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Developing a National Strategy for SARS-CoV-2 Serosurveys in the United States

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Executive Summary

This document describes the value of serosurveys (antibody studies) for SARS-CoV-2 infections, the different methods by which they can be performed, and the resources required to produce actionable information. It provides recommendations for the US government and states for performing these studies and deriving value from them.

There are now millions of confirmed cases of COVID-19, caused by the SARS-CoV-2 virus, and in the United States, the death toll has passed 100,000. Estimating the prevalence of SARS-CoV-2 infection and recovery is important for decision makers and public health workers at national, state, and local levels. Using these numbers, sound decisions can be made about allocation of personal protective equipment (PPE), mitigation efforts, and, ultimately, vaccine procurement and prioritization. The immediate effectiveness of various public health interventions in limiting virus spread can be assessed and compared, and the true case fatality rate of SARS-CoV-2 infections can be determined. Long-term questions regarding medical sequelae that may require specific interventions can also be addressed.

Serosurveys for SARS-CoV-2 infections are performed using serology/antibody testing (or, equivalently, serological testing), which may be used to identify whether people were previously infected by SARS-CoV-2. It is important to identify these previous infections through serology, because current PCR and other rapid diagnostic tests can identify only the presence of viral material in people who are currently infected. Not everyone who is infected with SARS-CoV-2 will have the opportunity to be tested before the virus is cleared from their bodies, and current Centers for Disease Control and Prevention (CDC) estimates predict that 35% of US infections are asymptomatic.[1] Furthermore, there are still many scientific unknowns about what a positive antibody test means, beyond having a history of infection. There are limited data on reinfections with SARS-CoV-2 after recovery from an initial infection, and emerging studies may be complicated by prolonged viral shedding.[2,3] While immunity is generally assumed after infection, and reinfections have not been confirmed, it is unclear how long immunity will last or what level or type of antibodies correlate with immunity.

Serosurveys require several ingredients to be meaningful, and they need to be carefully designed to include the following: the use of antibody tests with known accuracy levels; samples that reflect the demographics of the population being tested, including underserved populations; and sufficient numbers of samples so that meaningful statistical analysis can be performed. The accuracy of antibody tests currently in use is highly variable, complicating their use for serosurveys. Initially broadly encouraging of antibody test makers entering the market, the FDA imposed stricter controls on the accuracy of antibody tests on May 4 after observing that many of the tests were of poor quality.[4] However, many substandard tests are still in use.

There are several different types of serosurveys. The gold standard is the prospective cohort study, which involves sampling a group of individuals to measure the prevalence of SARS-CoV-2 over time. These individuals are tested for antibodies to SARS-CoV-2 at an initial time point, and these same individuals are followed over time to ascertain the incidence of new immune responses (antibodies) and assess how community prevalence changes over time. In addition, longer term follow-up can also help to identify risk factors for disease and the onset of long-term sequelae, or subsequent health issues. These studies may answer questions about the starting prevalence of disease, the continued incidence of disease, time trends, and correlation with other factors, including lingering medical sequelae.

Another option is a cross-sectional study, which is a snapshot of a population at a given point in time. There is no follow-up involved in cross-sectional studies, which saves time and resources, but they do not give researchers the ability to monitor incidence of new infections over time in a community. Cross-sectional studies can be a good option when the number of people who have been infected to date is needed quickly and the study must be done with fewer resources than a cohort study. Serosurveys may cost several million dollars, depending on the sample size; the cost of tests; the number of individuals needed to recruit, perform, and analyze test results; geographic spread; and transportation and storage of samples, among other factors.

Serosurveys have been undertaken by states, cities, the CDC, and in other nations; available studies are summarized in this report. They have even been initiated by large employers, although publicly available details are scant. Given the many scientific unknowns about antibodies and immunity to SARS-CoV-2, the plethora of inaccurate tests still being used, and the potential for false-positive and false-negative results, it is strongly recommended that antibody tests not be used to justify individual decision making, including work clearance decisions and release from physical distancing. In addition, the use of antibody tests, including for serosurveys, raises the potential for discrimination. For example, the US Department of Defense is currently considering making a history of SARS-CoV-2 infection a disqualifying condition for recruitment, as there may be long-term medical sequelae, and such thinking may motivate other employers to do the same.[5] Thus, many of these studies are ripe for misuse, if applied to individual decision making.

Serosurveys are important sources of information for public health, and this document aims to provide information that can be used as a National Action Plan. There are steps that can be taken to increase their value for public health and decision making, now and in the future:

1. **The US government should create a central repository for serosurveys.** Given the demand for serosurveys for SARS-CoV-2 infection, sharing of information (including methodologies) is important. While some details regarding ongoing serosurveys are available currently, most are announced when they are completed.

Sometimes, only the results are announced without much methodological detail. Providing information in this way deprives opportunities for one state, for example, to learn from ongoing studies in another state. A central repository, similar to ClinicalTrials.gov, would therefore be a valuable resource that could include all serosurveys, including their methodology, timelines, and purpose. Like ClinicalTrials.gov, such a repository could also be an international resource and could provide connections for others interested in initiating their own, similar studies. The CDC or another US Department of Health and Human Services (HHS) agency could host such a site.

2. **The CDC should lead a consistent, standardized effort to perform serosurveys nationwide.** The CDC has the ability to guide the public health system response in state and local health departments. This should be a published, standardized approach that could be shared across health departments throughout the country. While the CDC currently provides a standardized reporting method for SARS-CoV-2 diagnostics, there is no consistent, clear guidance on how this testing is occurring. National coordination of serosurveys would make better use of resources, improve efficiency, and foster harmonization of data. Further, the CDC should provide funding to state and local health departments to perform these serosurveys.

3. **The Food and Drug Administration (FDA), the National Institutes of Health (NIH), the CDC, and the National Cancer Institute (NCI) should release the results of their antibody test validation studies.** Validation of serological tests is critical to ensuring that the tests perform as they are intended, and a lack of validation has led to a patchwork of false positives and false negatives across the country, interfering with estimates of seroprevalence and seroincidence. Currently, tests need only to be internally validated for EUA approval, and outside studies have found discrepancies between the accuracy claimed by the manufacturer and their independent tests. On April 4, 2020, it was announced that the NCI would be initiating such independent validation studies, but no results have thus far been made public. Some results have begun to be listed in the package inserts for various antibody tests, but it is not transparent to the purchasers of tests nor the individuals who have received tests which tests have been independently validated. Given the variable quality of antibody tests, such independent validation is critical.

