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RESEARCH ARTICLE

Seroprevalence as an Indicator of Undercounting of COVID-19 Cases in a Large Well-Described Cohort

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Introduction: Reported confirmed cases represent a small portion of overall true cases for many infectious diseases. The undercounting of true cases can be considerable when a significant portion of infected individuals are asymptomatic or minimally symptomatic, as is the case with COVID-19. Seroprevalence studies are an efficient way to assess the extent to which true cases are undercounted during a large-scale outbreak and can inform efforts to improve case identification and reporting.

Methods: A longitudinal seroprevalence study of active duty U.S. military members was conducted from May 2020 through June 2021. A random selection of service member serum samples submitted to the Department of Defense Serum Repository was analyzed for the presence of antibodies reactive to SARS-CoV-2. The monthly seroprevalence rates were compared with those of cumulative confirmed cases reported during the study period.

Results: Seroprevalence was 2.3% in May 2020 and increased to 74.0% by June 2021. The estimated true case count based on seroprevalence was 9.3 times greater than monthly reported cases at the beginning of the study period and fell to 1.7 by the end of the study.

Conclusions: In our sample, confirmed case counts significantly underestimated true cases of COVID-19. The increased availability of testing over the study period and enhanced efforts to detect asymptomatic and minimally symptomatic cases likely contributed to the fall in the seroprevalence to reported case ratio.

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INTRODUCTION

Case counts are commonly used by health professionals as an indicator of the scope and impact of a disease outbreak. This approach is most useful with relatively rare diseases that are easily identifiable or among well-defined populations in which active case detection can be effectively implemented. However, the higher the asymptomatic or minimally symptomatic fraction of disease, the less useful case counts become in estimating the full extent of an outbreak.[1] For the first 2 years of the coronavirus

disease 2019 (COVID-19) pandemic, case counts (cumulative and daily) were the primary indicator communicated to the lay public. Although hospitalization rates and death rates also received some attention, these indicators are biased toward severe disease and cannot convey the broader impact from more mild infections.[2] Altogether, these measures provided an incomplete picture of the full scope of the COVID-19 pandemic.

Whereas molecular testing continues to be the gold standard for confirming severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in the individual, serologic surveillance studies provide a unique and efficient means of estimating the full impact of COVID-19. Utilizing the period prevalence of SARS-CoV-2—reactive antibodies across a population, seroprevalence studies are a superior modality to estimate cumulative case counts because they are able to detect the large number of asymptomatic and minimally symptomatic cases that do not present for molecular testing. Multiplexed assay design can be used to differentiate infection-induced seroreactivity from vaccine-induced seroreactivity through the detection of both spike protein and nucleoprotein immunoreactive targets, thereby eliminating a factor that can complicate seroprevalence studies when a vaccine is available. Serologic analysis can become especially informative over the course of an outbreak that spans several months or years because diagnostic laboratory testing data and passive reporting systems miss numerous cases and underrepresent the true burden of disease.[1,2]

Multiple studies of SARS-CoV-2 seroprevalence were completed early in the pandemic and provided important insights into the extent of COVID-19 infections.[3–6] These studies generally used cities or counties as the cohort. Complete case ascertainment and reporting in a geographic area poses numerous challenges. Therefore, these studies were limited in their ability to determine whether the serum samples were drawn from the same hypothetical cohort as the confirmed cases. Our study overcomes inherent case ascertainment bias by utilizing a large, well-defined cohort with mandatory reporting requirements. We utilized a representative sampling method of that cohort to estimate real-time seroprevalence, comparing these findings with cumulative case counts during the study period to assess the accuracy of this traditional reporting mechanism.

METHODS

Study Sample
Individuals were eligible for inclusion in this study if they served in an active status in any of the U.S. Department of Defense (DoD) branches during the period of May 2020 through June 2021. The study was restricted to active component service members because case reporting was more complete in this population than in the reserve components. Investigators utilized data from the Defense Medical Surveillance System (DMSS) and serum specimens from the Department of Defense Serum Repository (DoDSR) to conduct this study.[7,8] The DMSS is a continuously updated relational database that serves as a central repository of health information for the U.S. military and includes both medical and personnel data on all service members. Established in 1996, the DoDSR stores excess serum collected from U.S. military personnel as part of mandatory HIV surveillance testing across all DoD components. Each active component service member is tested upon entry into the military and then again at 2-year intervals. Therefore, the DoDSR is representative of the entire U.S. military population and includes samples obtained throughout the calendar year. DMSS data were used to identify service members with DoDSR specimens collected from May 1, 2020 to June 30, 2021. Approximately 1,300 specimens per month were randomly selected from those available in the DoDSR over this 14-month period. After selection, specimens were thawed, aliquoted, and transported on dry ice for serologic testing.

