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## Serosurveillance and the COVID-19 Epidemic in the US Undetected, Uncertain, and Out of Control

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**The true extent** of the coronavirus disease 2019 (COVID-19) epidemic in the US is unknown. The 3.4 million confirmed cases reported (as of July 15, 2020) likely represent only a fraction of all the infections that have occurred in the US thus far. Limited laboratory capacity and restrictive testing guidelines early in the epidemic resulted in large numbers of undetected incident infections. Approximately 40% of all SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) infections are thought to be asymptomatic,<sup>1</sup> and active surveillance for infections without symptoms is limited even now, nearly 5 months after the first COVID-19 cases were reported in Seattle<sup>2</sup> and Chicago.<sup>3</sup> The true cumulative incidence of infection—a basic but critically important measurement—remains uncertain at a time when communities nationwide are struggling to navigate an ongoing, unprecedented public health emergency, and while apprehensions about the near-term and long-term trajectories of the epidemic loom large.



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The study by Havers et al,<sup>4</sup> published in *JAMA Internal Medicine*, reports the first multisite state- and city-level serosurveillance data on SARS-CoV-2 infection in the US; regions spanned from New York to Washington State and from Minnesota to Utah. In a cross-sectional study that tested residual sera from clinical blood samples that had been obtained for routine testing from March 23 through May 12, 2020, from 16 025 persons from 10 different sites across the country, the authors report estimates for the proportion of individuals with prior SARS-CoV-2 infection (adjusted for performance characteristics of serological testing) ranging between 1.0% in San Francisco and 6.9% in New York City. The estimated total number of infections (extrapolated from the measured proportion of individuals with positive SARS-CoV-2 serologies) was between 6- and 24-fold higher than the number of confirmed COVID-19 cases reported in each location prior to the study.

Responding to the urgent need for data tracking the extent of the COVID-19 epidemic, epidemiologists, medical researchers, and public health officials have in recent months advanced an array of research efforts seeking to measure the cumulative incidence of COVID-19 via serologic evidence of prior infection. These serosurveillance efforts, many implemented as rapid pilot studies using unstructured or convenience sampling strategies, have nonetheless yielded some important, early, and actionable findings.<sup>5</sup> However, these studies are also challenging to interpret because of the limited reliability of some commercially available SARS-CoV-2 serology testing platforms<sup>6</sup> and the limitations inherent to convenience sampling.<sup>7</sup> Convenience sampling, although expedient and logistically less difficult than structured sampling, has numerous inherent biases, limiting generalizability. Virtually all of the early serologic studies have been narrow in scope, focused on specific geographic catchment areas<sup>5</sup> or local cohorts captured via unrestricted, “walk-up” enrollment.<sup>8</sup>

Havers et al<sup>4</sup> provide a substantial step forward in this rapidly changing landscape and an important reference point for contextualizing the profusion of SARS-CoV-2 serosurveillance studies anticipated in coming months. The authors comprehensively describe their data sources, including detailed maps on the geographic distribution of samples obtained in each study location and timelines comparing when sample collection occurred with respect to the epidemic trajectory in each location. This transparent approach provides important

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information for understanding these results in the context of the shortcomings of any seroprevalence study.

Two limitations, discussed by the authors, are important to highlight. First, data collection periods overlapped with active stay-at-home orders, when most medical appointments and elective admissions were deferred. Thus, the outpatient and inpatient populations included in the study are likely not representative of a typical prepandemic cohort; some of the discarded serum specimens from inpatients were likely obtained from patients hospitalized for COVID-19.

Second, timing of data collection in each region (shown in eFigure 2 in the article's supplement) coincides with different parts of the local epidemic curves, some of which were prior to peaks and some during peaks, and occurred when availability of polymerase chain reaction (PCR)-based testing for active infections was still widely variable across study locations. Reported gaps between serology-based cumulative incidence estimates and the number of PCR-detected cases are thus expected to reflect both differences in actual numbers of infections and differences in testing capacity between locations. Even so, this is the first population-based study in the US that elucidates regional variation of undetected SARS-CoV-2 infections.

