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Population-weighted seroprevalence from SARS-CoV-2 infection, vaccination, and hybrid immunity among U.S. blood donations from January-December 2021

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ABSTRACT

Background: Previous SARS-CoV-2 infection and coronavirus disease 2019 (COVID-19) vaccination, independently and combined ("hybrid immunity"), result in partial protection from subsequent infection and strong protection from severe disease. Proportions of the U.S. population that have been infected, vaccinated, or with hybrid immunity remain unclear, posing a challenge for assessing effective pandemic mitigation strategies.

Methods: In this serial cross-sectional study, nationwide blood donor specimens collected during January–December 2021 were tested for spike and nucleocapsid antibodies, and donor COVID-19 vaccination history of ≥1 dose was collected. Monthly seroprevalence induced from SARS-CoV-2 infection, COVID-19 vaccination, or both, were estimated. Estimates were weighted to account for demographic differences from the general population, and were compared temporally and by demographic factors.

Results: Overall, 1,123,855 blood samples were assayed. From January to December 2021, the weighted percentage of donations with seropositivity due to: vaccination without previous infection increased from 3.5% (95% CI, 3.4%-3.7%) to 64.0%, (95% CI, 63.5%-64.5%); previous infection without vaccination decreased from 15.6% (95% CI, 15.2%-16.0%) to 11.7% (95% CI, 11.4%-12.0%); hybrid immunity increased from 0.7% (95% CI, 0.6%-0.7%) to 18.9% (95% CI, 18.5%-19.3%); and from infection, vaccination, or both increased from 19.8% (95% CI (19.3-20.2) to 94.5% (95% CI, 93.5%-94.0% 0.1%). Infection- and vaccination-induced antibody responses varied significantly by age, race-ethnicity, and region, but not by gender.

Conclusions: Our results indicate substantial increases in population humoral immunity from SARS-CoV-2 infection, COVID-19 vaccination, and hybrid immunity during 2021. These findings are important to consider in future COVID-19 studies and long-term pandemic mitigation efforts.

Key Words: SARS-CoV-2, seroprevalence, antibodies, vaccination, immunity

Abbreviations:

American Red Cross (ARC)

antibodies for SARS-CoV-2 nucleocapsid antibodies (anti-N)

antibodies for SARS-CoV-2 spike antibodies (anti-S)

Centers for Disease Control and Prevention (CDC)

coronavirus disease 2019 (COVID-19)

donor history questionnaire (DHQ)

Food and Drug Administration (FDA)

immunoglobulin (Ig)

National Blood Donor Serosurveillance (NBDS)

nucleocapsid (NC)

severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

signal-to-cutoff ratio (S/CO)

spike (S)

BACKGROUND

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (COVID-19), has resulted in over 981,000 deaths and 80.1 million cases in the U.S. as of April 8, 2022 [1]. COVID-19 vaccinations [2], previous SARS-CoV-2 infections [3, 4], and especially hybrid immunity [5, 6] are protective against severe consequences of SARS-CoV-2 infection. Hybrid immunity has been defined as the immunological responses of individuals with histories of both previous SARS-CoV-2 infection and vaccination [5, 6]. Long-term public health prevention strategies remain a substantial challenge due to gaps including the accurate and timely determination of population immunity induced by SARS-CoV-2 infections and COVID-19 vaccinations.

There are logical reasons why population immunity against SARS-CoV-2 is difficult to assess. A sizeable proportion of SARS-CoV-2 infections are asymptomatic [7] or result in mild COVID-19 disease [8], which is less likely to be recognized [9]. Characterizing population immunity requires accounting for these un-diagnosed SARS-CoV-2 infections. This is difficult to accurately track with gold standard COVID-19 nucleic acid amplification tests [10] because their utility at the population level is constrained by narrow detection windows dependent on viral kinetics and clearance [11], high cost, and need for specialized laboratory facilities [10]. Many people may not seek diagnostic testing or only use at-home tests without reporting results. As a result, the estimated proportion of the population with infection-induced or hybrid immunity remains unclear. Moreover, national SARS-CoV-2 infection and vaccination data are often collected independently and are therefore difficult to combine into estimates for hybrid immunity.

Investigators have estimated seroprevalence via detection of SARS-CoV-2 spike (S) and nucleocapsid (N) protein antibodies [12-14]. Assays that can reliably detect and differentiate SARS-CoV-2 infection and vaccination-induced antibodies are optimal for serosurveillance [15]. Determining proportions of the population with antibodies from vaccination, infection, or both is needed to inform pandemic mitigation efforts.

Our study objective was to estimate national trends in the proportions of individuals with previous SARS-CoV-2 infection, COVID-19 vaccination, or both, in 2021, based on seroprevalence of SARS-CoV-2 antibodies and self-reported vaccination status among U.S. blood donors. We report population-weighted estimates temporally by calendar month and compare results by demographic factors.

METHODS

Settings and participants

The present analysis is part of a larger National Blood Donor Seroprevalence (NBDS) Study, which began in July 2020 and is funded by the Centers for Disease Control and Prevention (CDC) [12]. In the NBDS study, donor and donation data were collected in all 50 states, Washington, D.C., and Puerto Rico by 17 participating blood collection organizations, with results compiled in 66 study regions [12]. Random or convenience sampling was used to identify and test at least 2,000 blood specimens per month from every region in each blood collection organization's catchment area. When <2000 specimens were available, 100% were sampled. To facilitate comparisons by race and ethnicity, blood donor regions with higher proportions of racial and ethnic minorities were oversampled (4,000 blood samples/month). Detailed methods of this study have previously been published [12].

