurements partially exceeded the antibody assay's dynamic range. The model allowed us to infer peak antibody levels. However, censoring led to increased uncertainty in antibody predictions and model parameters, and to correlations between parameters describing the antibody boost after receipt of the second dose and acute waning.

Furthermore, this study is limited to the humoral immune response following the primary vaccination series against SARS-CoV-2. To predict antibody kinetics and duration of protection at present, boosting through both repeated vaccination and infection would need to be captured by the model. It was shown that the timing and number of booster vaccinations affect antibody kinetics and infection risk [17,30], and that hybrid immunity from vaccination and previous infection yields a higher antibody boost and provides improved protection against symptomatic infection [31]. Additionally, our analysis is limited to binding antibodies. However, it was shown that the correlation between binding and neutralizing antibodies has decreased with the changing variants [32], impeding the use of binding IgG antibody levels as a correlate of protection. Consequently, timing, number and order of boosting events would need to be considered as additional model factors modulating the anti-SARS-CoV-2 antibody response, including model calibration on both binding and neutralizing antibody data.

Binding antibody levels play a critical role in monitoring the infection risk for SARS-CoV-2. However, this is challenged by the waning of the antibody response and high variability between individuals that may be difficult to capture without continuous serosurveillance. In this study, we demonstrated how model predictions of an individual's antibody response to vaccination could be used to predict the duration of protection when serological data is limited. While we focused on primary vaccination, future work taking into account repeated vaccination, infection history and neutralization may benefit from the approach presented here. The approach further provides a platform for future pandemics, and could be applied as a tool to estimate population- and individual-level infection risk over time, identify vulnerable populations with an impaired immune response and support decision-making for vaccination strategies.

Methods

Data

We used data from a prospective longitudinal cohort study conducted in 4 868 healthcare workers at Sheba Medical Center, Israel [15]. Serum samples were collected before participants received the first dose of the BNT162b2 COVID-19 vaccine in December 2020. Administration of the first vaccine dose was followed by weekly serological testing for five weeks. The second dose was administered during week three in January 2021. Afterwards, serum samples were collected monthly for six months. Additionally, participating healthcare workers completed a questionnaire to collect information on demographics and comorbidities.

To be included in this study, healthcare workers had to have a negative anti-SARS-CoV-2 IgG assay when baseline serology was performed before receipt of the first dose. A positive SARS-CoV-2 PCR test or a positive anti-SARS-CoV-2 IgG serology test before vaccination led to exclusion from the study.

Samples of individuals with COVID-19 infection after vaccination were included up to the positive test and post-infection measurements were excluded. Infections were detected by PCR, which was readily available to all healthcare workers who had a possible or confirmed exposure to a SARS-CoV-2 infected person, and/or any COVID-19 associated symptoms (fever, myalgia, severe fatigue, change in smell or tase, cough, rhinorrhea, sore throat). To

identify potential exposures both at work and at home, a thorough investigation was conducted following identification of any new cases within the hospital. Additionally, healthcare workers were required to complete a daily questionnaire to report any symptoms in themselves or their household members.

We removed all participants with missing information on demographics or comorbidities from our analysis. Moreover, serum samples were not available for each individual at every time point. We excluded participants with less than two serological samples. Finally, we split the study population into a training and test data set for model calibration and prediction of antibody levels, respectively (S1 Appendix, Section S1).

Immunoassay. IgG levels against the receptor-binding domain (RBD) of the SARS-CoV-2 spike protein were measured using the Access SARS-CoV-2 RBD IgG assay (Beckman-Coulter, CA, U.S.A.). Seropositivity was defined by an IgG sample-to-cutoff (s/co) ratio greater than 0.62 [33]. In addition, peak IgG levels fall outside the assay's linear range, which can be observed in the clustering of data points around a maximum antibody level shortly after vaccination. Hence, we determined the upper limit of quantification (26.4 s/co) from serum samples collected in the month following administration of the second vaccine dose (days 25–38). During this period, the majority of measurements fall outside the assay's dynamic range, and we used the median minus one standard deviation to define the quantification limit.