4. **Large employers and universities that are using antibody tests should be strongly encouraged to register their studies in the central repository.** There is potential for the results to inappropriately inform decision making by and about individuals. This is particularly fraught, because there is insufficient information available about how long immune protection may last, and the quality of antibody tests may lead to many false positives and false negatives. The potential for long-term medical sequelae from SARS-CoV-2 infection adds to this concern. Additional protective measures may need to be taken if discrimination based on SARS-CoV-2–specific antibody status occurs, but the first step is to have transparency that these

tests are being used. Guidance should be released for large employers and universities using antibody tests, including how such studies should and should not be interpreted.

5. **State and local health departments should first focus on serial, cross-sectional serosurveys, followed by longitudinal cohort studies.** Because of budget, time, and resource limitations, cross-sectional studies are likely the most accessible in these initial serosurveys. While a single cross-sectional study provides only a snapshot of a population, serial cross-sectional studies are a way to monitor populations over time. Importantly, state and local public health departments should coordinate to simultaneously conduct cross-sectional evaluations. Each evaluation across the country should be conducted within the same time period, with careful sampling parameters to ensure population representation. The serial evaluations should be scheduled in waves to provide snapshots over time while balancing budgetary and resource constraints. These initial studies should be followed by longitudinal cohort studies to better characterize the spread of SARS-CoV-2, with representative sampling of populations and in-depth data collection of cohorts over time. This will better inform understanding of antibody dynamics and sequelae of SARS-CoV-2 infection. The NIH should provide funding support for such studies, as it has with other diseases.

What is a serosurvey?

A serosurvey shows what proportion of the population has antibodies to the SARS-CoV-2 virus at a particular point in time and thus have been previously infected, even if they did not have symptoms or receive a diagnosis of COVID-19. For the remainder of the document, SARS-CoV-2 infection and COVID-19 are differentiated. The term *SARS-CoV-2 infection* designates the infection of all individuals who have been infected by the virus, whether diagnosed, symptomatic, or asymptomatic. COVID-19 refers to the Coronavirus Disease-2019, which is the set of symptoms associated with a SARS-CoV-2 infection.

Critical to the effort to stem the disease is the monitoring of seroprevalence and seroincidence over time, as ongoing infections of SARS-CoV-2 either accelerate or decelerate in response to human behavior and public health control measures. With a serosurvey, the case fatality rate can be determined, including for specific demographic groups. Better decisions can be made about PPE resource allocation and mitigation efforts. The immediate effectiveness of different public health interventions in limiting virus spread can be assessed and compared. Critical long-term questions about the virus can be answered, including the possibility of medical sequelae years from now that may require specific interventions. While serial cross-sectional studies can track the spread of SARS-CoV-2 infection through the population, only prospective cohort studies performed over the long run can reliably identify long-term sequelae.

Some states have been reporting their antibody testing data mixed with their molecular testing data, presumably in an effort to demonstrate that they are performing many tests.[6] However, this is not a recommended practice and makes it difficult to interpret the data. Serology testing is testing for the body's immune response to a prior infection, while molecular testing (including rRT-PCR and antigen testing) is testing for virus present in an actively infected patient. Serology and molecular tests compare very different markers and timelines of infection; serology is post-infection, while molecular testing will yield positive results only if the patient is currently infected. In addition, the sensitivity and specificity of serology tests is generally lower than those of molecular testing. These defining factors of each type of test mean that the results of each type of test have very different accuracies and applications. Consequently, if the results from both types of testing are combined, then the results have little to no value. Any testing results from a serosurvey must remain separate from molecular test results of patients.

What makes a meaningful serosurvey?

A meaningful serosurvey requires several ingredients to make the results trustworthy: (1) accurate antibody tests; (2) representative sampling of the population, so that the results can be generalizable; and (3) sufficient numbers of participants so that statistics can be accurately applied, resulting in more precise estimates of seroprevalence and seroincidence that can be

compared across subgroups of interest. In addition, some studies may be designed so that they can provide more information than others.

1. Accurate antibody tests

Determining the true prevalence of SARS-CoV-2 infection depends on the use of accurate, reliable serology tests. Most tests will not be able to detect 100% of all cases accurately. While that complicates the value of the tests for an individual (who potentially may have received a false-positive result), the tests may still be valuable when performed for a population, as in a serosurvey, if the test accuracy level is known. Given that the market is flooded with antibody tests that have not been independently validated, the antibody test for a study should be chosen carefully.

The accuracy of the tests is described using the terms *sensitivity* and *specificity*. Sensitivity refers to the ability of a test to detect the true positives of a population, while specificity refers to the ability of the test to show who is truly negative. For serology tests, a "true positive" refers to a sample that contains antibodies to SARS-CoV-2. These measures vary among tests, and the overall accuracy can depend on the prevalence of the infection in the population. Importantly, as testing methods are refined and sensitivity and specificity measures improve, this can potentially have an impact on the results of longitudinal studies. For instance, if the sensitivity of a test improves from 90% to 95% over the course of the study, then it can complicate conclusions from the study. The test would capture more true positives by the end of the study than in the beginning, which could muddle the conclusions over increase in seroprevalence. Any such changes in manufactured tests that are used should be recorded in the methodology of the study. Essentially, an accurate test will have the highest sensitivity and specificity possible. Small variations in either measure can lead to significant false positives and negatives.[7]

For a meaningful serosurvey, the antibody test should have at least 95% sensitivity and specificity as validated with clinical samples. Current FDA guidance stipulates that any tests applying for Emergency Use Authorization (EUA) meet a threshold of 90% sensitivity and specificity, after validation with at least 30 clinical samples. The number of samples tested adds power to the value of sensitivity and specificity: The larger the number of samples tested, the less overall variance in the values and increased dependability on the measure. Establishment of these measures is primarily performed by the manufacturer in a process called "internal validation." While internal validation is valuable for applying for EUA from the FDA, independent validation should be the goal for evaluating diagnostics.

Independent validation bolsters confidence in reported sensitivity and specificity by testing the kit in a new environment with different samples and by different operators. Reproducibility is a tenet of good science and should be evaluated in new diagnostics. Importantly, the FDA, NIH, and NCI should seek to classify a test as a "gold standard"

against which new tests can be measured. For now, EUA molecular testing is the standard for determining sensitivity and specificity of serology tests.

Academic institutions can also play an important role in independently validating these tests. Recent validation efforts have shown reduced sensitivity and specificity in EUA-approved tests compared to the sensitivity and specificity listed by the manufacturer.[8] The FDA has initiated a partnership with NCI and the Biomedical Advanced Research and Development Authority (BARDA) to independently validate serology tests submitted for an EUA.[9] Some independent validation data have been reflected in package inserts for antibody tests. However, the results of these tests have not yet been published. Independent validation efforts should be supported and continued for all tests receiving an EUA, and this should be published so that consumers can make good choices for purchasing tests.