This analysis evaluated the subset of NBDS blood donors with vaccination history. Participants were individuals who donated blood at American Red Cross (ARC) and Vitalant, the two largest blood collection organizations in the U.S., representing 54 of 66 NBDS study regions. Inclusion criteria were having: 1) blood donation between January 1 and December 31, 2021; 2) residence in study regions; 3) satisfaction of U.S. Food and Drug Administration (FDA) regulations and each blood collection organization's donation requirements (e.g., age ≥ 16 years, >110 lbs., healthy including being afebrile); 4) measurement of SARS-CoV-2 antibodies; and 5) self-reported COVID-19 vaccination history. Excluded were: 1) persons making COVID-19 convalescent plasma donations; and 2) records missing demographic data.

Donor demographic and vaccination data

At each visit, donors were asked to provide demographic information (date of birth, gender, race and ethnicity, residential ZIP code) and completed a donor history questionnaire (DHQ) that included a question regarding having ever received a COVID-19 vaccination.

Laboratory assays for SARS-CoV-2 antibodies

All blood specimens were assayed for antibodies for SARS-CoV-2 spike glycoprotein (anti-S; VITROS chemiluminescent S1 total Ig assay; Ortho Clinical Diagnostics). Prior to August 31, 2021, only specimens that were anti-S seropositive were subsequently tested for antibody to SARS-CoV-2 N protein (anti-N; Roche Elecsys Total Ig Assay; Roche Diagnostics). From September 2021, donations were tested in parallel for anti-S and anti-N (VITROS chemiluminescent total Ig assays; Ortho Clinical Diagnostics); previous studies found that the impact of this algorithm would be minimal since 99% of specimens with anti-N antibodies have anti-S antibodies [16]. We previously validated these assays for sensitivity, specificity, and durability of detection of anti-S and anti-N antibodies following infection [16]. Testing of ARC and Vitalant donation specimens for the NBDS program was performed at five laboratories operated by Creative Testing Solutions. Seropositivity was defined as signal-to-cutoff ratio (S/CO) $\geq$1.0, per manufacturers' instructions.

Primary outcomes

We defined SARS-CoV-2 infection and COVID-19 vaccination status based on serologic assays for SARS-CoV-2 antibodies and self-reported COVID-19 vaccination history at each donation. SARS-CoV-2 infection was defined as seropositivity for anti-N or, in the absence of reported vaccination, for anti-S. Combined SARS-CoV-2 seropositivity was defined as having any of previous SARS-CoV-2 infection, COVID-19 vaccination, or both (the latter also called "hybrid immunity;" ***eTable 1***).

Statistical analyses

We used a complete-case analysis approach for observations without missing data (***Figure 1***). A small percentage (0.8%) of samples were excluded due to missing race or ethnicity information. Among a small number of observations with seropositivity for anti-S and missing values for anti-N (N=5,034; <0.5%),

we imputed anti-N seropositivity based on data from all participants with anti-N values and matching anti-S values (***eMethods***).

We used weights to adjust for demographic differences between blood donors in our study data and the population aged ≥ 16 years in blood donor catchment regions. All reported values are weighted unless stated otherwise. Details of the weighting methodology have been previously published [12] and are described in the ***eMethods.*** In brief, weights were calculated by calibrating (via raking and trimming) the final analytic subset to representative demographic data from the U.S. Census Bureau in blood donor catchment regions [17]. Specifically, the following variables and data from the 2014-2018 American Community Survey were utilized: age categories (16-24, 25-34, 35-44, 55-64, ≥65 years), biological sex, race and ethnicity (self-identified from 7 fixed categories), and geographic location [17]. Variance estimates (standard errors for confidence limits) were calculated using 50 replicate weights constructed by jackknife repeated replication, a resampling technique [18].

In each month's cross-sectional data, we generated population-weighted percentages and 95% CIs of seropositivity from previous SARS-CoV-2 infection and from COVID-19 vaccination (***eMethods***). We evaluated relative levels of antibody to S by calculating means (SDs) and medians (IQRs) of anti-S intensity ($\log_{10}$ S/CO) on the VITROS S1 Total Ig assay. For geographic comparisons, we combined donor ZIP codes into nine Census divisions (***eFigure 1***). Statistical analysis was conducted with SAS (version 9.4; SAS Institute; Cary, North Carolina, U.S.).

Comparisons between vaccination coverage estimates

We compared our estimated rate of vaccination in blood donors with the expected vaccination coverage derived from CDC data. We first identified 54 study regions across 31 states with available CDC vaccination data. To ensure that the same geographic areas were represented each month, sampled geographic regions from each blood collection organization were defined by ZIP codes where more than 90% of blood donors resided. Specimens from donors residing outside those ZIP codes were excluded (***eMethods***). From these aggregated ZIP codes, study regions were created based on state and metropolitan borders. CDC data specifically include daily numbers of people and percentages of adults

(aged ≥ 18 years of age) in each county who received ≥ one vaccine dose. Among study participants who donated in the study regions, we compared two versions of our weighted monthly vaccination estimates based on: 1) self-reported COVID-19 vaccination; and 2) self-reported COVID-19 vaccination with serologic confirmation (seropositivity for anti-S). Further details are described in the ***eMethods***.