Model of antibody kinetics

We describe antibody kinetics $A(t)$ following vaccination using a mathematical model that captures the generation of antibodies by short- and long-lived APCs (P_s and P_l), giving rise to an antibody response with a bi-phasic waning phase [13]. The model is defined as

$$\frac{dP_s(t)}{dt} = \rho\beta - c_s P_s(t) \tag{1}$$

$$\frac{dP_l(t)}{dt} = (1-\rho)\beta - c_l P_l(t) \tag{2}$$

$$\frac{dA(t)}{dt} = gP_s(t) + gP_l(t) - rA(t). \tag{3}$$

Plasma cells are produced at rate β. A proportion ρ of APCs are short-lived with decay rate c_s, while a proportion $(1-\rho)$ are long-lived with decay rate c_l. Antibodies are produced at rate g, and waning is described by the rate parameter r. This set of equations can be solved analytically for antibody concentration:

$$A(t) = A_0 + \sum_{j=1}^{b} gB_j \left[\rho \cdot \frac{e^{-c_s \cdot \Delta t_j} - e^{-r \cdot \Delta t_j}}{r - c_s} + (1-\rho) \cdot \frac{e^{-c_l \cdot \Delta t_j} - e^{-r \cdot \Delta t_j}}{r - c_l} \right] \tag{4}$$

$$\text{with} \quad \Delta t_j = \max(0, t - t_j - \delta_j) \tag{5}$$

and initial antibody concentration A_0. We allow for multiple boosting events j at times t_j due to repeated vaccination, and incorporate a delay δ in the humoral response after exposure [14]. Each event is characterized by the antibody boost gB, representing the overall antibody production by APCs, as the number of APCs, B, and rate g are not identifiable independently.

We estimated model parameters on longitudinal IgG measurements from study participants in the training data set. We defined parameters using mixed-effects models to account

for variation in antibody response between individuals, taking into consideration age, sex, BMI and coexisting conditions. The model was then fitted in a Bayesian hierarchical framework. More details on the statistical model and inference are provided in the Supplementary Material (S1 Appendix, Section S2).

Statistical analysis

We first evaluated the individual-level anti-SARS-CoV-2 antibody response based on the inferred antibody trajectories. We quantified the maximum IgG antibody level and examined the effects of demographic covariates and comorbidities in a multivariable linear regression. We analyzed IgG levels on the logarithmic scale and included age group (< 30, 30–45, 45–60 and ≥ 60 years), gender, BMI group (≤ 25, 25–30, $\geq 30\,kg/m^2$) and comorbidities as fixed effects. The results are expressed as the ratio of means between the examined factors and their reference levels. Similarly, we extracted and analyzed the duration of protection against infection provided by the initial vaccination series, where we defined the duration of protection as the time it takes for IgG levels to fall below a threshold previously determined to be protective against the delta variant [16].

Next, we applied the model to study participants in the test data set. To evaluate its prediction accuracy in the case of limited availability of serological data, we provided one measurement per individual to update the model and predict IgG antibody trajectories (S1 Appendix, Section S3). We then evaluated the overall accuracy of the model prediction and the accuracy of forward predictions in monthly increments using the root mean squared log error (RMSLE). Furthermore, we predicted the duration of protection for each individual that showed protective antibody levels at the time of serological testing and validated the predictions against the duration of protection inferred from the available longitudinal IgG measurements (S1 Appendix, Section S4).

Supporting information

S1 Appendix. Supplementary methods with details on data, model fitting and prediction.
(PDF)

S1 Fig. Parameter estimates and residuals. (**a**) Prior (blue) and posterior (purple) distributions of the estimated population-level parameters. (**b**) Estimated half-life of antibodies, and short- and long-lived antibody-producing cells (APCs) determined from the corresponding waning rates r, c_s and c_l. (**c**) Residuals over time and comparison of observed and estimated IgG levels. Grey points indicate measurements above the antibody assay's limit of quantification. (c) 95% interval estimates of the random effect parameters.
(TIF)