Measures
The U.S. Army Medical Research Institute of Infectious Diseases performed SARS-CoV-2 serologic testing of all specimens. Serum samples were tested through a multiplexed, magnetic bead—based immunoassay optimized to identify anti—SARS-CoV-2 IgG reactivity.[9,10] The assay was developed and validated at the U.S. Army Medical Research Institute of Infectious Diseases and run on the Luminex MAGPIX system. Validation for human serum samples was performed using a goat anti-human IgG phycoerythrin conjugate (P9170, Sigma-Aldrich, St. Louis, MO). Samples were considered SARS-CoV-2 antibody positive when demonstrating sufficient reactivity to at least 2 of 3 spike protein—based targets. Reactivity to the nucleoprotein was also assessed and was used as evidence of past infection because COVID-19 vaccines only utilize the spike protein for eliciting an immune response and on their own would not result in a serologic response to the nucleoprotein. A 95% mean fluorescence intensity cutoff for all 4 targets was determined from assay validation using 89 known positive and 276 pre—COVID-19—negative samples to minimize false positives that may occur from exposure to other known human coronaviruses causing seasonal respiratory illness. The overall sensitivity and specificity of the assay were estimated at 90.9% and 98.1%, respectively (data not shown).

Statistical Analysis

Results from the Luminex assay were merged with the demographic and vaccination data from DMSS for this analysis. The overall percentage seroprevalence of SARS-CoV-2 antibody (number of SARS-CoV-2 antibody−positive specimens divided by the number of specimens tested multiplied by 100) was calculated for each month of the study. CIs were calculated using the binomial-based exact Clopper−Pearson method. The contribution to overall seroprevalence from both vaccinated and unvaccinated individuals was determined using immunization records available for each service member in DMSS as well as serologic results from the Luminex assay. Individuals who were spike protein reactive with no nucleoprotein reactivity were classified as seropositive due to vaccination only, whereas those that were both spike and nucleoprotein reactive along with a DMSS record of vaccination were classified as seropositive with evidence of both vaccination and infection. The remaining individuals who did not have a DMSS record of vaccination but were reactive to both the spike and nucleoprotein targets were classified as seropositive due to infection alone.

To assess the extent to which reported case counts underestimated the true burden of COVID-19, an overall estimate of SARS-CoV-2 infections based on seroprevalence was compared with the cumulative confirmed DoD COVID-19 case counts reported during each month of the study period. The number of individuals demonstrating both spike protein and nucleoprotein reactivity on the Luminex assay was used to calculate seroprevalence resulting from infection. To calculate the estimated true number of SARS-CoV-2 infections, the seroprevalence rate resulting from infection was multiplied by the total active component force population number at the midpoint of each month. This estimate of SARS-CoV-2 infections was divided by the cumulative number of reported confirmed COVID-19 cases to determine the ratio between reported and estimated true infections for each month of the study. Cumulative confirmed COVID-19 case counts during this time period were obtained from DMSS and utilized a combination of laboratory results, including both reverse transcriptase polymerase chain reaction and antigen testing, as well as mandatory case reporting through the DoD's internal Disease Reporting System internet. This system compiles all mandatory disease reports for service members and other DoD medical beneficiaries and is the DoD's primary mechanism for collecting data on notifiable diseases.

This protocol was reviewed by an institutional office of human research oversight and considered exempt from IRB review because it was determined to be nonhuman subjects research on the basis of the use of anonymized residual serum samples for public health surveillance purposes. All statistical analyses were performed using SAS, Version 9.4 (SAS Institute, Cary, NC).

RESULTS

A total of 18,581 serum specimens from active component service members were randomly selected from the DoDSR from May 2020 through June 2021. The demographic characteristics of the study population mirrored that of the general U.S. military active component population at the time of the study (Table 1), although younger individuals (aged 17−24 years) and Army personnel were slightly overrepresented. A higher completion rate of HIV surveillance testing in the accession (new recruit) population, which is almost entirely composed of individuals in this younger age group, explains why they make up a larger proportion of DoDSR samples. The higher proportion of Army personnel in the study population is likely due to differences in the availability of serum specimens in the DoDSR for testing. Specimens were retrieved for testing on a monthly to a bimonthly schedule, so delays in receiving specimens from certain areas or services into the DoDSR could potentially impact the available population for sampling each month. Such delays were uncommon, and although they may have impacted the proportion of samples from each service, they were not significant enough to impact overall monthly seroprevalence estimates.

