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Estimated US Infection- and Vaccine-Induced SARS-CoV-2 Seroprevalence Based on Blood Donations, July 2020-May 2021

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IMPORTANCE People who have been infected with or vaccinated against SARS-CoV-2 have reduced risk of subsequent infection, but the proportion of people in the US with SARS-CoV-2 antibodies from infection or vaccination is uncertain.

OBJECTIVE To estimate trends in SARS-CoV-2 seroprevalence related to infection and vaccination in the US population.

DESIGN, SETTING, AND PARTICIPANTS In a repeated cross-sectional study conducted each month during July 2020 through May 2021, 17 blood collection organizations with blood donations from all 50 US states; Washington, DC; and Puerto Rico were organized into 66 study-specific regions, representing a catchment of 74% of the US population. For each study region, specimens from a median of approximately 2000 blood donors were selected and tested each month; a total of 1 594 363 specimens were initially selected and tested. The final date of blood donation collection was May 31, 2021.

EXPOSURE Calendar time.

MAIN OUTCOMES AND MEASURES Proportion of persons with detectable SARS-CoV-2 spike and nucleocapsid antibodies. Seroprevalence was weighted for demographic differences between the blood donor sample and general population. Infection-induced seroprevalence was defined as the prevalence of the population with both spike and nucleocapsid antibodies. Combined infection- and vaccination-induced seroprevalence was defined as the prevalence of the population with spike antibodies. The seroprevalence estimates were compared with cumulative COVID-19 case report incidence rates.

RESULTS Among 1 443 519 specimens included, 733 052 (50.8%) were from women, 174 842 (12.1%) were from persons aged 16 to 29 years, 292 258 (20.2%) were from persons aged 65 years and older, 36 654 (2.5%) were from non-Hispanic Black persons, and 88 773 (6.1%) were from Hispanic persons. The overall infection-induced SARS-CoV-2 seroprevalence estimate increased from 3.5% (95% CI, 3.2%-3.8%) in July 2020 to 20.2% (95% CI, 19.9%-20.6%) in May 2021; the combined infection- and vaccination-induced seroprevalence estimate in May 2021 was 83.3% (95% CI, 82.9%-83.7%). By May 2021, 2.1 SARS-CoV-2 infections (95% CI, 2.0-2.1) per reported COVID-19 case were estimated to have occurred.

CONCLUSIONS AND RELEVANCE Based on a sample of blood donations in the US from July 2020 through May 2021, vaccine- and infection-induced SARS-CoV-2 seroprevalence increased over time and varied by age, race and ethnicity, and geographic region. Despite weighting to adjust for demographic differences, these findings from a national sample of blood donors may not be representative of the entire US population.

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SARS-CoV-2 transmission has been reported in the US since early 2020, with approximately 36.3 million COVID-19 cases reported as of August 13, 2021.[1] Routine COVID-19 case reports probably underestimate the total number of infections because persons with mild disease or asymptomatic infection might not be identified or tested.[2] Seroprevalence studies can estimate the prevalence of persons with SARS-CoV-2–specific antibodies, which can be due to natural infection or induced by vaccination.[3-5]

Previous SARS-CoV-2 seroprevalence studies conducted in the US have focused on specific populations (eg, health care personnel) or have been limited in time or geographic region.[6] Few studies have been conducted after COVID-19 vaccine administration began or have differentiated infection- and vaccine-induced seroprevalence. Blood donation specimens are useful for serosurveillance because numerous specimens can be efficiently collected and tested.[4] Several countries have conducted SARS-CoV-2 seroprevalence studies using blood donation specimens, and US blood collection organizations have reported SARS-CoV-2 seroprevalence among donations.[6-8]

This study was conducted to estimate SARS-CoV-2 seroprevalence in the general US population aged 16 years and older using blood donation specimens collected from July 2020 through May 2021, adjusting for demographic differences between the blood donor sample and the general population.

Methods

This study was approved by institutional review boards of the University of California San Francisco and Westat as non-human participants research based on anonymization of data and routine consent for use of residual blood donation specimens for research purposes. It was reviewed by Centers of Disease Control and Prevention (CDC) and conducted consistent with applicable federal law and CDC policy.[9-13]

In March 2020, the National Heart, Lung, and Blood Institute Recipient Epidemiology and Donor Evaluation Study-IV-Pediatric (REDS-IV-P) program began a repeated cross-sectional SARS-CoV-2 seroprevalence study called the REDS-IV-P Epidemiology, Surveillance, and Preparedness of the Novel SARS-CoV-2 Epidemic (RESPONSE) study using 6000 monthly blood donation specimens from 6 metropolitan regions over 6 months.[14] Beginning in July 2020, the CDC expanded the study using established RESPONSE infrastructure and methodologies. This analysis includes samples of blood donations in the US from July 2020 through May 2021, and the final date of blood donation collection was May 31, 2021.

Sample Selection and Serologic Testing

In July 2020, 10 regional and national blood collection organizations began participation, which increased to 17 by October 2020, providing representation from all 50 US states; Washington, DC; and Puerto Rico (eFigure 1 and eTable 1 in Supplement 1). After excluding COVID-19 convalescent plasma donations, samples of approximately 2000 speci-

Key Points

Question Based on blood donations in the US from July 2020 through May 2021, how did infection- and vaccine-induced SARS-CoV-2 seroprevalence vary over time by demographic group and by geographic region?