Accuracy of the test also depends on its cross-reactivity, or the test's ability to react to other antibodies or molecules the patient may have in their blood, saliva, or other fluids, or to pathogens related to SARS-CoV-2. There are several circulating coronaviruses in humans that do not cause severe disease, such as HCoV-229E. Many people could have antibodies to these coronaviruses, so a dependable test should be able to detect antibodies specifically against SARS-CoV-2 but not another coronavirus.

As antibody tests were entering the market, FDA guidance was to encourage serology test development. This unfortunately led to fraudulent and inaccurate claims about the accuracy of the tests. The FDA updated their guidelines on serology tests on May 4, 2020, providing quality thresholds for tests applying for an EUA.[10] While there are hundreds of tests available for purchase worldwide, only 15 commercial test kits have been granted an EUA as of June 8, 2020. The FDA has also approved laboratories certified by the Clinical Laboratory Improvement Amendments (CLIA) to perform diagnostic tests, and those that have not been granted an EUA are for research use only. The FDA has allowed CLIA-certified labs to develop tests because of the need for testing resources nationwide. The FDA mandates that these CLIA-certified labs must apply for an EUA within 15 days of notifying the FDA of the test development. These CLIA lab–based tests must also undergo internal validation and clinical validation, which ensures that the test is accurate in laboratory and clinical settings. Many tests that were previously available for research use only have had this approval revoked, including SD Biosensor, Dynamiker, Innovita, and Sensing Self.[11] In several cases, this is because of poor test performance in external validation studies.[12] Tests that are not FDA approved for research use or for diagnostic use fall under subsection IV.D of the FDA's policy on diagnostics. Importantly, many of these tests have likely already been purchased and used in public health efforts or by large employers.[13] Tests that have not received an EUA may suffer from poor sensitivity or specificity, leading to false positives and negatives. These types of tests should not be used in serosurveys; all efforts should be to use EUA-approved serology tests for large-scale studies at this time.

2. Representative sampling of the population

In order to arrive at an accurate estimate of the prevalence of SARS-CoV-2 infection in a target population, it is critically important to sample individuals who are representative of the target population (including underserved populations) and who are not more or less likely to have had SARS-CoV-2 infection. As it is not possible to sample every single person within a population, a smaller group must be sampled, making the selection of a sample group even more critical. Selection of a group to assay should be as random as possible to avoid biases, in contrast to "convenience" sampling, in which a group is sampled based on ease of access (eg, all visitors to a clinic).

The sample selected from the target population should be representative of a population in many different ways, including age, gender, race, socioeconomic status, and relevant underlying conditions. The target population is the total group of individuals from which the samples could be taken, which could be all Americans or more narrowly defined. It should also address the many environments of the overall population, including some individuals from population-dense urban areas, small towns, and rural areas. As researchers design the study and enroll individuals for a serosurvey, they collect information on each of these factors. Then, after the study is completed, outcomes can be associated with each factor so that correlates are identified. For instance, by collecting demographic and gender data, researchers have found that men have a higher risk of severe COVID-19 than women.

Representative sampling is particularly important to understand disease prevalence in underserved populations and, ultimately, to target public health resources and tailor messages to reach those communities. Health disparities in the COVID-19 pandemic have already been observed. While black Americans comprise 13% of the US population, a recent study found that counties with higher populations of black residents accounted for 52% of COVID-19 cases.[14] Native Americans and Alaska Natives have also been disproportionately affected by the pandemic, with the Navajo reservation having the highest per capita rate in the country, despite comprising less than 1% of the American population.[15] Latinx communities are also experiencing negative impacts from SARS-CoV-2 infection, with Hispanic patients making up 12% of COVID-19 cases in Baltimore, for example, despite comprising only 5% of the population.[16] Rural populations also have health disparities and are projected to be disproportionately affected during the pandemic.[17] The LGBTQ+ community has been excluded from demographic surveys in California; the information was not collected, so it is not possible to determine if the LGBTQ+ community has been more or less affected by COVID-19 compared to the average state levels.[18]

It is crucial to include underserved populations in these studies in order to address emerging health disparities during the COVID-19 pandemic and communicate them effectively to each group. According to a June 4, 2020, update to the HHS CARES Act, all diagnostic tests for

SARS-CoV-2 infection must also include demographic information, such as race, ethnicity, and residential zip code.[19] This is an important step in ensuring proper reporting of test results, and such factors should be incorporated in any serosurvey. During the design of a study, partnerships with organizations such as the National Center for Minority Health and Health Disparities (NCMHD) and the Office of Minority Health (OMH) should be pursued. These offices have provided support to past surveillance studies, such as those completed in Louisiana after Hurricanes Katrina and Rita.[20] Recent work at the University of California San Francisco has resulted in a plan for PCR and serology testing in rural communities, with specific recommendations for registering individuals and setting up the drive-through method used.[21]

In addition, community partnerships are imperative for successful surveillance studies. Building these partnerships takes time but has immense benefit in gaining access to these underserved populations and deriving accurate results. This includes studies of Alzheimer's disease in high-risk groups, where active outreach to the community increased recruitment of minorities (including African American and Hispanic residents) by 4-fold.[22]

Previous studies have found that understanding cultural differences, especially regarding trust of healthcare providers and scientists, can improve participation over the course of the study. Gaining and keeping community trust can improve the study outcomes and build partnerships for future studies and interventions. During the study design, it is important to make representation a goal—by defining the proportion of underserved groups needed, or defining the geographic proportions and tailoring recruitment strategies accordingly.[23] In some cases, it is necessary to oversample particular underrepresented groups, and in these cases, it is important to adjust proportions accordingly. Throughout the study, using multiple referral and registration sites in the community can improve recruitment.[24] Efforts should be made to communicate openly with participants and disseminate information during the study, so that trust is maintained and to ensure that participants are having their health needs met. Engaging community leaders can help with this communication.

The sampling should be as random as possible to ensure representativeness and avoid sampling bias, or the skewing of selection of individuals. Random sampling is an ideal for surveillance studies, because the more random a sample, the fewer biases possible. It is important to note that any sampling method could have biases, whether they are related to sampling (is the location accessible only by car?) or to the population itself (in this subpopulation, is the age structure skewed?). These biases should be addressed as much as possible in designing the study. The registration or intake form for a participant should attempt to collect as much demographic information as possible. Then, potential biases can be analyzed once the study is completed. It is important to assess the inherent biases related to the response rates and access methods. For instance, if individuals sampled for past SARS-CoV-2 infection were all selected based on their shopping history at Whole Foods, this would

not be representative of the entire country and would not capture the individuals who shop at less expensive stores. This type of study sampling is called "convenience sampling" and is inherently more prone to creating bias. Studies that use convenience sampling can still provide useful information, but these results must be interpreted carefully in the appropriate context. If individuals were selected by a random phone number generator, this would be highly random and less likely to be skewed by selection biases.