Ethics

The study protocol was approved by the University of California, San Francisco, ARC, and Westat Institutional Review Boards. All donors provided voluntary, informed consent for use of their deidentified data and residual blood samples from routine blood donations for research. This study was deemed non-human subjects' research. This activity was reviewed by CDC and was conducted consistent with applicable federal law and CDC policy (e.g., 45 C.F.R. part 46; 21 C.F.R. part 56; 42 U.S.C. 241(d), 5 U.S.C. 552a, 44 U.S.C. 3501). We report study methodology according to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for cross-sectional studies [19].

RESULTS

This study included 1,123,855 blood donations collected from January 1 to December 31, 2021, across the U.S. (***eFigure 1, Table 1***). The number of donations included per month ranged between 92,096 and 97,170 (***eTable 2***). Overall, study donors had a mean age of 51.4 years; 51.2% were female, 87.9% were non-Hispanic White, 2.5% were non-Hispanic Black, and 5.6% were Hispanic, based on unweighted values (***Table 1)***. Demographic comparisons of study blood donors with the general population, in study regions and nationally, are in ***Table 1***; race-ethnicity differed between the study sample and national Census data.

From January to December 2021, the weighted monthly percentage of donations with seropositivity due to: (1) vaccination without previous infection increased from 3.5% (95% CI, 3.4%-3.7%) to 64.0%, (95% CI, 63.5%-64.5%), (2) previous infection without vaccination decreased from 15.6% (95% CI, 15.2%-16.0%) to 11.7% (95% CI, 11.4%-12.0%), and (3) hybrid immunity increased from 0.7% (95% CI, 0.6%-0.7%) to 18.9% (95% CI, 18.5%-19.3%; ***Figure 2A, eTable 2***). Combined seroprevalence from previous infection, vaccination, or both, increased from 19.8% to 94.5% (***eTable 2***).

By December, estimated population vaccination coverages were: 83.0% (95% CI, 82.6%-83.4%) from donor self-report, and 82.9% (95% CI, 82.5%-83.3%) from donor self-report with anti-S antibody confirmation (***Figure 2B***, ***eTable 2***). These estimates were similar to the CDC-data-derived estimate [20], which was 81.3% as of December 31, 2021. In January 2021, the vaccination coverage extrapolated from blood donors was higher than CDC vaccination estimates; differences declined during the last quarter of 2021. Among donations from donors who self-reported vaccination in the DHQ, 97.4% had anti-S antibody during 2021, and >99% had anti-S antibody between June and December 2021 (***eTable 2***).

Monthly estimates of the percentage of individuals with infection- and vaccination-induced antibody responses varied by age (***Figure 3***), race and ethnicity (***Figure 4***), and region (***Figure 5***), but not by gender (***eFigure 2)***. Estimated seroprevalence from vaccination was positively associated with age: the percentage among older individuals (aged ≥65 years) was highest during all months except January (***Figure 3, eTable 3***). In December, estimated seroprevalence from vaccination was 89.0% (95% CI, 88.4%-89.7%) among individuals ≥65 years, 85.6% (95% CI, 85.1%-86.1%) among individuals 50-64 years, 82.7% (95% CI, 82.0%-83.4%) among individuals 30-49 years, and 75.2% (95% CI, 74.1%-76.3%) among individuals 16-29 years. Estimated seroprevalence from previous infection was inversely associated with age group; across all timepoints, individuals between 16-29-years had the highest prevalence and those ≥65 years had the lowest prevalence. Estimated seroprevalence from hybrid immunity was similar among age groups from January to July, and inversely associated with age during the remaining months. By December, estimated seroprevalence from hybrid immunity was 24.0% (95% CI, 22.7%-25.2%) among individuals 16-29 years and 12.5% (95% CI, 11.8%-13.1%) among individuals ≥65 years.

In December, estimated seroprevalence from infection was 40.0% (95% CI, 38.0%-41.9%) among Hispanic people, 34.8% (95% CI, 33.0%-36.6%) among Black (non-Hispanic) people, 28.7% (95% CI, 28.3%-29.2% among White (non-Hispanic) people and 22.3% (95% CI, 20.0%-24.5%) among Asian people (***Figure 4; eTable 3***). Estimated seroprevalence from hybrid immunity was 26.5% (95% CI, 24.8%-28.3%) among Hispanic people, 20.7% (95% CI, 19.0%-22.6%) among Black (non-Hispanic)

people, 17.3% (95% CI, 16.9%-17.7%) among White (non-Hispanic) people, 16.3% (95% CI, 13.9%-19.2%) among people categorized as Other race and ethnicity, and 15.4% (95% CI, 13.5%-17.6%) among Asian people.

Comparing by Census divisions, estimated seroprevalence from vaccination was similar during the first quarter of 2021 (***Figure 5, eTable 3***). Estimated seroprevalence from infection was lower in the New England and Pacific Census divisions during most months, whereas seroprevalence from infection was highest in the East South Central, West South Central and Mountain divisions. For example, in the New England division estimated seroprevalence from infection increased from 9.9% (95% CI, 8.7%-11.3%) to 20.0% (95% CI, 18.7%-21.4%) over the year, whereas in the East South-Central Division seroprevalence increased from 22.7% (95% CI, 21.1%-24.3%) to 40.2% (95% CI, 38.6%-41.8%).