Findings In this repeated cross-sectional study that included 1 443 519 blood donation specimens from a catchment area representing 74% of the US population, estimated SARS-CoV-2 seroprevalence weighted for differences between the study sample and general population increased from 3.5% in July 2020 to 20.2% for infection-induced antibodies and 83.3% for combined infection- and vaccine-induced antibodies in May 2021. Seroprevalence differed by age, race and ethnicity, and geographic region of residence, but these differences changed over the course of the study.

Meaning Based on a sample of blood donations in the US from July 2020 through May 2021, estimated SARS-CoV-2 seroprevalence increased over time and varied by age, race and ethnicity, and geographic region.

mens from allogeneic donors were compiled monthly from blood donor regions in each blood organization's catchment area using pseudorandom or convenience sampling strategies (eMethods, eTable 2, and eFigure 2 in Supplement 1). From blood donor regions with more blood donors from racial and ethnic minority groups, 4000 specimens were compiled monthly to increase representation. From 2 blood donor regions that included 3 states each, 6000 specimens were compiled monthly to ensure sufficient samples from each state.

To ensure the same geographic areas were represented each month, sampled geographic regions from each blood collection organization were defined by a set of zip codes where more than 90% of blood donors resided. Specimens from donors residing outside those zip codes were excluded (eMethods in Supplement 1). From these aggregated zip codes, 66 study regions were created based on state and metropolitan borders (eFigure 1 and eTable 3 in Supplement 1). Each study region contributed approximately 500 to 4000 specimens monthly.

Specimens were tested for antibodies against the S-1 portion of the spike (S) protein using the VITROS chemiluminescent S1 total Ig assay (Ortho Clinical Diagnostics). Specimens with S antibodies were tested for nucleocapsid (N) antibodies using the chemiluminescent Roche Elecsys Total Ig Assay (Roche Diagnostics). These assays were chosen because they received Emergency Use Authorization from the US Food and Drug Administration (FDA) prior to study initiation, had reported sensitivity of 88.3% to 100% and specificity of 99.1% to 100%, and had demonstrated stable high sensitivity for 6 months or longer after infection.[14-17] From July through December 2020, only specimens with borderline positive S antibody results (ie, signal-to-cutoff ratio, 1-10) were tested for N antibodies.[14] Based on previous results, all specimens collected during 2020 with S antibody signal-to-cutoff ratio greater than 10 were assumed to have N antibodies.[14] Beginning in January 2021, after COVID-19 vaccine administration began, all specimens with S antibodies

were tested for N antibodies to differentiate infection- and vaccination-induced seropositivity. Both SARS-CoV-2 infection and COVID-19 vaccines currently authorized under an Emergency Use Authorization or fully FDA approved result in production of S antibodies but only infection results in production of N antibodies.[18]

Two blood collection organizations asked blood donors if they had received a COVID-19 vaccine prior to donation.

Outcomes

The primary outcomes were the combined infection- and vaccination-induced SARS-CoV-2 seroprevalence (defined as prevalence of specimens with S antibodies and referred to as combined seroprevalence) and infection-induced SARS-CoV-2 seroprevalence (defined as prevalence of specimens with both S and N antibodies) (eMethods and eTable 4 in Supplement 1), with a final date of blood donation collection of May 31, 2021.

Statistical Methods

Blood collection organizations provided routinely collected, deidentified demographic information for each blood donation, including donor age, sex, race and ethnicity (self-identified from 7 fixed categories), and zip code of residence. Researchers chose to assess race and ethnicity because infection and vaccination rates vary by these characteristics.[1,6,8] Donations with missing demographic information were excluded. Because demographics of the blood donor population differ from the US general population,[19] seroprevalence estimates were weighted in an effort to ensure that the demographic characteristics of the blood donor sample matched that of the general population (eMethods in Supplement 1). Monthly estimation weights were computed by raking, a statistical calibration technique, using the 2018 American Community Survey 5-year estimates for age, sex, and race and ethnicity compositions for blood donor regions (eMethods in Supplement 1).[20] Monthly sets of 50 replicate weights were created to estimate the variance.[21] Only weighted seroprevalence estimates are presented.

Combined and infection-induced seroprevalence rates were estimated for each study region, then for each US Census region by combining study regions within a Census region (eTable 3 and eFigure 2 in Supplement 1), and studywide. Seroprevalence was estimated by age, race and ethnicity, and sex. To determine whether the addition of 7 blood organizations after July 2020 affected trends, analyses were also performed after restricting inclusion to organizations that began participation in July 2020.

Comparisons of distributions of seroprevalence estimates across demographic categories were performed using χ^2 tests, while pairwise comparisons of seroprevalence estimates were performed using 2-sided t tests. Both tests were performed on the weighted data sets with a significance level of .05, using the replicate weights for inference. Because of the potential for type I error due to multiple comparisons, findings for secondary analyses should be interpreted as exploratory.