Random sampling methods can still be prone to flaws; for example, phone samples might capture only people who are home at certain times of the day, people who have access to a landline, and people who answer the phone. Because of this and other reasons for differential participation, it is important to ensure that demographics are representative of the overall population. Another challenge is in reaching difficult to reach populations, such as those who are stigmatized or typically underserved—including those who are unstably housed or are incarcerated. These subpopulations may also be disproportionately affected by the disease. For instance, individuals experiencing homelessness in Boston were shown to have a high prevalence of SARS-CoV-2 infection, measured by molecular rRT-PCR.[25]

Random sampling approaches may need to be supplemented with approaches that specifically target such groups through sampling at sentinel sites, social network–based strategies, and other approaches. One such targeted strategy includes respondent-driven sampling, which is often used in HIV surveillance studies.[26] This relies on social networks to inform sampling, and while it is not perfectly random, it allows greater access to vulnerable populations. Therefore, there should be a balance of random sampling when possible, with efforts to include the appropriate proportions of American populations so that any results of the serosurvey are generalizable and relevant to all Americans.

3. Sufficient numbers of participants

For a serosurvey, it is important that a sufficient number of participants are included both to arrive at a precise estimate of prevalence (and potentially incidence) and to have sufficient statistical power to make comparisons across key subgroups of interest (eg, race, age, sex). A too-small sample size will not provide usable results.

When designing a serosurvey, it is important to account for a sample size to be tested that can provide powerful and precise conclusions. Precision is particularly important when the seroprevalence can inform characteristics of the disease, such as case fatality rate. Prevalence is often presented as a proportion (or percentage) that has a confidence interval. The confidence interval is a way of showing the variation around the average: the more precise, the narrower the confidence interval. Sampling a large number of individuals can contribute to greater precision and, consequently, a greater ability to compare averages between different subgroups.

One element that contributes to precision is statistical power. Statistical power refers to the ability of the researcher to reach a conclusion (ie, accept or reject a hypothesis) based on the sample size or number of individuals tested. When researchers provide a conclusion based on data collected, they usually want to ensure that the value is as dependable as possible. This often means that there is minimal variance, or noise, around that value. Briefly, a low sample size generally leads to high variation around the average value of a test. Therefore, it is difficult to reach a conclusion about the sampled population, because there is so much "noise" around the conclusion. Statistical power analyses can be performed *before* a study (with software such as SAS), so that the researchers can ensure they have enough individuals sampled to reach the statistical power needed.[27] There are 3 main elements of statistical power:

1. Sample size: How many individuals are tested?[28]

2. Effect size: How much of a difference between groups is needed to reach a conclusion?[29]

3. Power: What is the probability of finding a meaningful difference between different groups?[30]

These 3 elements interact, with larger effect sizes generally leading to greater power. Larger sample sizes generally give more precise values and are more representative of the population about which conclusions are being made, which also increases the power. Determining values for 2 of these, then, can help researchers determine the third value. While it is tempting to have very large sample and effect sizes, large sample sizes can result in high study costs, and large effect sizes may not be biologically feasible. Consequently, these elements must be balanced when designing a study.

What can serosurveys tell us?

Serosurveys can determine the proportion of the population that has an immune response to SARS-CoV-2. Depending on the type of study, this proportion can be at a given "snapshot" in time, or it can show how immune responses change over time. This proportion of the population that has an immune response can present the true footprint of the virus's spread. Rather than relying on molecular tests, which are time sensitive and will result in a positive reading only if the person is actively infected, serology tests can show us if a person was infected weeks to months ago. Consequently, even a "snapshot" of serology can provide us with significant information on the virus's past spread. This will provide the true prevalence of infection in the population. Then, mortality data can be combined with this true prevalence to determine an accurate estimate of case fatality rates. Serosurveys are important in order for researchers to draw conclusions at the population level on viral spread.

While serosurveys reveal important public health information at the population level, they cannot inform individual health or immune status. At present, the levels, persistence, and memory of the immune response sufficient to protect against SARS-CoV-2 infection are not

well established. The presence of antibodies as detected in a serology test cannot provide reliable individual health information. In other words, the presence of antibodies does not necessarily mean an individual is protected against reinfection.

The results of serosurveys can inform about the path the virus has taken through the population, but they should not be used in campaigns such as those to determine who is fit to work, whether states or counties can reopen, or whether students will be protected from classroom spread. Serosurveys can tell us about the past behavior of the virus, but they cannot predict the future of the pandemic.

Funding of Serosurveys

Serosurveys may cost several million dollars, depending on the sample size; the cost of tests; the number of individuals needed to recruit, perform, and analyze test results; geographic spread; and transportation and storage of samples, among other factors. Surveillance studies of influenza are an example of common surveillance studies in the United States, which require millions of dollars (eg, $3.53 million for 1 project) in funding.[31] HIV epidemics are also monitored through surveillance studies that are funded with hundreds of thousands of dollars (eg, $708,000 for 1 project), with some focusing on novel serology assays to better characterize these vulnerable populations.[32] Many of these studies will likely be funded through the NIH or CDC. Academic institutions have already created testing project funds, such as the Stanford COVID-19 Seroprevalence Studies fund.[33] The type of test used can help to reduce costs; for example, tests that use dried blood spots or finger sticks will likely cost less than those that use venipuncture.[34] In addition, cross-sectional (1-time) studies are likely to be less expensive than longitudinal (follow-up) studies in a given population.

These surveys can collect samples that may be used in future studies, mitigating the up-front cost. Serosurveys will require collection of blood samples through fingerstick, dried blood spot, or venipuncture. These samples could be later used to characterize other factors associated with SARS-CoV-2 infection and in some cases may be preserved. Preserved samples can be used to characterize cell types and responses in a patient. This includes peripheral blood mononuclear cells (PBMCs), which are immune cells that can be later used in research studies to determine reactivity to viruses.

Budget must be carefully considered when designing serosurveys. The priorities of the study should be balanced with cost. For instance, while a sample size of 100,000 might be ideal, the cost of reaching that many individuals could be prohibitive. In addition, there could be increased costs to create multiple registration sites and to involve community leaders to ensure representative sampling. Highly representative sampling may lead to an overall smaller sample size, but the sample taken would be more representative of the entire population. A cost estimate should balance the cost of the tests and associated costs for lab

facilities, healthcare professionals, and other elements of the study. The quality of the study should not suffer because of cost; it is still essential to include underserved populations and at-risk populations and to use appropriate approaches to access these populations.

What are different types of serosurveys?

As with all epidemiologic studies, there are several different designs that one could pursue for a serosurvey, depending on the research questions, resources available, and amount of time available to complete the study. The way in which the study is designed will have a direct effect on how the gathered data can be interpreted. Some study designs may be quicker or cheaper to perform but will not allow researchers to obtain answers to critical questions.