Mean log anti-S S/CO values were highest among donors with seropositivity from hybrid immunity, followed by that among those with vaccination (without previous infection), and lowest among those with previous infection but no vaccination (***Figure 6A***). These differences were significant throughout the year. There was a transient decline in anti-S antibody levels from August through November. Although the mean levels of anti-S were consistently highest among those with hybrid immunity compared to those with vaccination-induced or infection-induced immunity, there was substantial overlap in the distribution of antibody levels among these subgroups (***Figure 6B***).

DISCUSSION

Our findings demonstrate that U.S. population-weighted, estimated seroprevalence from SARS-CoV-2 infection, vaccination, or both, increased from 19.8% in January 2021 to 94.5% in December 2021. This study is the first to report national estimates of the proportion of the population with hybrid immunity, which reached 18.9% by December 2021.

We found the proportion of adult blood donors reporting at least 1 dose of vaccine was approximately 80% by December, similar to CDC vaccination-data-derived estimates. Infection-induced seroprevalence estimates derived from blood donors are similar to seroprevalence estimates among adults reported by a nationwide seroprevalence study using commercial laboratory remnants [1]. This suggests that although

blood donors differ from the general population, our donor-derived and weighted seroprevalence estimates might be representative of the adult U.S. population. From June through December 2021, >99% of donors with self-reported vaccination had anti-S antibodies. This suggests that nearly all healthy individuals who qualified as blood donors seroconverted after vaccination; this finding is consistent with findings from vaccine clinical trials and observational studies in immunocompetent populations [21, 22]. The proportions of infection-induced, vaccination-induced, and infection-and-vaccine-induced seroprevalence differed by age, racial-ethnic subgroup, and geographic region. These observations are consistent with prior studies demonstrating differential vaccination coverage and SARS-CoV-2 infections among demographic subgroups [23-27]. Because demographic subgroups with higher estimated vaccine-induced seroprevalence had lower estimated infection-induced seroprevalence, demographic differences in the combined seroprevalence from vaccination, infection, or both, were generally small. We note that some observed temporal patterns coincided with the delta variant surge and vaccination rollout in the U.S. For example, the proportion of younger unvaccinated individuals (16-29 years) with seropositivity from previous infection increased during the last quarter of 2021; incident infections from the delta variant are a likely explanation, as reported cases were higher among younger than older adults during the delta surge [1]. Increased proportions of infection among younger adults are potentially related to lower vaccination rates prior to the delta surge.

We estimated that nearly one in five individuals had hybrid immunity, based on vaccination history and serologic evidence of previous infection, by the end of 2021. People with hybrid immunity have been reported to possess more robust immune responses [28], and increased protection from infection and severe disease [29], compared to persons with either vaccination or previous infection alone [6, 30]. However, rapid waning of neutralizing antibody and IgG antibody to the S protein has been reported [31]. Studies in the U.S. and other countries demonstrate substantial numbers of infections in vaccinated persons, and of reinfections, associated with variants of concern, particularly omicron [32-39].

Given the high seroprevalence among NBDS donors and the limitations of the cross-sectional study design, monthly serosurveillance was discontinued in December 2021 after 18 months of data collection.

In the next study phase, we have established a longitudinal cohort study comprised of approximately 142,000 repeat blood donors in the ARC and Vitalant blood collection networks throughout the continental U.S. SARS-CoV-2 binding antibody assays, including anti-S (IgG; quantitative), anti-N (total Ig) and neutralizing antibody assays, will be performed on serially collected blood specimens donated between July 2020 and December 2022. Donor survey questionnaires will capture detailed histories of COVID-19 vaccination, diagnostic testing, and clinical outcomes. Key study objectives include determining: 1) stability and waning of anti-S, anti-N and neutralizing antibody among donors who were previously infected, vaccinated, or both, 2) rates of reinfection and of infections in vaccinated persons; and 3) vaccine effectiveness and serologic correlates of protection against omicron and future variants. This study has several limitations. First, seroprevalence among blood donors might not represent the seroprevalence in the general population. Second, vaccination history was self-reported at the time of each donation and did not include vaccination details (brands/types, number of doses, dates received). Third, given the monthly cross-sectional study design of the NBDS, we were unable to determine if those with hybrid immunity had been infected first and subsequently vaccinated, or vice versa, nor could we determine the precise timing of infection and vaccination. Fourth, anti-S reactive, anti-N nonreactive donors might have incorrectly reported no previous COVID-19 vaccination and have been misclassified as infected. Fifth, the antibody assays used in this study are authorized from the FDA for use as qualitative assays and quantitative results should be interpreted with caution. However, a strength of the current study is that the antibody assays used are optimal for serosurveillance because they maintain reactivity for more than a year following infection or vaccination, allowing ascertainment of cumulative infection or vaccination-induced humoral immune responses [16, 27].

