Prior infection and age impacts antibody persistence after SARS-CoV-2 mRNA vaccine

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Abstract

Determining the duration of immunity to SARS-CoV-2 vaccines is critical for informing the timing of booster immunization. Many host factors could influence both the magnitude and persistence of the antibody response. Here, we showed that SARS-CoV-2 infection before vaccination and age affected the decay of antibody responses to the SARS-CoV-2 mRNA vaccine.

Introduction

SARS-CoV-2 mRNA vaccines have been shown to be effective at preventing severe coronavirus disease 2019 (Covid-19) [1, 2]. The durability of vaccine-mediated protection or antibody immunity is not known, but antibody levels could be detected for the Moderna mRNA 1273 vaccine through six months [3]. Recent studies have demonstrated that individuals with prior SARS-CoV-2 infection had increased levels of SARS-CoV-2 spike protein binding and neutralizing antibodies after vaccination compared with individuals with no previous infection [4-6]. Here, we determined antibody levels soon after SARS-CoV-2 vaccination and over 7 months after vaccination to identify factors that influence antibody decay rates.

Methods

Antibody levels were determined after two-dose vaccination with the Pfizer BNT162b2 SARS-CoV-2 mRNA vaccine in healthcare workers with laboratory confirmed SARS-CoV-2 infection (by PCR test) 30-60 days prior to vaccination (Recent history of infection; n=36), or workers without history of infection (No history of infection; n=152; **Table S1**) [4, 7]. At baseline, serological testing was performed against the SARS-CoV-2 nucleocapsid protein to confirm history of infection and to identify potentially asymptomatic seropositive individuals as previously described [4, 7]. We collected peripheral blood at baseline (week 0), three weeks after the first dose (week 3), four weeks after the second dose (week 7). In addition, 110 of the 188 individuals (Recent history of infection, n=25; No history of infection; n=85) had blood collected later at weeks 16, 24 or 28. The biospecimens from vaccine recipients were obtained at Children's Mercy Kansas City and their use was reviewed and approved by the Children's Mercy institutional review board. Immunoglobulin (IgG) titers against SARS-CoV-2 spike proteins S1, S2 and receptor-binding domain (RBD) were determined from plasma using a multiplex bead-binding assay (Milliplex SARS-CoV-2 Antigen Panel 1 IgG, Millipore) [4, 7, 8]. As a proxy for measuring virus-neutralizing antibodies, we used an *in vitro* assay that allows indirect detection of potential SARS-CoV-2-neutralizing antibody through

determination of antibody blocking of the SARS-CoV-2 RBD binding to the host receptor angiotensin-converting enzyme 2 (ACE2) (SARS-CoV-2 Surrogate Virus Neutralization test kit, Genscript)[4, 7-9]. Antibody half-life was calculated using an exponential decay model computed using the lme4 package in R, which assumes a steady decay rate over time [3] (**Supplemental Methods**).

Results

Individuals with recent SARS-CoV-2 infection before vaccination had significantly higher binding antibody levels to the SARS-CoV-2 spike S1, S2 and RBD at baseline and after primary immunization (week 3) compared to individuals with no history of infection (**Figure 1A**). After the second dose of the vaccine the levels were still significantly different for S1, S2 but not RBD between the groups. However, the magnitude of difference between the two groups at week 7 was small, indicating that a second dose was indeed necessary in individuals without prior infection to achieve equivalent binding antibody levels as those with recent history of infection (**Figure 1A & Table S2**). At week 28, both groups had a decreased antibody levels to the S1, S2 and RBD, but levels remained significantly higher in those with a recent history of infection before vaccination compared to those without prior infection (**Figure 1A & Table S2**). Next, we measured viral-host receptor blocking as a proxy for neutralizing antibodies. We observed similar dynamics of potential neutralizing antibodies, with higher primary response titers at week 3 and higher levels at weeks 24 and 28 in individuals with recent infection before vaccination (**Figure 1B & Table S3**).

In individuals with no history of infection prior to vaccination, we did not find significant differences in antibody magnitude between males and females at any timepoint measured (**Figure 1C**). However, when we stratified individuals into two age groups, we found that individuals who were 18-49 years old had significantly higher blocking antibody titers at week 3 and week 28 compared to older individuals who were 50+ years old (**Figure 1D**).

Antibody half-life after vaccination was calculated using an exponential decay model and varied in duration depending on the binding or blocking assay used (**Figure 1E**). In all cases, we

observed longer antibody half-life in individuals with prior COVID-19 before vaccination compared with individuals with no infection history and in individuals aged 18-49 compared with older individuals (**Figure 1E, Table S4 & S5**). The lowest antibody half-life calculated was 24.76 weeks for individuals with a recent history of infection and 13.60 weeks for individuals with no history of infection using the binding measures over time to the S1 spike subunit (**Figure 1E, Table S4 & S5**).