What do the study results mean for the next phase of the COVID-19 epidemic in the US? First, and most important, the study rebukes the idea that current population-wide levels of acquired immunity (so-called herd immunity) will pose any substantial impediment to the continued propagation of SARS-CoV-2 in the US, at least for now. The size of the epidemic projected through early May 2020 in this study falls far short of the estimated herd immunity threshold of approximately 60% to 70%;<sup>9</sup> 7 of the 10 study locations are currently experiencing substantial, as-yet uncontrolled increases in new COVID-19 cases. These data should also quickly dispel myths that dangerous practices like "COVID parties" are either a sound or safe way to promote herd immunity.

Second, increasing evidence suggests that acquired immunity may be short-lived in some persons with SARS-CoV-2 infection, particularly those with mild or asymptomatic infections.<sup>10</sup> Importantly, whatever protection population-level seropositivity might confer may be less durable than initially anticipated. The results reported by Havers et al<sup>4</sup> also challenge the idea that there is a trade-off between implementing a prompt, effective public health response to the epidemic and acquiring higher levels of population-level immunity that might be protective in the future. As the authors underscore, the vast majority of individuals in all 10 study locations had no serologic evidence of prior SARS-CoV-2 infection, both in locations with relatively contained epidemics (San Francisco) and in those that were affected most heavily (New York).

The study also highlights how active surveillance strategies, deploying widespread PCR- or antigen-based testing to identify those with replicating virus (both clinically evident and asymptomatic), are urgently needed to blunt the trajectory of the epidemic in the US. Large differences between known, reported cases and the serology-based estimates reported by Havers et al underscore how limited PCR-based testing capacity, including both the massive shortfalls that derailed the early

epidemic response and the ongoing lack of testing for active surveillance, have left enormous numbers of infections undetected, circulating in the community, and propagating the epidemic. Recent estimates project that at this point in the epidemic, the US would need to increase PCR-based testing capacity nearly 18-fold, and test approximately 4.3 million people each day, to effectively help suppress further disease transmission.<sup>11,12</sup> While meeting this benchmark will require massive, sustained expansion of laboratory and public health resources, it is difficult to imagine a successful next phase of the epidemic response that does not address the vast numbers of undetected infections still at large in the community.

Comparing the cumulative incidence estimates reported in the study by Havers et al to earlier serosurveillance studies reveals some informative and disturbing discrepancies. Across multiple studies in New York,<sup>8,13</sup> there is wide variance in the reported proportion of individuals with serologic evidence of prior infection. Although part of this variation is certainly attributable to differences in study design, it likely also represents the unfortunate truth that these studies have captured true heterogeneity in cumulative incidence between different geographic areas or populations in New York. Preliminary evidence suggests that differences in daily mobility between neighborhoods correlate to neighborhood-level disparities in cumulative incidence observed in New York City.<sup>13</sup> These differences in mobility patterns likely reflect neighborhood-level disparities in the proportion of residents who have been required to work outside their homes during the epidemic, including frontline workers providing essential services like food service and childcare.

The seroprevalence data should motivate expanded, concerted work to understand the occupational, household, and demographic risk factors that drive apparent geographic, racial, and ethnic disparities in SARS-CoV-2 exposure, which has been a critical gap in the current understanding of its epidemiology. Most important, these findings should drive the implementation of science-based, equity-driven testing strategies that prioritize access and convenience for individuals at high risk for exposure, thereby working to eliminate these disparities.

Measuring the size, extent, and heterogeneity of the SARS-CoV-2 epidemic, and updating these measurements as the epidemic continues to unfold, is a wide-reaching, labor-intensive scientific effort; the study by Havers et al<sup>4</sup> represents substantial progress. Structured, rather than convenient, strategies for obtaining samples or recruiting participants can help enumerate important and still poorly understood biases. Focused studies, stratified across potential determinants of exposure risk, can help delineate and quantify the likely multiple drivers behind observed heterogeneity in cumulative incidence.

Scientists, public health workers, and policy makers will be tasked with extracting meaningful, actionable findings demonstrated in these studies, many that may rely on imperfect or even flawed data sources. This is no easy task, much uncertainty will likely remain, and these data will only be influential in an environment of evidence-based, scientifically driven public health leadership.

## ARTICLE INFORMATION

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