From evaluation of over 1.1 million blood samples, our donor-derived and population-weighted estimates of seroprevalence demonstrate increases in population humoral immunity due to SARS-CoV-2 infection, COVID-19 vaccination, or both during 2021. Percentages of estimated seroprevalence differed by age, race-ethnicity, and geographic region. Seroprevalence studies in representative big datasets like this one, with additional details that can be stratified based on number of vaccination doses and timing of each

vaccine dose are important to consider in future COVID-19 studies and long-term pandemic mitigation efforts, particularly in the context of antibody waning, booster vaccination schedules, and emergent SARS-CoV-2 variants.

NOTES

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The present analysis is part of a larger National Blood Donor Seroprevalence (NBDS) Study, which began in July 2020. This analysis evaluated the subset of blood donors with vaccination history. Results of the larger study that did not incorporated vaccine history have been previously published, including in a manuscript for results through May 2021 (ref. 12 Jones JM, Stone M, Sulaeman H, et al. Estimated US Infection- and Vaccine-Induced SARS-CoV-2 Seroprevalence Based on Blood Donations, July 2020-May 2021. *JAMA* 2021; 326(14): 1400-9) and results through December 2021 on a CDC website (https://covid.cdc.gov/covid-data-tracker/#nationwide-blood-donor-seroprevalence).

The Nationwide Blood Donor Seroprevalence Study is the responsibility of the following persons:

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Disclaimer

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Conflict of interest

MPB reports being an employee of Vitalant Research Institute and receiving grant funding for their institution. EG reports research funding to their employer Vitalant Research Institute from Ortho Clinical Diagnostics. They also report the provision of reagents for other studies from Ortho Clinical Diagnostics and Roche.

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FIGURE LEGENDS

Figure 1: Flowchart of blood samples from American Red Cross and Vitalant donors

[a] Excluding blood samples from Chicago, Northern New Jersey, and Pittsburgh Vitalant sites due to no available self-reported vaccination history.
Abbreviations: severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

Figure 2: Previous SARS-CoV-2 infection was defined as seropositivity for anti-N or, in the absence of reported vaccination, for anti-S. Vaccination was defined at as self-report of ≥1 COVID-19 vaccine dose on the donor history questionnaire (eTable 1). Estimated vaccination coverage from CDC data was defined as ≥1 COVID-19 vaccine dose among residents aged ≥18 years in counties in the catchment area of the study (eFigure 1).

Abbreviations: American Red Cross (ARC), Centers for Disease Control and Prevention (CDC), coronavirus disease 2019 (COVID-19), donor history questionnaire (DHQ), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

Figure 3: Population-weighted percentages (95% CIs) of seropositivity by previous SARS-CoV-2 infection and COVID-19 vaccination status, stratified by age subgroups. Previous SARS-CoV-2 infection was defined as seropositivity for anti-N or, in the absence of reported vaccination, for anti-S. Vaccination was defined at as self-report of ≥1 COVID-19 vaccine dose on the donor history questionnaire (eTable 1).
Abbreviations: coronavirus disease 2019 (COVID-19), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

Figure 4: Population-weighted percentages (95% CIs) of seropositivity by previous SARS-CoV-2 infection and COVID-19 vaccination status, stratified by race and ethnicity. Previous SARS-CoV-2 infection was defined as seropositivity for anti-N or, in the absence of reported vaccination, for anti-S. Vaccination was defined at as self-report of ≥1 COVID-19 vaccine dose on the donor history questionnaire (eTable 1).
Abbreviations: coronavirus disease 2019 (COVID-19), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), non-Hispanic (NH).

Figure 5: Population-weighted percentages (95% CIs) of seropositivity by previous SARS-CoV-2 infection and COVID-19 vaccination status, stratified by geographic location. Previous SARS-CoV-2 infection was defined as seropositivity for anti-N or, in the absence of reported vaccination, for anti-S. Vaccination was defined at as self-report of ≥1 COVID-19 vaccine dose on the donor history questionnaire (eTable 1).
Abbreviations: coronavirus disease 2019 (COVID-19), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

Figure 6: Population-weighted mean and distribution of SARS-CoV-2 spike protein antibody (S/CO), stratified by month and previous SARS-CoV-2 infection and COVID-19 vaccination status). Previous SARS-CoV-2 infection was defined as seropositivity for anti-N or, in the absence of reported vaccination, for anti-S. Vaccination was defined as self-report of ≥1 COVID-19 vaccine dose on the donor history questionnaire (eTable 1). **Fig 5A**: Weighted, log-normalized mean and standard deviation values of anti-S antibodies (S/CO values) were reported among blood samples from donations in each calendar month of 2021, stratified by previous infection and vaccination status subgroups. **Fig 5B**: Weighted, log-normalized median and interquartile ranges (25^{th}, 75^{th} percentile) values of weighted anti-S S/CO values were reported, stratified by month, previous infection and vaccination subgroup status of blood donors.
Abbreviations: coronavirus disease 2019 (COVID-19), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), signal-to-cutoff ratio (S/CO), Centers for Disease Control and Prevention (CDC), spike protein (S)