Seroprevalence was estimated for each month of the study period beginning in May 2020. These results are displayed in Figure 1 and are stratified into 3 categories to demonstrate which exposure (infection versus vaccination) resulted in seroconversion. The estimated overall seroprevalence in May 2020 was 2.3% (95% CI=1.6, 3.2), indicating that only a small portion of service members had been infected during the initial months of the pandemic. Seroprevalence did not exceed 10% until December 2020, at which point there was a marked rise over the next several months as vaccinated individuals comprised an increasing proportion of all seropositive specimens and ultimately reached 74.0% (95% CI=71.6, 76.3) by the conclusion of the study in June 2021.

Applying these seroprevalence rates to the total active component population each month provided a similar trend in total estimated cumulative COVID-19 cases during the study period (Figure 2). The estimated cumulative case count based on seroprevalence increased from 30,424 in May 2020 to 210,436 in June 2021. A comparison of these monthly estimates with the

**Table 1.** Demographic Characteristics of Study Population

Variables	Study population		Active component (as of November 1, 2021)	
	n	%	*n*	%
Total	18,581	100.0	1,335,460	100.0
Sex				
Male	15,198	81.8	1,105,001	82.7
Female	3,362	18.1	230,457	17.3
Unknown	21	0.1	2	0.0
Age category, years				
17−24	8,660	46.6	526,330	39.4
25−34	6,689	36.0	521,721	39.1
35−44	2,673	14.4	239,334	17.9
45−54	506	2.7	44,877	3.4
≥55	29	0.2	3,183	0.2
Unknown	24	0.1	15	0.0
Race/ethnicity				
White	9,937	53.5	733,883	55.0
Black	3,062	16.5	215,670	16.2
Hispanic	3,264	17.6	231,625	17.3
Other	2,318	12.5	154,282	11.6
Service				
Army	7,716	41.5	482,403	36.1
Air Force	3,357	18.1	329,589	24.7
Marine Corps	2,783	15.0	180,940	13.6
Navy	4,725	25.4	342,528	25.7