Seroprevalence was estimated by study region, which was defined by zip codes, whereas COVID-19 cases are reported by county as part of routine public health surveillance.[1] To estimate the number of SARS-CoV-2 infections per case reported, each study region was analyzed using the group of counties located within it. A county was included in a study region if the total population of all study region zip codes that overlapped with that county comprised 30% or more of the county population. To estimate the number of total infections per reported case, infection-induced seroprevalence estimates for each study region were divided by the number of cumulative case reports per 100 population for counties included in each study region. Cumulative COVID-19 case numbers were based on aggregate counts reported by state and territorial jurisdictions to the CDC.[1] All analyses were conducted using SAS version 9.4 (SAS Institute).

Results

Overall, 1 443 519 blood donation specimens were included. Because additional blood organizations began participation from August through October 2020, the number of monthly specimens included in the analysis increased from approximately 117 000 in July 2020 to 135 000 from November 2020 through May 2021 (eTable 1 and eTable 5 in Supplement 1), and the proportion of the US population residing in all study regions increased from 69.2% to 73.9%. In total, 150 844 specimens were excluded, including 108 501 (6.8%) because donors resided outside the study regions and 42 343 (2.9% of remaining) because of missing demographic data (eFigure 3 in Supplement 1). The monthly median number of specimens contributed by individual study regions was 1878 (25th-75th percentile, 1396-2296). Compared with the general population residing within the study regions, significantly more blood donors in the study were non-Hispanic White (85.0% vs 61.2%) and aged 50 to 64 years (36.5% vs 24.4%); significantly fewer donors were aged 16 to 29 years (12.1% vs 24.1%), Hispanic (6.2% vs 17.1%), non-Hispanic Asian (2.9% vs 6.2%), or non-Hispanic Black (2.5% vs 12.7%) (Table 1).

Studywide Seroprevalence Trends

From July through December 2020, the studywide infection-induced seroprevalence estimate increased from 3.5% (95% CI, 3.2%-3.8%) to 11.5% (95% CI, 11.1%-11.8%) (Figure 1; eFigure 4 and eFigure 5 in Supplement 1). After the FDA issued the first Emergency Use Authorization for a COVID-19 vaccine, COVID-19 vaccine administration began on December 14, 2020. By May 2021, the combined infection- and vaccination-induced seroprevalence estimate increased to 83.3% (95% CI, 82.9%-83.7%), and the infection-induced seroprevalence estimate increased to 20.2% (95% CI, 19.9%-20.6%) (Figure 1 and Figure 2).

Studywide Seroprevalence Trends Stratified by Census Region and by Demographic Group

In July 2020, the infection-induced seroprevalence estimate for the Northeast (6.8% [95% CI, 5.5%-8.3%]) was significantly higher than estimates for other Census regions

Table 1. Demographics of Donors of Sampled Blood Donations, the General Population Located Within Study Regions, and the US General Population, July 2020-May 2021[a]

	No. (%)		
	Study sample of blood donors	General population aged ≥16 y, in study regions[a]	US population aged ≥16 y
No.	1 443 519	191 742 111	260 534 061
Age, y[b]			
16-29	174 842 (12.1)	46 133 543 (24.1)	62 732 069 (24.1)
30-49	449 858 (31.2)	62 935 422 (32.8)	84 217 499 (32.3)
50-64	526 561 (36.5)	46 872 053 (24.4)	63 705 642 (24.5)
≥65	292 258 (20.2)	35 801 093 (18.7)	49 878 851 (19.1)
Sex			
Men	710 467 (49.2)	93 148 586 (48.6)	126 998 469 (48.7)
Women	733 052 (50.8)	98 593 525 (51.4)	133 535 592 (51.3)
Race and ethnicity[c]			
No.	1 422 607	191 742 111	260 534 061
American Indian	5004 (0.3)	1 020 178 (0.5)	1 616 856 (0.6)
Asian	41 824 (2.9)	11 877 914 (6.2)	14 295 323 (5.5)
Black	36 654 (2.5)	24 353 741 (12.7)	30 855 020 (11.8)
Hispanic	88 773 (6.1)	32 858 274 (17.1)	43 854 340 (16.8)
White	1 226 745 (85.0)	117 378 746 (61.2)	164 254 508 (63.0)
≥1 race	10 589 (0.7)	3 310 108 (1.7)	4 446 443 (1.7)
Other	13 018 (0.9)	943 149 (0.5)	1 211 571 (0.5)
Repeat donation status			
First time	191 004 (13.2)	NA	NA
Repeat	1 252 468 (86.8)	NA	NA

Abbreviation: NA, not applicable.

[a] Study regions are geographic regions uniquely defined for this study based on state and metropolitan borders that blood donors consistently reside in. See eFigure 1 in Supplement 1 for geographical mapping of these study regions. All study regions, including those that include donations from blood collection organizations that began participation after July 2020, are included.

[b] Blood donor must be aged ≥16 years in most states. There is no maximum donor age limit.