Discussion

These data demonstrated that individuals that had SARS-CoV-2 infection prior to vaccination and younger aged individuals had significantly higher levels of antibodies after primary immunization with a SARS-CoV-2 mRNA vaccine and had significantly longer antibody half-life measured at 7 months after vaccination. The rate of antibody decay observed here are consistent with reports of other vaccine platforms and convalescent individuals after infection [3, 10]. In this study, individuals had recent infection within 60 days prior to the administration of vaccine. It will be critical to determine if individuals with SARS-CoV-2 infection beyond 60 days before vaccination also have higher antibody responses that are maintained longer. The serological assays used to measure binding antibody levels and surrogate neutralizing antibodies were performed using SARS-CoV-2 spike proteins with the original amino acid sequences and do not capture differences in antibody responses to any of the emerging viral variants. Future studies determining the cross-reactivity of antibody levels to viral variants will be required to understand the impact of potential antibody escape mutants. Antibody levels that correlate with vaccine efficacy or the breadth of response to viral variants have not been determined for SARS-CoV-2 infection or vaccines. These data suggest that the duration of protective antibody immunity may be influenced by prior infection history, age and other factors that may affect timing of additional immunization. Thus, ongoing studies monitoring immune responses will be required to determine optimal booster vaccine strategies.

NOTES

Conflict of Interest

The authors declare no conflicts of interest

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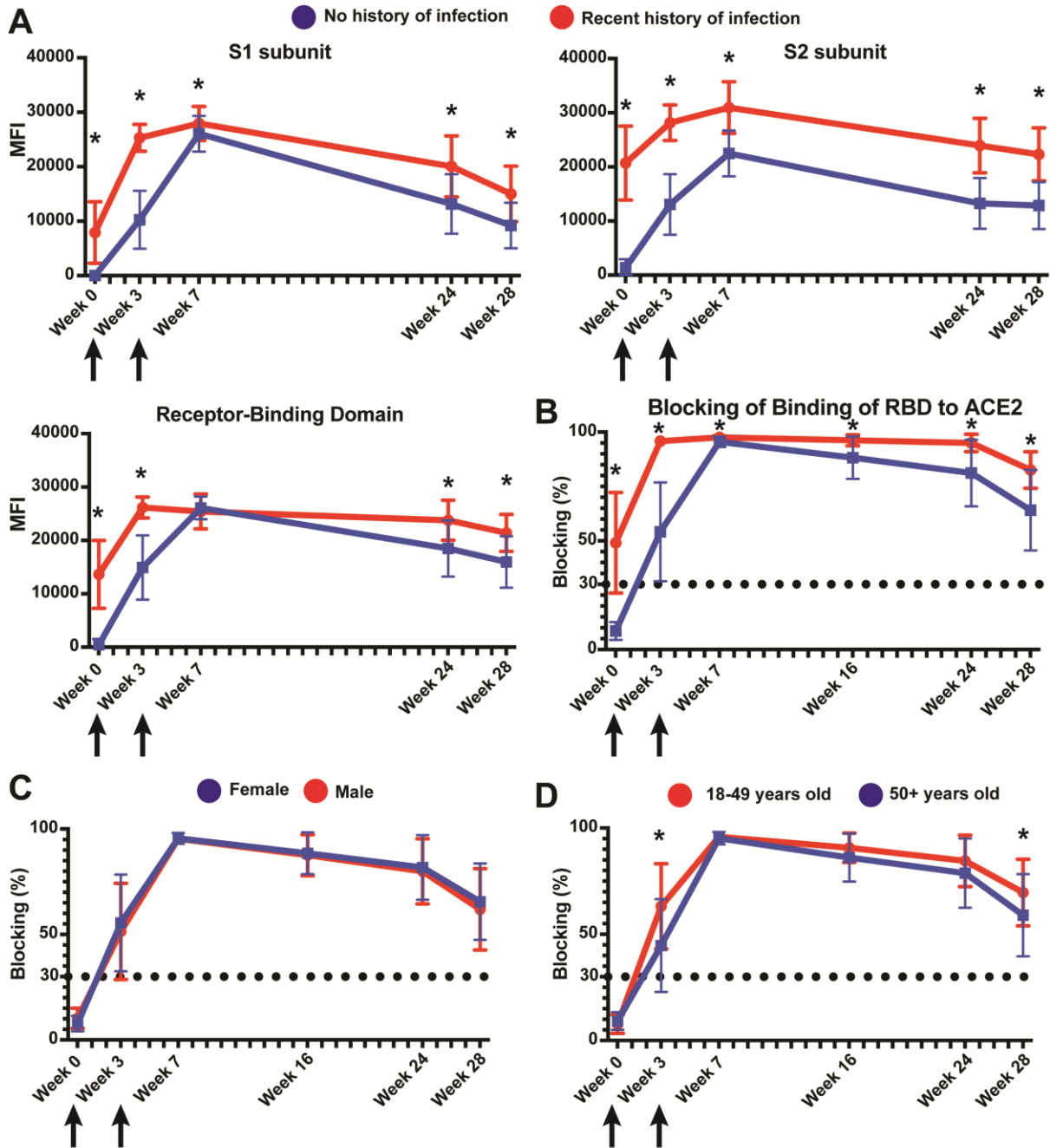
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Figure Legend