cumulative number of reported confirmed COVID-19 cases each month demonstrated a large number of cases that were not counted. This undercounting was most pronounced early in the pandemic, with the number of true infections in May 2020 estimated to be 9.3 times greater than the number of reported confirmed cases. By August 2020, this ratio had decreased to 4.3 and then trended steadily downward to 1.7 by June 2021. Overall,
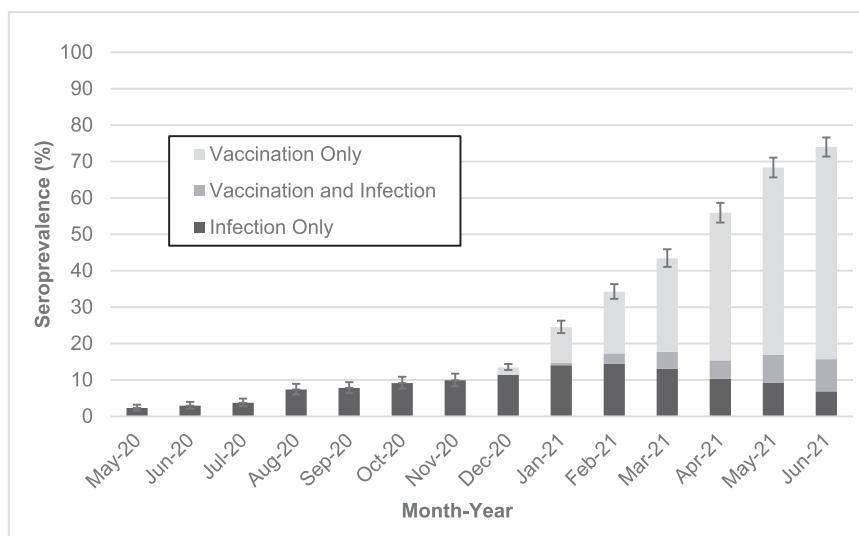
Figure 1. Monthly seroprevalence of SARS-CoV-2 antibody by vaccination/infection status, May 2020−June 2021.
Apr, April; Aug, August; Dec, December; Feb, February; Jan, January; Jul, July; Jun, June; Mar, March; Nov, November; Oct, October; Sept, September.
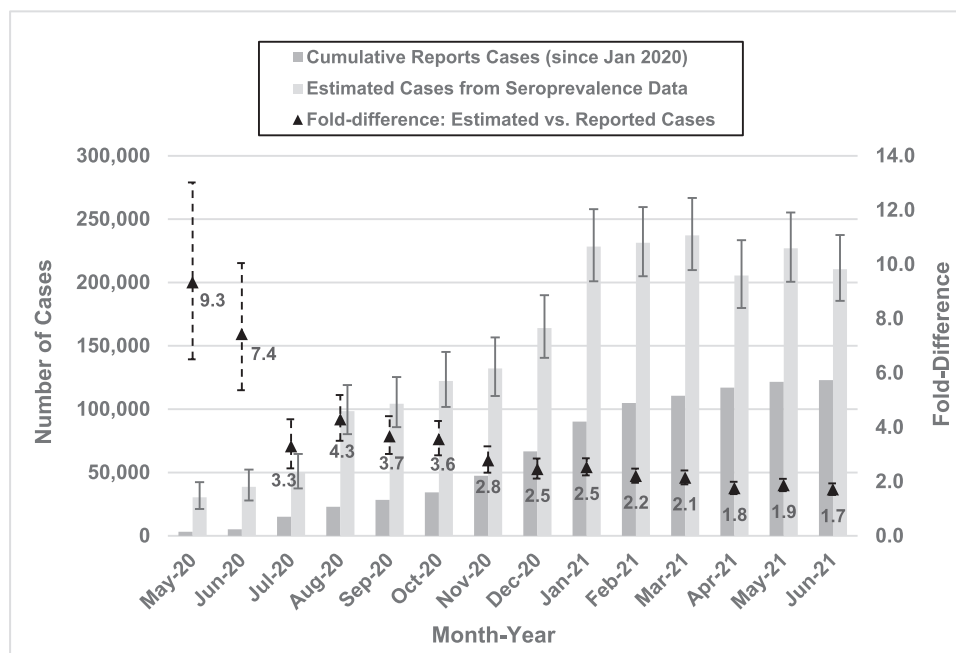
Figure 2. Comparison of seroprevalence estimate of COVID-19 cases with monthly cumulative confirmed cases, May 2020–June 2021.
Apr, April; Aug, August; Dec, December; Feb, February; Jan, January; Jul, July; Jun, June; Mar, March; Nov, November; Oct, October; Sept, September.

this represents an increase in true case detection from 10.7% to 58.8% over the course of the study.

DISCUSSION

In this study, we tested sera from 18,581 active component military service members collected between May 2020 and June 2021 from locations across the U.S., observing a rise in SARS-CoV-2 seroprevalence that estimated a true cumulative COVID-19 case count that was well above the reported case counts at the time. This is the largest serologic study of its kind within a well-described population, and it complements several other cross-sectional seroprevalence studies conducted within civilian populations.[3,4,11] This study was unique in its ability to assess seroprevalence in a population that was simultaneously subject to mandatory case reporting as a means of conducting surveillance for COVID-19, confirming earlier studies that have noted a significant undercounting of cases through traditional means of case detection and reporting.[12–14]

In comparison with data released by the U.S. Centers for Disease Control and Prevention from commercial laboratory and blood donor seroprevalence surveys, the findings in this study show a similar trend in seroprevalence rates in the early phase of the pandemic.[15,16] COVID-19 seroprevalence was comparable with that of the general U.S. population throughout much of 2020, rising on average by 1.6% each month from May to December of that year. This corresponds with a surge of infections that occurred nationwide at that time from November 2020 to February 2021.[17] It also coincides with the introduction of COVID-19 vaccination in the U.S. Seroprevalence in our study population continued to rise at a rapid rate from January 2021 onward, averaging a monthly increase of 9.9% through the conclusion of the study in June 2021. However, this rate of increase was actually outpaced by seroprevalence in the broader U.S. population during this time period, as demonstrated in the commercial laboratory and blood donor seroprevalence surveys conducted by the U.S. Centers for Disease Control and Prevention. The lower seroprevalence rate in our study population than in the U.S. general population from March 2021 onward is likely due to the difference in age characteristics of the 2 groups because both infection rates and vaccination rates were higher among individuals aged >50 years during this phase of the pandemic. Public health measures and prevention strategies dictated by DoD policy are also contributing factors that may have resulted in lower infection rates among U.S. military personnel during this time period. Also of note, after the initial surge of cases observed in December 2020 and January 2021, most of the increase in seroprevalence each month was in individuals who had a history of prior COVID-19 vaccination. This is consistent with findings by Jones et al. that showed a similar trend in seroprevalence among the general U.S.