We discuss 2 main sampling methods: random sampling and convenience sampling. Random sampling, as described above, is often preferable, because it reduces the likelihood of bias in the results. This type of sampling can be quick to perform, such as randomly choosing phone numbers. It can also be more carefully designed, as demonstrated by multistage probability design. Multistage probability design, as seen in the National Health and Nutrition Examination Survey (NHANES), involves dividing populations into more manageable subdivisions and then randomly sampling those.[35] Convenience sampling is often easier and cheaper than random sampling and is typically a sample taken from a population already involved in the healthcare system. This includes taking extra serum from previously collected, routine blood samples, blood donations, or samples from pregnant women who have been admitted to a hospital for delivery.[36,37] Table 1 describes the ideal study design based on the question that political leaders, researchers, or funders want to answer.

Table 1. Data that Can Be Generated from Various Types of Serosurveys

What questions are you asking from this study?	Ideal study design to answer that question	Why is this the ideal study design?	What can a non-ideal study design tell you?
What percentage of the population has been infected with SARS-CoV-2 at a specific point in time?	Cross-sectional	Fast, cheap, easy to undertake. Sampling biases may be present, but study should provide a quick, rough estimate of seroprevalence. Biases may also be addressed by careful sampling design, such as multistage probability design or random phone number generation.	If the sampled population is not representative of the target population, rough estimates of seroprevalence can be useful for future research.

How quickly is SARS-CoV-2 infection spreading through a certain population?	Cohort with multiple time points	Sampling the same individuals multiple times allows researchers to establish temporality of new infections compared to starting estimates.	Serial cross-sectional studies could provide snapshot prevalence estimates at different time points, but results cannot be directly interpreted as incidence estimates, particularly if there are major changes in the sample between the 2 time points.
How is the SARS-CoV-2 infection time course different between distinct populations in the same community?	Cohort with multiple time points	Sampling the same individuals multiple times allows researchers to establish temporality of new infections compared to starting estimates. Two separate populations of interest can be observationally compared.	Serial cross-sectional studies could provide snapshot prevalence estimates at different time points, but they still cannot be conflated as incidence estimates. It is more difficult to draw comparisons between different populations if different methodologies and sampling intervals are used.
How is SARS-CoV-2 infection incidence different between 1 community and a similar community in a different state?	Cohort with multiple time points and harmonized protocols between different states	Sampling the same individuals multiple times allows researchers to establish temporality of new infections compared to starting estimates. Two separate populations of interest can be observationally compared against each other when sampling biases between different populations are correctly accounted for.	Cross-sectional studies could provide snapshot prevalence estimates of different areas of the country around the same time. It is more difficult to draw comparisons between different populations if different methodologies and sufficiently dissimilar groups are used.
How is SARS-CoV-2 infection prevalence changing in different parts of the country?	Cohort with multiple time points and harmonized protocols between different states	Sampling the same individuals multiple times allows researchers to establish temporality of new infections compared to starting estimates. Two separate populations of interest can be observationally compared against each other when sampling biases between different populations are correctly accounted for.	Serial cross-sectional studies could provide snapshot prevalence estimates at different time points, but they still cannot be conflated as incidence estimates. It is more difficult to draw comparisons between different populations if different methodologies and sampling intervals are used.

Prospective cohort studies: the gold standard for incidence

For COVID-19, prospective cohort studies involve identifying a group of participants who are assayed for a history of SARS-CoV-2 infection over time. These studies may answer questions about the starting prevalence of disease, the continued incidence of disease, time trends, and correlation with other factors, including lingering medical sequelae. Importantly, prospective cohort studies can inform calculations of the incidence of a disease, which is the proportion of the population who develop antibodies to SARS-CoV-2 infection over a distinct period of time. This is different from prevalence, which is the proportion of a population with antibodies at a single point in time or over a concrete period of time, usually expressed as a percentage of the population. In other words, incidence refers to new cases developing in a certain period of time, and prevalence refers to all cases in a certain period of time, no matter when they developed antibodies. Longitudinal cohort studies that sample a representative population are the gold standard for SARS-CoV-2 infection serosurveys, whenever resources are available, because they provide the most information for current decision making and for future questions. While these studies provide the most information, they are also the most time consuming and expensive. They require continuous follow up with participants over a defined period of time.

Cohort studies will be essential to understand how different factors, temporal or otherwise, contribute to the spread of SARS-CoV-2 through a population. These studies can inform resource allocation, medical practices, and other research related to COVID-19. However, it is important that these studies are based on solid methodology and sampling techniques; if not, conclusions that can be made from the resulting data could be limited. Table 2 describes some key differences between cohort and cross-sectional studies and how their outcomes are influenced by different sampling techniques. These differences are important for policymakers to note, because the study design has a direct effect on what conclusions can be drawn and what messages can be distributed to the public on the results.

Table 2. Advantages and Disadvantages of Study Design and Sampling Methods in Serosurveys

	Random sample (*sample reflective of the target population*)	**Convenience sample** (*easily accessible sample, such as blood donors, incoming freshmen, employees at 1 workplace*)
Cohort (Longitudinal)	May estimate the *incidence* or *prevalence* of disease in the *target* population Time-consuming, but may provide more information on incidence than cross-sectional studies Less potential for bias in results Results can be generalized to the target population	May estimate the *incidence* or *prevalence* of disease in the *study* population, which may not be representative Time-consuming, but may provide more information than cross-sectional studies **High potential for bias in results** **Results *cannot* be generalized to the target population**
Cross-sectional (Snapshot)	May estimate the *prevalence* of disease in the *target* population at one point in time Faster and cheaper than a cohort study, addresses prevalence of SARS-CoV-2 infection, but more limited in the conclusions that may be drawn regarding incidence of SARS-CoV-2 infection. Less potential for bias in results Results can be generalized to the target population	May estimate the *prevalence* of disease in the *study* population at one point in time Faster and cheaper than cohort studies, but more limited in the conclusions that can be drawn **High potential for bias in results** **Results *cannot* be generalized to the target population**

Cross-sectional studies

Cross-sectional studies act as "snapshots" of a population at a given point in time. There is no follow up involved in these studies, which saves resources but does not give researchers the ability to establish incidence of disease spread in a community. Cross-sectional studies can be a good option in cases in which researchers need to know quickly how many people have been infected to date and when the study must be done with fewer resources than a cohort study. Care should still be taken to obtain a representative, and ideally random, sample from the population.

Aside from obtaining 1-time estimates of SARS-CoV-2 infection prevalence, cross-sectional studies can also be used to validate the accuracy of different antibody tests. For example, blood samples obtained from participants in a cross-sectional study could be used to compare

several different rapid diagnostic tests against a gold-standard laboratory-based assay. Using this kind of study, researchers can validate multiple serological tests and obtain prevalence estimates from their study population. These studies are more common in the current COVID-19 literature because they can be executed more quickly than cohort studies.