Table 1: Demographic characteristics

January - December 2021	Selected sample with vaccination data (ARC and Vitalant)		U.S. Population aged ≥ 16 years, in ARC and Vitalant study regions		U.S. Population aged ≥ 16 years [a]	
	N	%	N	%	N	%
Total	1,123,855	100%	144,161,836	100%	260,534,061	100%
Male	548,541	49%	70,204,212	49%	126,998,469	49%
Female	575,314	51%	73,957,624	51%	133,535,592	51%
Age (years) [b]						
16 to 29	130,352	12%	34,882,830	24%	62,732,069	12%
30 to 49	327,868	29%	47,186,683	33%	84,217,499	29%
50 to 64	407,597	36%	35,244,590	24%	63,705,642	36%
65+	258,038	23%	26,847,733	19%	49,878,851	23%
Race and ethnicity						
White, non-Hispanic	987,660	88%	92,913,479	64%	164,254,508	63%
Black, non-Hispanic	28,066	2%	17,505,250	12%	30,855,020	12%
Hispanic	62,417	6%	21,213,139	15%	43,854,340	17%
Asian, non-Hispanic	27,332	2%	8,434,430	6%	14,295,323	5%
Other	18,380	2%	4,095,538	3%	7,274,870	3%
Census Division						
1 New England	113,637	10%	10,558,443	7%	12,163,848	5%
2 Middle Atlantic	78,115	7%	15,879,225	11%	33,526,678	13%
3 East North Central	111,607	10%	11,937,628	8%	37,478,378	14%
4 West North Central	121,484	11%	12,221,003	8%	16,752,533	6%
5 South Atlantic	188,133	17%	29,061,803	20%	51,532,352	20%
6 East South Central	84,581	8%	8,588,941	6%	15,109,636	6%
7 West South Central	41,437	4%	8,419,508	6%	30,499,604	12%
8 Mountain	260,402	23%	22,432,600	16%	18,707,146	7%
9 Pacific	124,459	11%	25,062,685	17%	41,984,697	16%

[a] Donations from Puerto Rico are included in the total but excluded from Census division strata since Puerto Rico is not included in any Census division.

Abbreviations: American Red Cross (ARC)

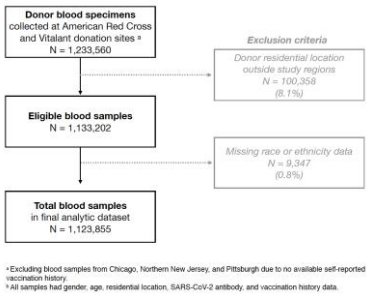

Figure 1
50x39 mm (.17 x DPI)

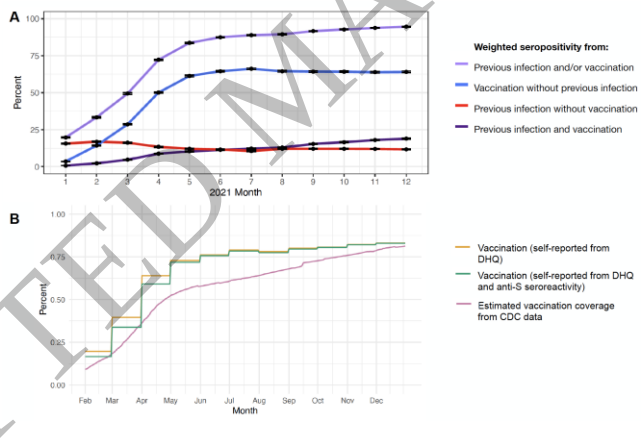

Figure 2
84x56 mm (.17 x DPI)