population.[11] That study, which was conducted among voluntary blood donors from July 2020 to May 2021, demonstrated a rapid rise in combined seroprevalence (both vaccine and infection induced) that began in January 2021, with vaccine-induced seroprevalence becoming the predominant contributor to overall seroprevalence by the conclusion of the study.

Comparison of reported confirmed cases with the estimated cumulative case counts based on seroprevalence findings demonstrated substantial undercounting of true cases throughout the study period. This was most pronounced at the beginning of the study when an estimated 9 of 10 infections went unreported. Although COVID-19 incidence at this time was relatively low, limited availability of testing and incomplete reporting of laboratory results through routine surveillance mechanisms likely contributed to a more pronounced undercounting of cases than was observed later in the pandemic. The difference between reported and estimated case counts narrowed considerably after June 2020 as access to testing improved. Implementation of screening programs later in the pandemic in high-risk settings such as healthcare facilities and recruit training environments as well as policies that required testing of traveling personnel also likely contributed to improved case detection and reporting. Undercounting of cases only showed modest decreases after November 2020, with roughly one half of all cases unreported during the last 6 months of the study period. This is similar to findings by Jones et al., which showed that the estimated number of cumulative infections in November 2020 was 2.4 times greater than the number of reported cases among blood donors in the U.S., eventually decreasing to 2.1 infections per reported case by May 2021.[11]

Limitations

This study is subject to 3 main limitations. First, the fraction of infected or vaccinated individuals (or those with both vaccine and natural infection) who develop detectable SARS-CoV-2 antibodies and the duration those antibodies remain detectable have not been clearly defined to date. Studies have indicated that SARS-CoV-2 antibodies persist in most individuals for up to 9 months and perhaps as long as 20 months after infection.[18−21] Similar findings have been reported in studies investigating antibody response after vaccination, although duration of seroreactivity may be less.[19,22−24] Assuming that a decrease in antibody titers over time is possible in some individuals, the estimate of true to confirmed cases mentioned earlier likely represents a lower limit of the actual ratio. Additional studies on antibody persistence will be necessary to further refine these estimates. Second, this study did not assess the case status of individuals that

were identified as seropositive but instead compared seroprevalence from a random sample with cumulative case reports from the source population. Therefore, this study cannot be used to draw conclusions about variables that may increase or decrease the likelihood of underreporting. Third, the study was conducted in a military population with demographic characteristics that differ from those of the general U.S. population. Nearly all U.S. military personnel are aged between 17 and 55 years and typically are in better health than their corresponding civilian age cohorts. This may limit the ability to generalize findings from this study to the broader U.S. population. However, infection rates are similar among age and sex groups, suggesting that any difference in demographics may not have a substantial impact when generalizing these findings. There are other characteristics unique to the U.S. military (e.g., living conditions, public health policy directives, universal access to medical care) that potentially impact COVID-19 transmission and that may also limit comparison of this study's findings with those from the broader U.S. population.

CONCLUSIONS

This analysis of SARS-CoV-2 seroprevalence within a DoD service-member population demonstrates that reported confirmed case counts substantially underestimated true cases during the first 18 months of the COVID-19 pandemic. Although case detection and reporting improved considerably with the expansion of diagnostic capabilities and the implementation of enhanced screening measures, significant underreporting of cases continued throughout the study period. By capturing the impact of asymptomatic or minimally symptomatic cases that are often undetected through routine surveillance measures, seroprevalence studies are an important addition to the surveillance capabilities of public health authorities and can provide crucial visibility on the full scope of an outbreak when traditional diagnostic modalities are still in development. Additional cross-sectional seroprevalence studies are needed to continue monitoring these trends because further evolution of SARS-CoV-2 may offer new opportunities for the virus to surge again in populations with diminished immunity.

CREDIT AUTHOR STATEMENT

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