When researchers define their target population—that is, the group for which they want to obtain information—this group can be as broad or narrow as necessary to provide them answers to their research questions. For example, Major League Baseball recently participated in a cross-sectional serosurvey in collaboration with Stanford University, the University of Southern California, and the Sports Medicine Research and Testing Laboratory.[38,39] The stated goals of the larger study were to assess the prevalence of SARS-CoV-2 infection in metropolitan areas, with MLB volunteering to participate. The MLB portion of the study allowed researchers to compare prevalence in different team locations across the United States. This study included 27 of the 30 teams and more than 5,754 MLB employees, including athletes, concession stand workers, security personnel, office staff, trainers, and others.[40] Approximately 0.7% of this sample was found to possess SARS-CoV-2–specific antibodies, much less than the researchers had anticipated. While these results paint an interesting picture of the employees of a nationwide organization, they are only generalizable to MLB employees, and conclusions cannot be drawn about national seroprevalence. The sample population was not reflective of the general population—men comprised 60% of the study subjects, and 80% of those surveyed were white—so the findings cannot be extrapolated. Further stratifications were not disclosed, but numerous biases (including socioeconomics, age, and preexisting conditions) could influence these findings.

SARS-CoV-2 unknowns that affect serosurveys

SARS-CoV-2 infection is an emerging disease, and there remain significant gaps in knowledge, although researchers are learning more about its characteristics every day. Given the novel nature of SARS-CoV-2 infection, researchers must carefully monitor several components that could affect the outcomes of serosurveys. Some of these unknown components are inherent in the virus itself, while others depend on changing host factors, and still others depend on the quality of the serological test.

Virus mutations

If SARS-COV-2 mutates, particularly in proteins such as the spike protein or nucleocapsid protein, the antibodies that infected people will make in response may be different from those observed in initial studies. It is possible that current tests will not detect patient antibodies after disease. If this situation were to occur, the results could skew toward false negatives in a serosurvey.

Cross-reactivity

SARS-CoV-2 belongs to a large group of human coronaviruses, some of which circulate frequently among human populations but only cause symptoms similar to the common cold. There have been concerns that anyone who previously recovered from one of these milder coronavirus infections might have antibodies that would be similar enough to SARS-CoV-2–specific antibodies to produce false-positive results. Currently, it appears as though there is little to no cross-reactivity between antibodies specific to SARS-CoV-2 and antibodies specific to other known coronavirus infections. However, the potential for cross-reactivity must be carefully monitored going forward, as problems with test specificity could greatly skew serosurvey results.

Timing of the test

If the timing of the serosurvey happens too soon for many of its participants to develop antibodies, then the results of the study could be incorrectly biased toward false negatives. If the serosurvey occurs too late after detectable levels of antibodies have faded, the results of the study could also be influenced by false negatives. Current research indicates that antibodies specific to SARS-CoV-2 begin to appear around 6 to 10 days after symptom onset. In an immune response, there are several types of antibodies that have specific roles. IgM antibodies are the first responders, increasing in numbers early on in infection. Other antibodies, like IgG and IgA, take longer to develop but are more specific and tailored to the infection. The antibody IgM appears to peak around day 12 post-onset and persist until around day 35, when its levels begin to decline. IgG appears to peak around day 17 post-onset and persist for at least 49 days. These current studies are following patients for as long as the study is active. However, research efforts to follow patient antibody dynamics for longer periods, as the pandemic progresses, will be valuable. It is difficult at this time to predict how long these antibodies will last and whether they are at effective levels to provide protective immunity. Performing longitudinal cohort studies where possible can help to offset some of these difficulties of capturing all people who have seroconverted or will seroconvert in response to SARS-CoV-2. Following a study population at different points in time may help capture those whose antibody levels are not yet detectable.

Quality of the test

Any serological test should always be validated against positive controls and maintained in storage according to the manufacturer's instructions to prevent degradation of the test materials. Until independent validation studies are performed, much of the knowledge of test quality depends on what is released by the manufacturer. Tests with high sensitivity and specificity that are properly stored and used are ideal, but aberrations in these could affect serosurveys. For instance, storage of kits at extreme temperatures could affect their performance, which could have a negative impact on the serosurvey results.

How serosurveys are currently being implemented for COVID-19 in the US and globally

Below are examples of serosurveys for COVID-19. This is not an exhaustive list of COVID-19 serosurveys but illustrates the differences in approach and methodology that researchers are using.

Table 3. Case Studies of Serosurveys Currently Being Conducted for COVID-19

	Random sample	Convenience sample
Cohort (Longitudinal)	Spain study (random, representative selection based on province/region population size)	An example might include a college selecting incoming freshmen who visit student health services and following them throughout the semester.
Cross-sectional (Snapshot)	Geneva, Switzerland, study (involved a random sample of people in Geneva who participated in an annual health survey, not representative) Sweden Study (involved a random, voluntary sample of people in Sweden willing to provide samples for antibody testing; testing about 1,200 samples per week over several weeks in spring 2020.)	New York study (sample selected based on customers at certain supermarkets and employees of certain professions) Santa Clara study (recruited through targeted Facebook ads; anyone who saw the ad was eligible to register, but not necessarily eligible to participate. Inclusion in the study was not randomized.) MLB study (all employees of the MLB were eligible for inclusion; not a random sample, but allows for a large sample size)

Spain study[41]
Type: Cohort study, random sample
Scale and scope: National, with weighted representation from all regions and provinces. A cohort of 60,000 people was randomly selected from each region and will include follow up over time.
Results: The overall seroprevalence of IgG is 5%, although in urban areas it is higher (6.4%).
Stratifications: Age, gender, essential versus nonessential worker, comorbidities/preexisting conditions, type of profession
Potential for bias: From the preliminary results, it appears there is undersampling of the 25- to 34-year-old age group. Some regions had more undersampling of this age group than others.

Reunion Island study[42]
Type: Cohort, convenience
Scale and scope: Of 90 individuals hospitalized in March, 20 were followed for 10 to 64 days.

Results: IgG and IgM decrease over time, even in severe cases.

Stratifications: Severe versus nonsevere cases

Potential for bias: There was small sample size, lack of stratifications for age and gender, and the study examined only symptomatic cases.

Wuhan study[43]

Type: Cross-sectional, convenience sample

Scale and scope: 797 healthcare workers, of which 705 were female, who were asymptomatic for COVID-19 were tested for antibodies.

Results: 4.4% seroprevalence in this population

Stratifications: Exposure type, occupation, high-risk operations, gender

Potential for bias: The sampling method included only healthcare workers with intensive exposure to COVID-19 patients, so there may be a higher prevalence in this specific population than the general healthcare worker population. Also, there was a majority of females in the study, which is not reflective of the general population.