S2 Fig. Observed vs predicted antibody levels by sample time between M1 and M6 (columns) used to update the random effect parameters of the model for individuals in the test data set, and time of observation (rows). The provided data points are shown in blue, the remaining data points (black) are unknown to the model. Lighter shades indicate observations above the limit of quantification.
(TIF)

S3 Fig. Prediction of antibody levels without model adjustment. (a) Predicted IgG antibody trajectory (yellow) for one example individual from the test data set without model adjustment. The solid line represents the geometric mean prediction, the shaded area indicates the 90% posterior predictive interval. (b) Residuals and the RMSLE for antibody levels after receipt of the second vaccine dose (median, IQR) are shown for the full test population.

(c) Observed vs predicted antibody levels by time of observation between M1 and M6, where geometric mean predictions display lower inter-individual variability than the observed data. Lighter shades are used for measurements above the limit of quantification.
(TIF)

S1 Table. Pearson correlation coefficients between the estimated parameters based on posterior samples. Correlation coefficients are displayed for positive and negative correlations stronger than +0.50 and –0.50, respectively.
(XLSX)

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References

1. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med. 2020;383(27):2603–15. https://doi.org/10.1056/NEJMoa2034577 PMID: 33301246
2. Thomas SJ, Moreira ED Jr, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine through 6 Months. N Engl J Med. 2021;385(19):1761–73. https://doi.org/10.1056/NEJMoa2110345 PMID: 34525277