[c] Donations with missing donor demographic data were excluded (eFigure 3 in Supplement 1). Race and ethnicity data are routinely collected by blood collection organizations. Blood donors self-identify race and ethnicity from 7 fixed mutually exclusive categories. "Other" race and ethnicity means the donor provides a response besides one of the named categories. However, the blood collection organization in the Puerto Rico study region did not systematically collect race and ethnicity data. The 20 912 donations from Puerto Rico are not displayed under the race and ethnicity categories but are included in the other analyses. All categories are non-Hispanic unless otherwise indicated.

(Figure 3; eFigure 5 in Supplement 1). In September 2020, infection-induced seroprevalence estimates for the Northeast (5.9% [95% CI, 5.3%-6.6%]) and South (6.0% [95% CI, 5.6%-6.5%]) were significantly higher than estimates for the West (3.4% [95% CI, 3.1%-3.8%]) and Midwest (3.8% [95% CI, 3.4%-4.2%]). In December 2020, the infection-induced seroprevalence estimate for the Midwest (15.8% [95% CI, 15.1%-16.5%]) was significantly higher than estimates for other Census regions. In May 2021, the infection-induced seroprevalence estimates for the Midwest (23.5% [95% CI, 22.7%-24.3%]) and South (22.2% [95% CI, 21.7%-22.8%]) were significantly higher than estimates for the Northeast (19.3% [95% CI, 18.2%-20.5%]) and West (16.7% [95% CI, 16.1%-17.2%]). The combined seroprevalence estimate for the Northeast (87.2% [95% CI, 86.2%-88.2%]) was significantly higher than estimates for other Census regions and the estimate for the South (80.2% [95% CI, 79.6%-80.8%]) was significantly lower in May 2021.

For all months, infection-induced seroprevalence estimates for persons aged 16 to 29 years (5.5% [95% CI, 4.6%-6.6%] in July 2020 and 27.0% [95% CI, 25.7%-28.4%] in May 2021) were significantly higher than infection-induced esti-

mates for all other age groups, and the infection-induced estimates for persons aged 65 years and older (1.3% [95% CI, 1.0%-1.8%] in July 2020 and 11.7% [95% CI, 11.2%-12.2%] in May 2021) were significantly lower (Figure 3). However, in May 2021, the combined seroprevalence estimate for persons aged 65 years and older (92.2% [95% CI, 91.8%-92.7%]) was significantly higher than combined seroprevalence estimates for other age groups; the combined seroprevalence estimate for persons aged 16 to 29 years (76.1% [95% CI, 75.0%-77.2%]) was significantly lower.

From July through November 2020, the infection-induced seroprevalence estimates for men and women did not significantly differ (Figure 3). From December 2020 through May 2021, the monthly combined seroprevalence estimates for women were significantly higher than the corresponding monthly estimates for men. In May 2021, the combined seroprevalence estimate was 84.2% (95% CI, 83.7%-84.6%) for women and 82.3% (95% CI, 81.8%-82.9%) for men. However, the infection-induced seroprevalence estimates for women (20.2% [95% CI, 19.7%-20.6%]) and men (20.3% [95% CI, 19.8%-20.9%]) did not significantly differ in May 2021.

Among racial and ethnic groups, the infection-induced seroprevalence estimates in July 2020 for Hispanic (6.8% [95% CI, 5.8%-8.1%]) and non-Hispanic Black (6.6% [95% CI, 4.7%-9.3%]) persons were significantly higher than infection-induced estimates for other racial and ethnic groups (Figure 3). For the infection-induced seroprevalence in May 2021, the estimate for Hispanic persons (30.0% [95% CI, 28.7%-31.4%]) was significantly higher than the estimates of all other racial and ethnic groups, the estimate for non-Hispanic Black persons (21.1% [95% CI, 19.4%-23.0%]) was significantly higher than the estimates for all other racial and ethnic populations except Hispanic persons, and the estimate for non-Hispanic Asian persons (13.0% [95% CI, 11.7%-14.3%]) was significantly lower than the estimates for other racial and ethnic groups, including non-Hispanic White persons (18.5% [95% CI, 18.2%-18.8%]). The combined seroprevalence estimates in May 2021 for non-Hispanic Asian persons (91.0% [95% CI, 89.6%-92.2%]) was significantly higher than the estimates for all other racial and ethnic populations, and the estimate for non-Hispanic White persons (83.8% [95% CI, 83.5%-84.0%]) was significantly higher than the estimates for non-Hispanic Black (79.2% [95% CI, 77.1%-81.2%]) and Hispanic (81.5% [95% CI, 80.2%-82.7%]) persons.

Seroprevalence estimates restricted to blood samples contributed by organizations that participated for the entire duration of the study (beginning July 2020) are shown in eFigure 6 in Supplement 1.

Among 92 390 blood donation specimens collected during May 2021 from donors with known COVID-19 vaccine status, 67 731 (73.3%) reported receiving a previous COVID-19 vaccine.

Comparison of Cumulative Case Reporting Rate and Seroprevalence

Based on infection-induced seroprevalence estimates, the estimated number of SARS-CoV-2 infections per reported COVID-19 case decreased from 3.1 (95% CI, 2.8-3.4) in July 2020 to 2.1 (95% CI, 2.0-2.1) in May 2021 (**Table 2**) but varied by study region (eTable 6 in Supplement 2).