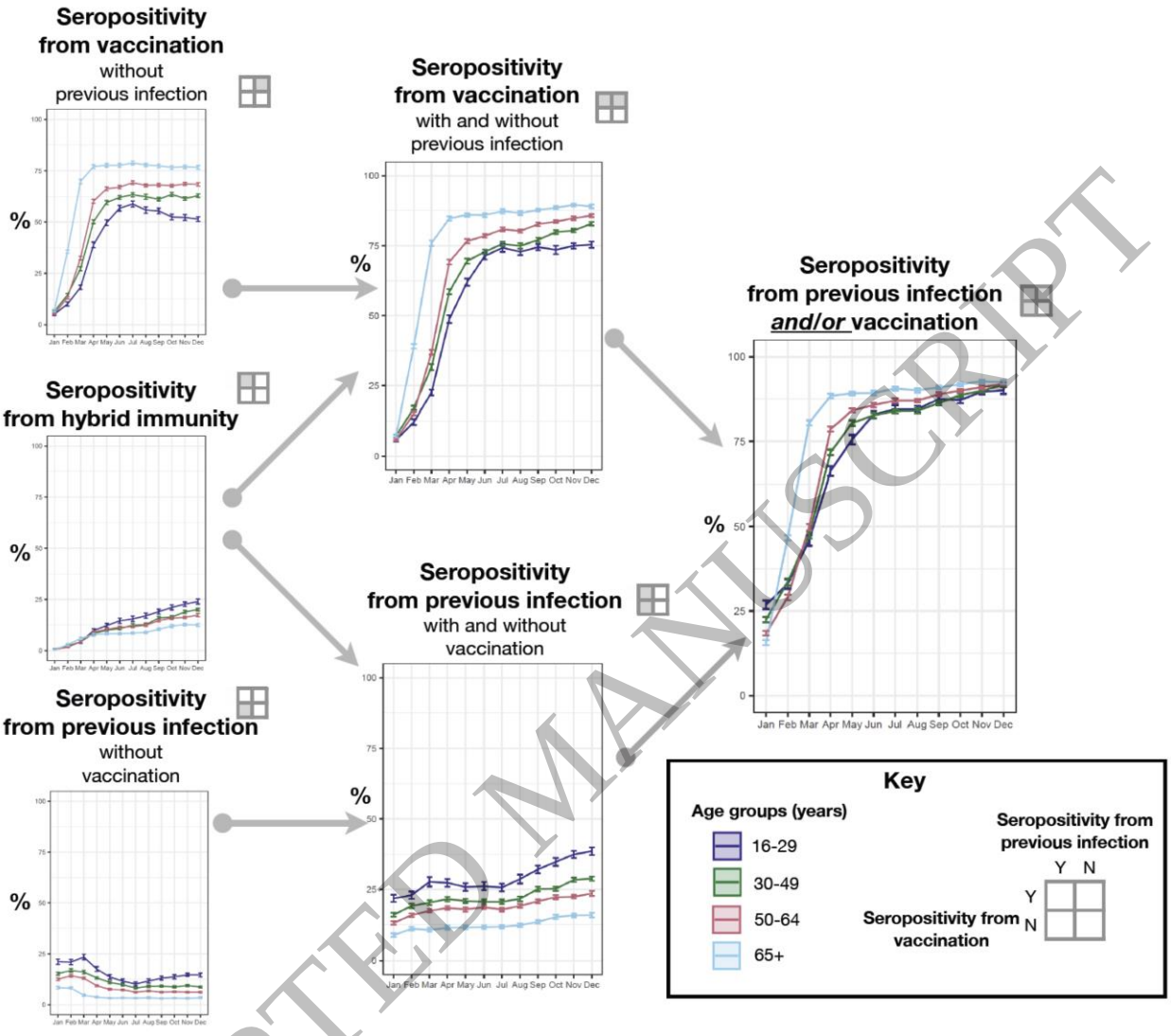

Figure 3
165x146 mm (.17 x DPI)

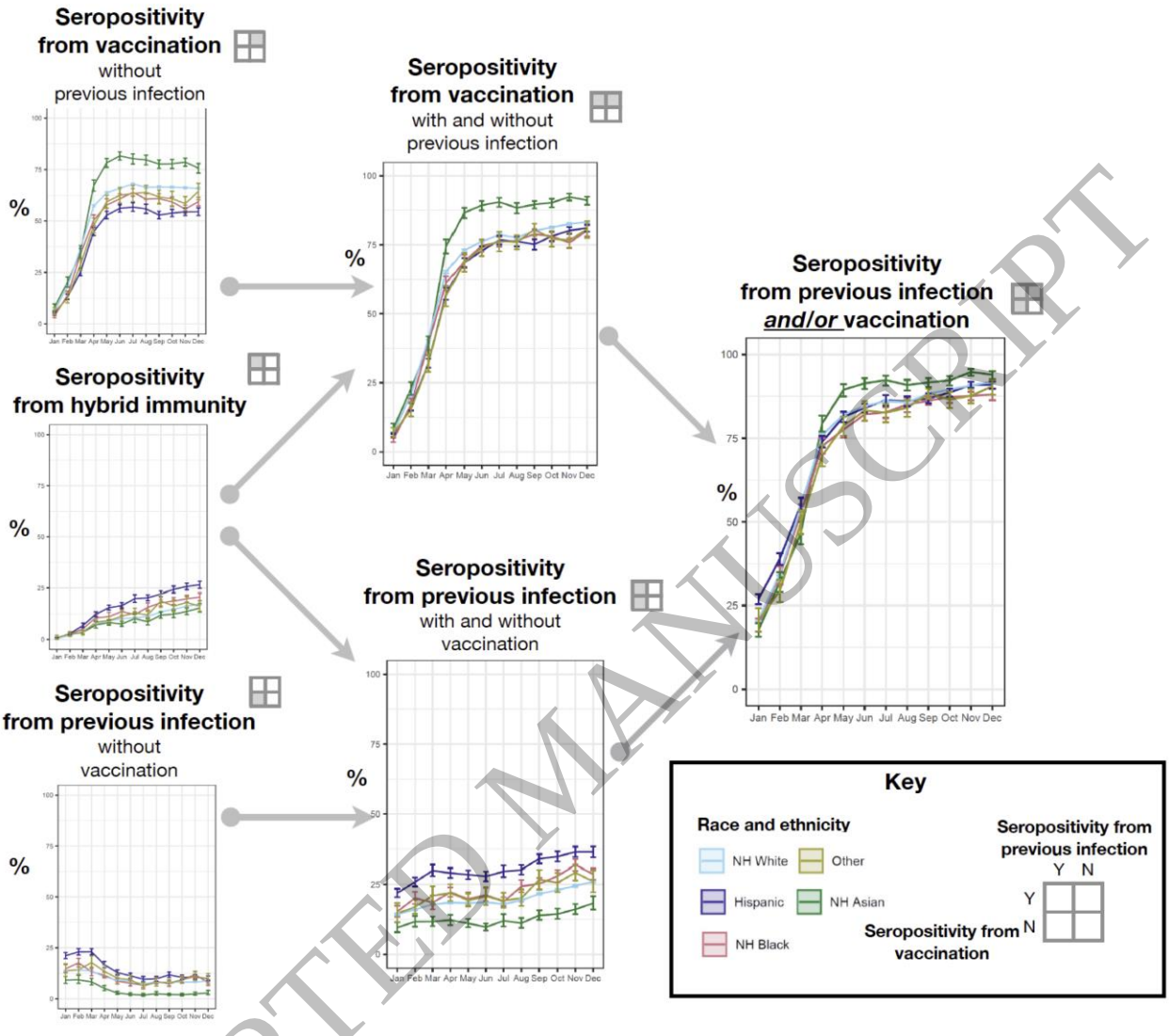

Figure 4
165x146 mm (.17 x DPI)