3. Pritchard E, Matthews PC, Stoesser N, Eyre DW, Gethings O, Vihta K-D, et al. Impact of vaccination on new SARS-CoV-2 infections in the United Kingdom. Nat Med. 2021;27(8):1370–8. https://doi.org/10.1038/s41591-021-01410-w PMID: 34108716
4. Harris RJ, Hall JA, Zaidi A, Andrews NJ, Dunbar JK, Dabrera G. Effect of vaccination on household transmission of SARS-CoV-2 in England. N Engl J Med. 2021;385(8):759–60. https://doi.org/10.1056/NEJMc2107717 PMID: 34161702
5. Goldberg Y, Mandel M, Bar-On YM, Bodenheimer O, Freedman L, Haas EJ, et al. Waning immunity after the BNT162b2 vaccine in Israel. N Engl J Med. 2021;385(24):e85. https://doi.org/10.1056/NEJMoa2114228 PMID: 34706170
6. Bergwerk M, Gonen T, Lustig Y, Amit S, Lipsitch M, Cohen C, et al. Covid-19 breakthrough infections in vaccinated health care workers. N Engl J Med. 2021;385(16):1474–84. https://doi.org/10.1056/NEJMoa2109072 PMID: 34320281
7. Khoury DS, Cromer D, Reynaldi A, Schlub TE, Wheatley AK, Juno JA, et al. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. Nat Med. 2021;27(7):1205–11. https://doi.org/10.1038/s41591-021-01377-8 PMID: 34002089
8. Asamoah-Boaheng M, Goldfarb DM, Karim ME, OBrien SF, Wall N, Drews SJ, et al. The relationship between anti-spike SARS-CoV-2 antibody levels and risk of breakthrough COVID-19 among fully vaccinated adults. J Infect Dis. 2023;227(3):339–43. https://doi.org/10.1093/infdis/jiac403 PMID: 36197948
9. Pelleau S, Woudenberg T, Rosado J, Donnadieu F, Garcia L, Obadia T, et al. Kinetics of the severe acute respiratory syndrome coronavirus 2 antibody response and serological estimation of time since infection. J Infect Dis. 2021;224(9):1489–99. https://doi.org/10.1093/infdis/jiab375 PMID: 34282461
10. Slifka MK, Antia R, Whitmire JK, Ahmed R. Humoral immunity due to long-lived plasma cells. Immunity. 1998;8(3):363–72. https://doi.org/10.1016/s1074-7613(00)80541-5 PMID: 9529153
11. Shrotri M, Fragaszy E, Nguyen V, Navaratnam AMD, Geismar C, Beale S, et al. Spike-antibody responses to COVID-19 vaccination by demographic and clinical factors in a prospective community cohort study. Nat Commun. 2022;13(1):5780. https://doi.org/10.1038/s41467-022-33550-z PMID: 36184633
12. Kim JS, Sun Y, Balte P, Cushman M, Boyle R, Tracy RP, et al. Demographic and clinical factors associated with SARS-CoV-2 spike 1 antibody response among vaccinated US adults: the C4R study. Nat Commun. 2024;15(1):1492. https://doi.org/10.1038/s41467-024-45468-9 PMID: 38374032
13. White MT, Griffin JT, Akpogheneta O, Conway DJ, Koram KA, Riley EM, et al. Dynamics of the antibody response to Plasmodium falciparum infection in African children. J Infect Dis. 2014;210(7):1115–22. https://doi.org/10.1093/infdis/jiu219 PMID: 24719471
14. Perez-Saez J, Zaballa M-E, Lamour J, Yerly S, Dubos R, Courvoisier DS, et al. Long term anti-SARS-CoV-2 antibody kinetics and correlate of protection against Omicron BA.1/BA.2 infection. Nat Commun. 2023;14(1):3032. https://doi.org/10.1038/s41467-023-38744-7 PMID: 37230973
15. Levin EG, Lustig Y, Cohen C, Fluss R, Indenbaum V, Amit S, et al. Waning immune humoral response to BNT162b2 Covid-19 vaccine over 6 months. N Engl J Med. 2021;385(24):e84. https://doi.org/10.1056/NEJMoa2114583 PMID: 34614326
16. Regev-Yochay G, Lustig Y, Joseph G, Gilboa M, Barda N, Gens I, et al. Correlates of protection against COVID-19 infection and intensity of symptomatic disease in vaccinated individuals exposed to SARS-CoV-2 in households in Israel (ICoFS): a prospective cohort study. Lancet Microbe. 2023;4(5):e309–18. https://doi.org/10.1016/S2666-5247(23)00012-5 PMID: 36963419
17. Lustig Y, Gonen T, Meltzer L, Gilboa M, Indenbaum V, Cohen C, et al. Superior immunogenicity and effectiveness of the third compared to the second BNT162b2 vaccine dose. Nat Immunol. 2022;23(6):940–6. https://doi.org/10.1038/s41590-022-01212-3 PMID: 35534723
18. Lustig Y, Sapir E, Regev-Yochay G, Cohen C, Fluss R, Olmer L, et al. BNT162b2 COVID-19 vaccine and correlates of humoral immune responses and dynamics: a prospective, single-centre, longitudinal cohort study in health-care workers. Lancet Respir Med. 2021;9(9):999–1009. https://doi.org/10.1016/S2213-2600(21)00220-4 PMID: 34224675
19. Collier DA, Ferreira IATM, Kotagiri P, Datir RP, Lim EY, Touizer E, et al. Age-related immune response heterogeneity to SARS-CoV-2 vaccine BNT162b2. Nature. 2021;596(7872):417–22. https://doi.org/10.1038/s41586-021-03739-1 PMID: 34192737
20. Khoury J, Najjar-Debbiny R, Hanna A, Jabbour A, Abu Ahmad Y, Saffuri A, et al. COVID-19 vaccine—long term immune decline and breakthrough infections. Vaccine. 2021;39(48):6984–9. https://doi.org/10.1016/j.vaccine.2021.10.038 PMID: 34763949