Discussion

In this nationwide study that included more than 1.4 million blood donation specimens from July 2020 through May 2021, vaccine- and infection-induced SARS-CoV-2 seroprevalence increased over time and varied by age, race and ethnicity, and geographic region. Introduction of SARS-CoV-2 vaccines resulted in increased population spike antibody seroprevalence.

These data demonstrate the increases in SARS-CoV-2 seroprevalence that occurred due to vaccination and illustrate differences in infection- and vaccine-induced antibody prevalence. The study will continue until at least December 2021, and results will be made available on the CDC's website.[1] Infection-induced seroprevalence (indicating the proportion of population previously infected) and combined seroprevalence (which might indicate the proportion of population po-

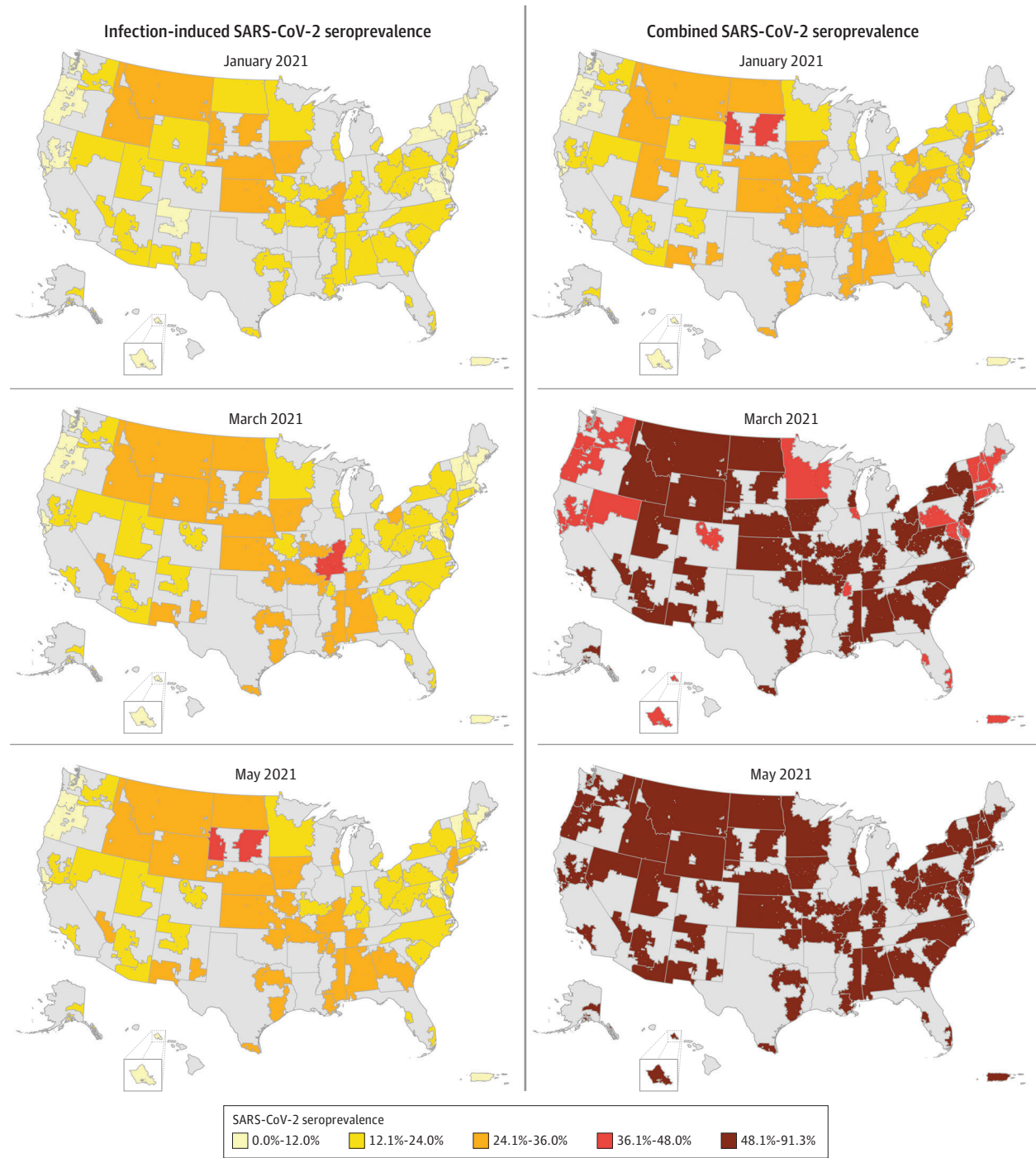### Figure 1. Weighted SARS-CoV-2 Seroprevalence, US, July 2020-May 2021
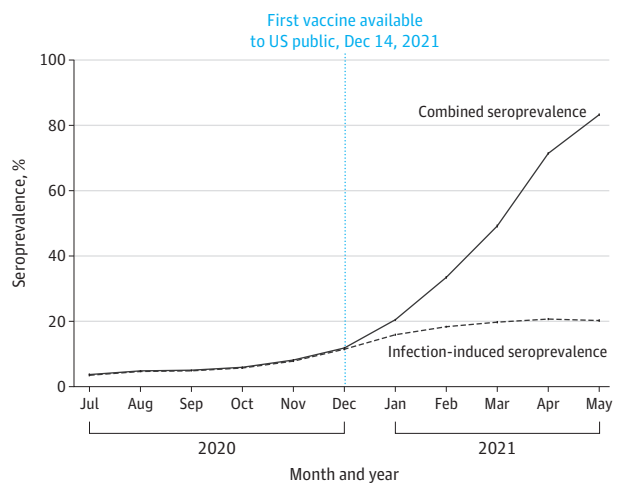
Because the number of participating blood collection organizations increased, the number of blood donations included increased from 116 513 in July 2020 to 134 949 in May 2021 (see eTable 1 and eTable 5 in Supplement 1). Blood donations were collected from a catchment area representing 69% of the US population in July, increasing to 74% of the US population from October 2020 through May 2021. The solid black line illustrates the weighted spike antibody seroprevalence, representing the proportion of the population with antibodies from infection, vaccination, or both (combined seroprevalence). The dashed line illustrates the weighted seroprevalence of the population with both spike and nucleocapsid antibodies, representing the proportion of the population with antibodies from infection (infection-induced seroprevalence). Displayed error bars are 95% CIs. The x-axis tick marks indicate the middle of each month. For median specimen collection date each month, see eTable 5 in Supplement 1.