Figure 1. Antibody levels after SARS-CoV-2 mRNA vaccination. (A) Multiplex bead-based antibody binding assay that measures the IgG antibody response to SARS-CoV-2 spike subunit 1 (S1), spike subunit 2 (S2) and receptor-binding domain (RBD). Weeks of the study are along the x-axis starting with baseline at week 0. Immunization timing with COVID-19 mRNA vaccine indicated with arrows. Individual values of Median Fluorescent Intensity (MFI) are calculated; background subtraction has been used to remove nonspecific signal. Geometric mean titers are displayed for each group (recent history of SARS-CoV-2 infection before vaccination, red; no history of infection before vaccination, blue). Error bars represent 95% CI. * indicate P < 0.05 of a Wilcoxon-Mann-Whitney test corrected for multiple comparisons (FDR, Benjamini) when comparing groups at each timepoint. **(B-D)** Neutralization antibody proxy assay that determines the level of antibodies that block binding of the spike protein receptor-binding domain to the human host receptor angiotensin-converting enzyme 2 (ACE2), expressed as the percentage of binding that was blocked relative to a control with no plasma (representing maximum binding). The assay threshold for positivity was 30% indicating the presence of neutralizing antibodies. Weeks of the study are along the x-axis starting with baseline at week 0. Immunization timing with COVID-19 mRNA vaccine indicated with arrows. Geometric mean titers of the percent blocking are displayed for each group **(B)** Recent history of SARS-CoV-2 infection before vaccination, red; no history of infection before vaccination, blue **(C)** Individuals with no history of infection prior to vaccination stratified by male (red) and female (blue). **(D)** Individuals with no history of infection prior to vaccination stratified by age (18-49 years old, red; 50+ years old, blue). Error bars represent 95% CI. * indicate P < 0.05 of a Wilcoxon-Mann-Whitney test corrected for multiple comparisons (FDR, Benjamini) when comparing groups at each timepoint. **(E)** Rate of decay and half-life of antibodies from week 7 to week 28 for each group and assay using an exponential decay model. Antibody half-life displayed in weeks.

Figure 1

A

No history of infection ● **Recent history of infection** ●

S1 subunit

MFI — 40000, 30000, 20000, 10000, 0

Week 0, Week 3, Week 7, Week 24, Week 28

S2 subunit

MFI — 40000, 30000, 20000, 10000, 0

Week 0, Week 3, Week 7, Week 24, Week 28

Receptor-Binding Domain

MFI — 40000, 30000, 20000, 10000, 0

Week 0, Week 3, Week 7, Week 24, Week 28

B

Blocking of Binding of RBD to ACE2

Blocking (%) — 100, 50, 30, 0

Week 0, Week 3, Week 7, Week 16, Week 24, Week 28

C

Female ● **Male** ●

Blocking (%) — 100, 50, 30, 0

Week 0, Week 3, Week 7, Week 16, Week 24, Week 28

D

18-49 years old ● **50+ years old** ●

Blocking (%) — 100, 50, 30, 0

Week 0, Week 3, Week 7, Week 16, Week 24, Week 28

E

	Blocking antibodies		S1 antibodies		S2 antibodies		RBD antibodies		Blocking antibodies	
	Recent infection	No infection	Recent infection	No infection	Recent infection	No infection	Recent infection	No infection	18-49 years old	50+ years old
Decay Rate	-0.0022456	-0.0063529	-0.0126686	-0.0221372	-0.0068698	-0.013048	-0.0031034	-0.0105675	-0.0050276	-0.0077994
Half-life (weeks)	134.05	47.38	23.76	13.60	43.82	23.07	97.00	28.49	59.88	38.60