21. Shachor-Meyouhas Y, Hussein K, Szwarcwort-Cohen M, Weissman A, Mekel M, Dabaja-Younis H, et al. Single BNT162b2 vaccine dose produces seroconversion in under 60 s cohort. Vaccine. 2021;39(47):6902–6. doi:10.1016/j.vaccine.2021.10.016
22. Herrera-Esposito D, de Los Campos G. Age-specific rate of severe and critical SARS-CoV-2 infections estimated with multi-country seroprevalence studies. BMC Infect Dis. 2022;22(1):311. https://doi.org/10.1186/s12879-022-07262-0 PMID: 35351016
23. Demonbreun AR, Sancilio A, Velez ME, Ryan DT, Pesce L, Saber R, et al. COVID-19 mRNA vaccination generates greater immunoglobulin G levels in women compared to men. J Infect Dis. 2021;224(5):793–7. https://doi.org/10.1093/infdis/jiab314 PMID: 34117873
24. Gao M, Piernas C, Astbury NM, Hippisley-Cox J, O'Rahilly S, Aveyard P, et al. Associations between body-mass index and COVID-19 severity in 6·9 million people in England: a prospective, community-based, cohort study. Lancet Diabetes Endocrinol. 2021;9(6):350–9. https://doi.org/10.1016/S2213-8587(21)00089-9 PMID: 33932335
25. van der Klaauw AA, Horner EC, Pereyra-Gerber P, Agrawal U, Foster WS, Spencer S, et al. Accelerated waning of the humoral response to COVID-19 vaccines in obesity. Nat Med. 2023;29(5):1146–54. https://doi.org/10.1038/s41591-023-02343-2 PMID: 37169862
26. Prendecki M, Clarke C, Edwards H, McIntyre S, Mortimer P, Gleeson S, et al. Humoral and T-cell responses to SARS-CoV-2 vaccination in patients receiving immunosuppression. Ann Rheum Dis. 2021;80(10):1322–9. https://doi.org/10.1136/annrheumdis-2021-220626 PMID: 34362747
27. Clairon Q, Prague M, Planas D, Bruel T, Hocqueloux L, Prazuck T, et al. Modeling the kinetics of the neutralizing antibody response against SARS-CoV-2 variants after several administrations of Bnt162b2. PLoS Comput Biol. 2023;19(8):e1011282. https://doi.org/10.1371/journal.pcbi.1011282 PMID: 37549192
28. Martín Pérez C, Aguilar R, Jiménez A, Salmerón G, Canyelles M, Rubio R, et al. Correlates of protection and determinants of SARS-CoV-2 breakthrough infections 1 year after third dose vaccination. BMC Med. 2024;22(1):103. doi:10.1186/s12916-024-03304-3
29. Kenny G, O'Reilly S, Wrigley Kelly N, Negi R, Gaillard C, Alalwan D, et al. Distinct receptor binding domain IgG thresholds predict protective host immunity across SARS-CoV-2 variants and time. Nat Commun. 2023;14(1):7015. https://doi.org/10.1038/s41467-023-42717-1 PMID: 37919289
30. Matsuura T, Fukushima W, Nakagama Y, Kido Y, Kase T, Kondo K, et al. Factors impacting antibody kinetics, including fever and vaccination intervals, in SARS-CoV-2-naïve adults receiving the first four mRNA COVID-19 vaccine doses. Sci Rep. 2024;14(1):7217. https://doi.org/10.1038/s41598-024-57931-0 PMID: 38538722
31. Epsi NJ, Richard SA, Lindholm DA, Mende K, Ganesan A, Huprikar N, et al. Understanding "hybrid immunity": comparison and predictors of humoral immune responses to severe acute respiratory syndrome coronavirus 2 Iinfection (SARS-CoV-2) and coronavirus disease 2019 (COVID-19) vaccines. Clin Infect Dis. 2023;76(3):e439–49. https://doi.org/10.1093/cid/ciac392 PMID: 35608504
32. Favresse J, Gillot C, Bayart J-L, David C, Simon G, Wauthier L, et al. Vaccine-induced binding and neutralizing antibodies against Omicron 6 months after a homologous BNT162b2 booster. J Med Virol. 2023;95(1):e28164. https://doi.org/10.1002/jmv.28164 PMID: 36131356
33. Oved K, Olmer L, Shemer-Avni Y, Wolf T, Supino-Rosin L, Prajgrod G, et al. Multi-center nationwide comparison of seven serology assays reveals a SARS-CoV-2 non-responding seronegative subpopulation. EClinicalMedicine. 2020;29:100651. https://doi.org/10.1016/j.eclinm.2020.100651 PMID: 33235985