tentially protected from infection) can supplement public health surveillance to identify groups potentially at higher risk of infection to implement public health prevention measures. These data can also inform infectious disease modeling and other research (eg, estimating infection-mortality ratios, ecologic analyses of associations between population immunity and case incidence).

Additional research is needed on the association between combined seroprevalence, protection, and herd immunity. Several large studies have shown that among individuals who are seropositive from prior SARS-CoV-2 infection, COVID-19 incidence is reduced by 80% to 95%, similar to vaccine efficacy estimates.[22,23] However, infection- and vaccination-induced protection might be reduced in the setting of SARS-CoV-2 variants, and infection-induced protection might wane more quickly than vaccine-induced protection.[22] Limited evidence suggests quantitative spike binding antibody and neutralizing antibody titers correlate with vaccine-induced protection, but it is unknown whether this correlation will persist as antibody levels wane or apply to infection-induced antibodies.[24-26] Additional research is also needed on how humoral and cellular immunity contribute to protection after infection and vaccination.[22]

Infection-induced SARS-CoV-2 seroprevalence was consistently highest in Hispanic and non-Hispanic Black persons, mirroring case trends.[1] However, by May 2021, non-Hispanic Asian and White persons had significantly higher

Figure 2. Weighted SARS-CoV-2 Seroprevalence by Study Region, US, January-May 2021


Infection-induced SARS-CoV-2 seroprevalence

January 2021

March 2021

May 2021

Combined SARS-CoV-2 seroprevalence

January 2021

March 2021

May 2021

SARS-CoV-2 seroprevalence

☐ 0.0%-12.0%   ☐ 12.1%-24.0%   ☐ 24.1%-36.0%   ☐ 36.1%-48.0%   ☐ 48.1%-91.3%

Maps display weighted seroprevalence by study region and month. On the left, spike and nucleocapsid antibody seroprevalence representing antibodies from infection. On the right, spike antibody seroprevalence representing antibodies from infection, vaccination, or both. The maps show the lower 48 states, the District of Columbia, Alaska, Hawaii, and Puerto Rico, and are Lambert Conformal projections that maintain direction, angle, and shape but not area or distance. See eTables 1 and 5 in Supplement 1, eTable 7 in Supplement 3, and eTable 8 in Supplement 4 for detailed data.

combined seroprevalence estimates, likely because non-Hispanic Asian and White persons received vaccinations at a greater rate than Hispanic and non-Hispanic Black persons.[27] Despite having disproportionately higher COVID-19 mortality rates, persons aged 65 years and older consistently had the lowest infection-induced seroprevalence, consistent with other seroprevalence studies and case data[1,8,28,29] and potentially attributable to immunosenescence or older US adults practicing COVID-19 prevention behaviors more than younger persons.[30,31]