Sweden study[44]

Type: Serial, cross-sectional, random sample

Scale and scope: Originally, the study included samples collected from laboratories in clinical chemistry and clinical immunology in 9 regions throughout Sweden. They aim to test 1,200 samples per week. The most recent findings, from May 20, 2020 (week 18), were from 1,104 samples.

Results: In Stockholm, there was 7.3% seroprevalence. Elsewhere in the country, levels were closer to 3% to 4%. The average, across the entire population, was 6.7%.

Stratifications: Age

Potential for bias: While it appears the samples were randomly taken from clinical samples, this is biased toward those giving blood samples in the first place. This could miss asymptomatic cases, or individuals who have not recently sought health care. It also did not stratify, at least in what was published, by gender or any other factor, which could leave out important demographic information.

Germany study (Luebeck)[45]

Type: Cross-sectional, convenience sample

Scale and scope: 162 patients were identified as COVID-19 positive by the local public health authorities, and 110 of these provided written consent to participate and had available blood samples; 51 of these patients had antibodies analyzed at 2 different time points.

Results: 70% of patients with positive molecular tests developed antibodies by 3 weeks post-infection.

Stratifications: Gender, age, disturbance of taste/smell, symptom severity

Bias: The sample size is relatively small and includes only patients who had been molecularly tested for COVID-19. This could exclude asymptomatic cases, or people who did not seek health care because of mild symptoms, or financial reasons.

Switzerland study (Geneva)[46]
Type: Cross-sectional, random sample
Scale and scope: Tested 760 residents of Geneva, randomly sampled from a pool of individuals who had participated in an annual public health survey.
Results: 5.5% seroprevalence
Stratifications: Gender, age
Potential for bias: This excluded those who did not participate in the public health survey, so the results may be skewed to individuals who are aware of or involved in public health research.

New York study[47]
Type: Cross-sectional study, convenience sample
Scale and scope: Initially, tested 3,000 people at supermarkets in New York State. As of April 30, 2020, this was closer to 8,000. Also tested FDNY and NYPD members: 1,000 New York City Fire Department officers and 1,000 New York City Police Department officers from 5 boroughs.
Results: In New York City, there was 21% seropositivity in the general public. Statewide, the seroprevalence was 14%; 17.1% of FDNY and EMT employees tested positive, and 10.5% of NYPD officers tested positive.
Stratifications: Gender
Potential for bias: The grocery store–based study is reflective only of individuals able to go out to the grocery store, potentially reflective of socioeconomic status or social-distancing behaviors, and was not designed to provide representative sampling of the New York population. The FDNY and NYPD study is also biased toward individuals likely encountering the public far more often than an average citizen and may not be reflective of the overall New York population.

Santa Clara study[48]
Type: Cross-sectional study, convenience sample
Scale and scope: Tested 3,300 (3,285 adults and 889 children) by finger prick, RDT assay. Recruiting was via targeted ads on Facebook (this could limit sampling to people with internet access and a Facebook account). They had 2 classes of ads: ads aimed at a representative population of the county by zip code, and specially targeted ads to balance the sample for underrepresented zip codes.
Results: 2.8% seroprevalence
Stratifications: Zip code of residence, age, sex, race/ethnicity, underlying comorbidities, and prior clinical symptoms
Potential for bias: There is potential for bias toward individuals actively participating in social media, excluding those without internet access or social media accounts.

Who is collecting the data from serosurveys?

For the majority of serosurveys, the primary group collecting the data are the researchers themselves. In the context of COVID-19, cases must also be reported to the local department of public health. This is then reported to the CDC through their case report form, which clearly distinguishes molecular test results from serology test results.[49] On May 31, 2020, the CDC stated their intent to perform large-scale serosurveys for SARS-CoV-2 infections.[50] The CDC is also performing community-level surveys and special population surveys.[51,52] They primarily want to use the data to inform their measure of prevalence of SARS-CoV-2 infection in the population and to understand how the virus has spread through populations. At the international level, the World Health Organization (WHO) has also provided guidance on serosurveys for COVID-19.[53]

The community level surveys are in collaboration with local health departments, using "systemic sampling" to identify previously infected individuals in particular communities. An ongoing community-level survey is being conducted in the metro Atlanta area, where US Census Bureau data are being used to randomly sample households. The large-scale population studies began with COVID-19 hotspots that first initially reported community transmission, including Washington, DC, and New York. Today, these studies are expanding to include prevalence studies from blood donors, a type of convenience sampling. In addition, the CDC is partnering with commercial labs to test submitted blood samples in Washington, New York (metro), California, Connecticut, Florida, Louisiana, Minnesota, Missouri, Pennsylvania, and Utah. About 1,800 blood samples that have been submitted for routine tests from each of these 10 areas will be tested every 3 to 4 weeks for antibodies. This is another type of convenience sampling, using previously submitted samples as a way of surveilling the general population.

Serosurveys as one of many public health tools, including contact tracing

Incorporating serosurveys into public health efforts

Serosurveys can provide important information to ongoing public health efforts, such as which populations have higher prevalence of SARS-CoV-2 infection. In order to respond to the COVID-19 pandemic, public health authorities must perform contact tracing, diagnostic testing, and tracking of the spread of SARS-CoV-2 throughout their community to create targeted interventions. Public health is already well practiced in incorporating seroprevalence and seroincidence data into these efforts from experience with other infectious diseases, such as HIV and other sexually transmitted diseases.[54–56]especially at the local level. We combined two population-based data sources to estimate prevalence of diagnosed HIV infection, HIV-associated risk-behaviors, and HIV testing patterns among sexually active MSM in New York City (NYC Seroprevalence estimates from these studies can be used to adjust resource allocation or target certain at-risk populations.

COVID-19 is a nationally reportable disease, meaning that state and local health departments are required by law to report any cases to the CDC. The reporting form for COVID-19 includes demographic information, symptom information, and space to report both diagnostic and serological test results. At the national level, this information can keep public health authorities and policymakers informed on regional trends and levels of testing. It should be noted that this will likely capture only symptomatic cases. State and local health departments can also use this information to inform ongoing contact tracing and to implement targeted interventions to potential hotspots. For these purposes, cohort studies should be conducted with regular testing time points in order to give state and local public health authorities better temporal information on the spread of SARS-CoV-2 infection. If the resources are not available to perform full cohort studies, serial cross-sectional studies can be used to give a rough estimate of these trends.