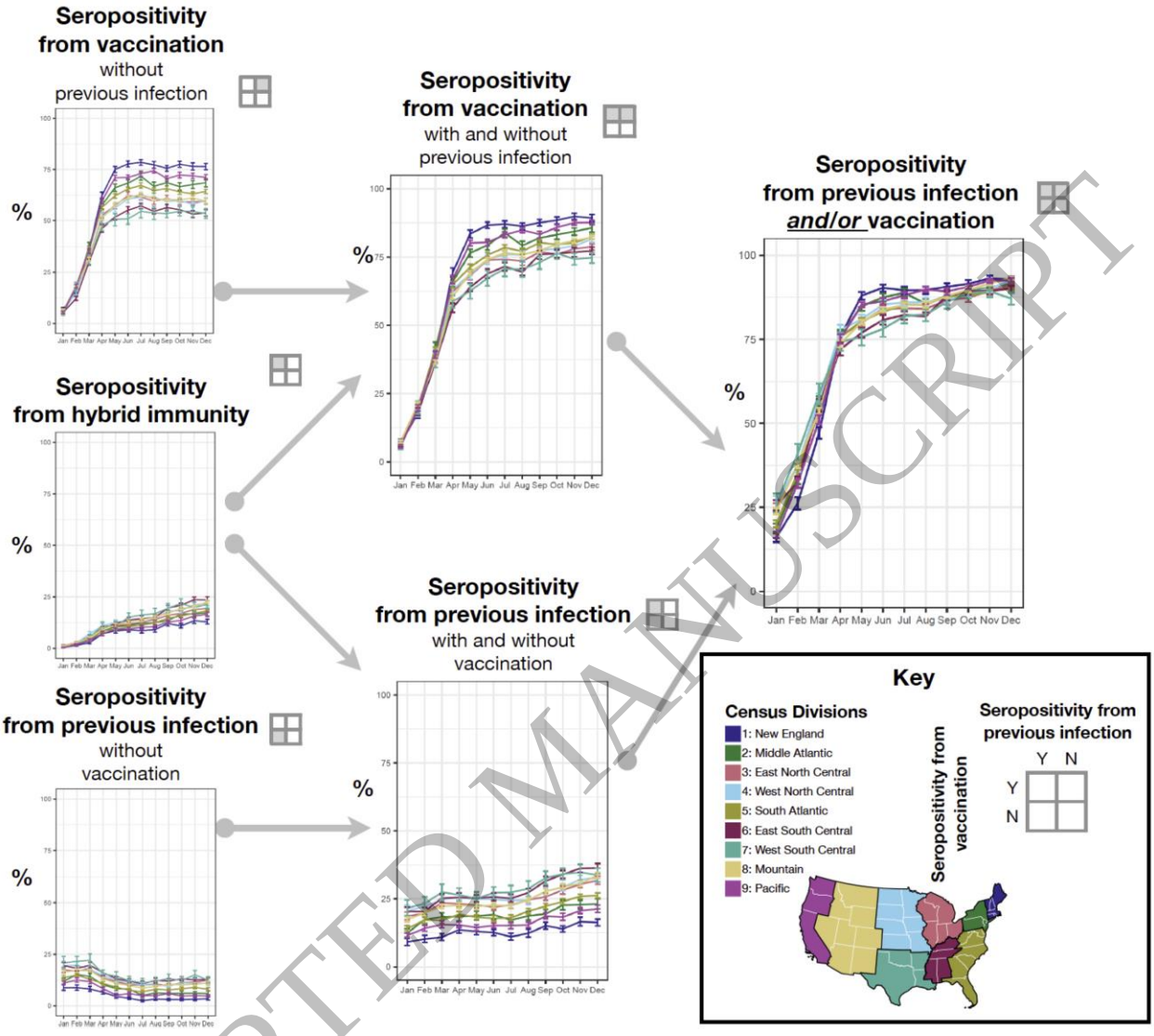

Figure 5
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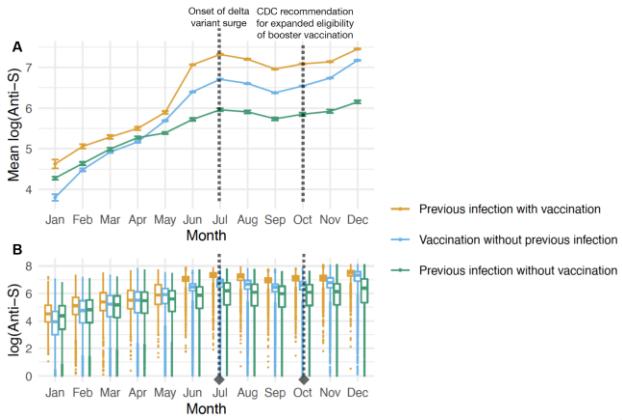

Figure 6
82x55 mm (.17 x DPI)