Figure 3. Weighted SARS-CoV-2 Seroprevalence by Census Region, Race and Ethnicity, Sex, and Age Group, US, July 2020-May 2021
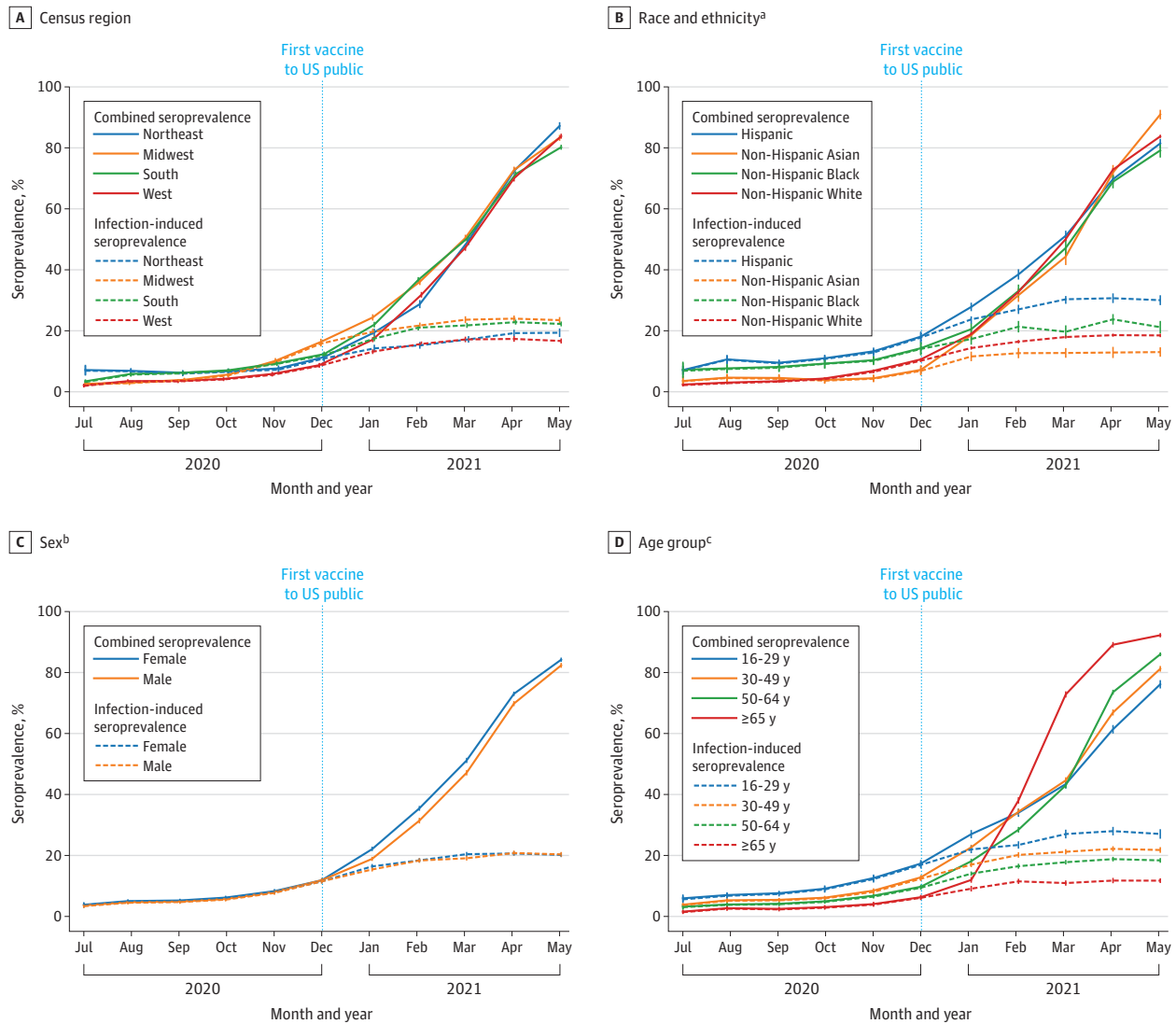
Blood donations were collected from a catchment area representing 69% of the US population in July, increasing to 74% of the US population from October 2020 through May 2021. The solid lines illustrate the weighted spike antibody seroprevalence, representing the proportion of the population with antibodies from infection, vaccination, or both (combined seroprevalence). The dashed lines illustrate the weighted seroprevalence of the population with both spike and nucleocapsid antibodies, representing the proportion of the population with antibodies from infection (infection-induced seroprevalence). Displayed error bars are 95% CIs. All blood donor specimens missing race and ethnicity data were excluded except for specimens collected in the Puerto Rico study region, in which donor race and ethnicity data were not collected. The x-axis tick marks represent the middle of each month (range, 12th-15th day of each month). See eTables 1 and 5 in Supplement 1, eTable 7 in Supplement 3, and eTable 8 in Supplement 4 for detailed data.

[a] The monthly median number of blood donations was 8172 (25th-75th percentile [Q1-Q3], 7996-8223) for Hispanic persons, 3934 (Q1-Q3, 3758-3967) for non-Hispanic Asian persons, 3440 (Q1-Q3, 3187-3526) for non-Hispanic Black persons, and 114 172 (Q1-Q3, 110 818-114 910) for non-Hispanic White persons.

[b] The monthly median number of blood donations was 65 940 (Q1-Q3, 65 547-66 477) for males and 68 263 (Q1-Q3, 65 793-68 658) for females.

[c] The monthly median number of blood donations was 16 091 (Q1-Q3, 14 947-16 894) for people aged 16-29 years, 40 882 (Q1-Q3, 40 105-42 123) for people aged 30-49 years, 48 290 (Q1-Q3, 47 672-49 966) for people aged 50-64 years, and 26 798 (Q1-Q3, 26 160-27 496) for people aged ≥65 years.

Seroprevalence estimates indicate that the number of COVID-19 cases reported are fewer than the number of SARS-CoV-2 infections that have occurred, likely because many mildly symptomatic and asymptomatic individuals did not seek testing or clinical care.[2] The data in this study suggest that for every COVID-19 case reported, the number of people infected and with detectable SARS-CoV-2 antibodies decreased from 3.1 in July 2020 to 2.1 in May 2021. A previous blood donor seroprevalence study reported a similarly decreasing ratio from March through August 2020 for 6 regions.[14] Increases in testing supplies, access to testing, and serial testing programs at universities, long-term care facilities, and other locations may

Table 2. Studywide Number of Projected Cumulative SARS-CoV-2 Infections With Detectable Antibodies Based on Seroprevalence per Reported COVID-19 Case, US, July 2020-May 2021

	Month and year										
	2020						2021				
	July	August	September	October	November	December	January	February	March	April	May
Infection-induced seroprevalence, % (95% CI)[a]	3.5 (3.2-3.8)	4.7 (4.4-4.9)	4.9 (4.6-5.1)	5.6 (5.3-5.8)	7.7 (7.5-8.0)	11.4 (11.1-11.8)	15.9 (15.6-16.2)	18.4 (18.1-18.7)	19.8 (19.4-20.1)	20.7 (20.4-21.0)	20.2 (19.9-20.6)
Cumulative reported cases per 100 population[b]	1.12	1.60	1.99	2.35	3.17	4.79	6.85	8.06	8.65	9.28	9.71
No. of cumulative infections per reported case, ratio (95% CI)[c]	3.1 (2.8-3.4)	2.9 (2.8-3.1)	2.4 (2.3-2.5)	2.4 (2.3-2.5)	2.4 (2.4-2.5)	2.4 (2.3-2.5)	2.3 (2.3-2.4)	2.3 (2.2-2.3)	2.3 (2.2-2.3)	2.2 (2.2-2.3)	2.1 (2.0-2.1)

[a] Seroprevalence estimates of the population with both spike and nucleocapsid antibodies, representing the proportion of the population with infection-induced seroprevalence, including those who were vaccinated before or after infection. Seroprevalence estimates were weighted to account for age, race and ethnicity, sex, and geographic distribution differences between the blood donor sample and general population.

[b] Number of cumulative infections reported to the Centers for Disease Control and Prevention for all counties included in study regions per 100 population.

[c] Seroprevalence divided by cumulative reported cases per 100 persons. The displayed 95% CI is that of the seroprevalence divided by the cumulative reported cases per 100 persons.

have contributed to increased case detection and reporting,[32-34] but waning of antibodies may also be contributing.

Limitations

This study has several limitations. First, while seroprevalence estimates were weighted to account for demographic differences between the sample blood donor population and general population, the blood donor population differed from the general adult US population in measurable demographic variables, while other potential population differences could not be measured.

Second, although the serology assays used appear to have high sensitivity for 6 months after infection,[15] estimates were not adjusted to account for a sensitivity less than 100% or potential waning of sensitivity after 6 months.

Third, infection-induced seroprevalence estimates might be underestimated because persons with acute or long-term COVID-19 symptoms might have been excluded from donating.[35] However, influenza seroprevalence studies have shown similar influenza infection rates in blood donors and the general population, suggesting SARS-CoV-2 infection-induced seroprevalence might also be similar in blood donors and the general population[36]; additionally, the infection-induced seroprevalence estimates in this study were similar to those of a nationwide seroprevalence study using commercial laboratory specimen remnants.[1,29]

Fourth, vaccine-induced seroprevalence might be higher in blood donors than in the general population. For May 2021, among donations from donors with a known vaccine history, 73.3% were from donors who self-reported receiving a previous COVID-19 vaccine, compared with CDC estimates that 57.0% of US adults aged 18 years and older had received 1 dose or more of vaccine by May 2021.[37] Blood donors are more likely than the general US population to be employed and have attended college,[38] factors potentially associated with increased rates of vaccination and lower rates of infection.[39,40]

Fifth, the combined and infection-induced seroprevalence estimates might be overestimates because several par-

ticipating blood collection organizations implemented and advertised SARS-CoV-2 antibody testing for blood donors, potentially attracting donors who were exposed.[8] However, the effect of test-seeking donors was likely low given that test seeking would have been more likely among first-time donors, who contributed 13.9% of study specimens.

Sixth, the studywide estimates only represented the geographic areas covered by study regions, which covered an estimated 74% of the US population.

Seventh, the zip code–based study region seroprevalences were compared with county-based cumulative case report rates; counties only partially represented by study region zip codes may have had case report rates that differed between included and excluded zip codes in the study regions.

Eighth, the analysis of infections per reported case is ecological. The seroprevalence estimates and cumulative case reporting data applied to broad geographic areas; the true values likely vary based on local patterns of transmission, testing for COVID-19, and other factors. Therefore, the estimated number of cumulative infections per reported case should be interpreted with caution.

Ninth, children aged younger than 16 years cannot donate blood and were not included in this study.

Tenth, the findings in this analysis predate the surge in SARS-CoV-2 infection in the US related to transmission of the Delta variant.

Conclusions

Based on a sample of blood donations in the US from July 2020 through May 2021, vaccine- and infection-induced SARS-CoV-2 seroprevalence increased over time and varied by age, race and ethnicity, and geographic region. Despite weighting to adjust for demographic differences, these findings from a national sample of blood donors may not be representative of the entire US population.

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