Serosurveys cannot paint the whole picture

Although serosurveys will be an important component of the ongoing response to COVID-19, they can only provide certain types of information, and the interpretations of this information will vary from study to study. Even a gold-standard random representative sample is only 1 sample for a population; it is necessary to take repeated measures of the same population over time to understand how SARS-CoV-2 infections are spreading. A 1-time serosurvey will miss many people who are early in infection and who have not yet developed antibodies. Some of these people may be asymptomatic, subclinical, or show very mild symptoms that would not otherwise lead them to seek a diagnostic test. Widespread, accessible diagnostic testing must be used in tandem with serological testing to adequately describe the prevalence of SARS-CoV-2 infection.

While there is a hope that high seroprevalence in a population will equate to widespread protection against future SARS-CoV-2 outbreaks or resurgence, there is not enough information on the correlation of antibody development to protective immunity. With this link between antibodies and protective immunity not yet established, serosurveys alone cannot be used to make decisions on reopening businesses or lifting travel restrictions. We must also understand the trends in severity of disease, host factors contributing to disease, development of protective immunity, and best practices to mitigate transmission. While seroprevalence and seroincidence can provide information on some of these questions, other public health and scientific research is required to fill in the gaps.

Workplace serosurveys

As more information on SARS-CoV-2 seroprevalence becomes available, there is increasing interest from private and public workplaces in conducting their own serosurveys. These businesses, large or small, may look to serosurveys as a way that they can be more reasonably assured that a certain percentage of their employees will not transmit SARS-CoV-2. While the research on protective immunity and post-recovery transmission is still developing,

there could be value in conducting workplace serosurveys to collect data now if a correlation between recovery and immunity is established in the future. Currently, it is premature for employers to use the results of serosurveys to draw such conclusions when making decisions on reopening measures.

Unlike publicly funded serosurveys, there is little information available about ongoing workplace serosurveys. There is no central repository where methodologies, study populations, or results can be retrieved. Most information on these workplace studies must be obtained from media reports or company press releases. These formats offer little opportunity for their methods and results to be closely evaluated or reviewed, increasing the chances that a flawed study could be used to improperly influence workplace policies. For example, a study that is biased toward workers whose jobs include more person-to-person interaction might incorrectly report a higher workplace seroprevalence and prematurely reopen their facilities.

It is unclear whether these tests are conducted in conjunction with trained researchers or whether employers simply distributed serological tests among their employees and encouraged or required them to report back their results. Further, employers are not required to declare what answers or outcomes they hope to obtain from these types of studies. Whatever their intended outcomes, serosurveys cannot be used to determine whether or not employees can return to work as normal without also implementing physical distancing and heightened hygiene measures. With low current estimates of disease prevalence in the population (less than 10%), serological tests have a greater risk of false negatives due to the impact of prevalence on test accuracy (positive predictive value). Furthermore, workplaces cannot interpret an employee's seropositive result as a guarantee of protection in either the short or long term.

With little or no oversight from public health authorities or government officials, workplace serosurveys could be misinterpreted or misapplied in a discriminatory way. As more is understood about the implications of antibodies, protective immunity, and medical sequelae following recovery, a seropositive status could be used to discriminate between employees. The Department of Defense is currently considering permanently disqualifying recruits who have a SARS-CoV-2–specific seropositivity.[57] While the final policy is still being revised, some military officials state that the restriction will be only on those who were hospitalized for COVID-19, potentially rendering them medically unable to serve due to the long-term impacts of recovery.[58] Similarly, a seronegative status could also be used in a discriminatory manner to prohibit employees from returning to work where they could potentially take legal action against their employer for workplace exposure. Employees who refuse to participate may also be discriminated against if employers are unsure of their sero-status. Therefore, care must be taken by government officials and public health authorities to prevent discriminatory application of serosurveys conducted in the workplace.

Needs and considerations for local and national serosurveys

Validity of diagnostic tests

Central to the success of any serosurvey is a reliable, validated serology test. For serosurveys in the United States, researchers should select a test with emergency use authorization (EUA) from the FDA. The selected test should have high sensitivity (ideally greater than 95%) to minimize false-negative results. Importantly, in a disease with low prevalence in the population, specificity should be prioritized. While false-positive results would also skew data, current evidence suggests that many of the serology tests with EUA approval have high specificity and exhibit little to no cross-reactivity with other related coronaviruses. Therefore, researchers should focus on optimizing sensitivity, particularly while SARS-CoV-2–specific seroprevalence is still quite low. Sequential testing also presents an opportunity to ensure accuracy of serosurveys. The first test, with high sensitivity, would capture many of the positive cases. The second test, with high specificity, would exclude the false positives of the first population identified. There is also an opportunity to cross-validate different serology tests using blood samples from the same study participants. Studies with this addition could contribute valuable information to the growing pool of available serology tests.

Balancing need for information with careful design of studies

In designing the serosurvey, there must be a balance of careful, forward-thinking study structure with efficient undertaking of the study. State and local governments will be under pressure from constituents and businesses for data on seroprevalence, which will lead to time constraints. Surveillance studies must be implemented as rapidly and as responsibly as possible. Balancing the priorities of timeliness and data collection can be addressed in the type of study design used. For a study with priorities of rapid data collection and analysis, a cross-sectional study may be preferred. Given that this is a single time point of collection, the quality of data should be prioritized. Consequently, a quantitative serology test (such as an ELISA) would be beneficial in providing immediate information on the presence or absence of antibodies in the population. It could also provide the quantities, or titers, of antibodies that could be useful in future studies once protective immunity thresholds have been better established. On the other hand, a longitudinal cohort study would require extensive time, tracking of subjects, and follow-up screening. In this case, given a limited budget, a qualitative test (such as an RDT) may be preferable.

The study design can also be affected by the funding mechanisms or hosting institutions. Cross-sectional, budget-friendly studies may be favored by state and local health departments. This would focus the need for staff and volunteers to a single time of data collection. In addition, this would provide the corresponding government authorities with data to share with constituents in a shorter time frame. Academic and industry institutions,

however, could focus on more time- and research-intensive cohort studies. These may have greater funding mechanisms, as well as students, researchers, and principle investigators who could invest more time in the follow-up necessary for such studies.

Work with community leaders for better integration of testing

As outlined above, representative sampling is crucial to ensure that the results of a serosurvey accurately portray the true level of disease within the community. Even a perfectly designed study is reliant on the responsiveness of potential participants. Some populations may require more strategic planning than others during the recruitment phase to ensure their participation. For example, undocumented immigrants may be hesitant to participate in serosurveys because of language barriers or distrust of government. Still, it is important to incorporate these populations into SARS-CoV-2 infection studies in order to understand the true landscape of disease prevalence. Researchers should work with community leaders to ensure that all community members have equal access to participate in the study and to increase their willingness to participate. Trusted community leaders should ideally be invited to help in the design of recruitment materials and strategies in order to maximize community participation.

Prepare a communication strategy for accurate interpretation of results

It can be easy to over-interpret the results of a serosurvey. With the weight of potentially important economic and public health decisions resting on the answers to tests, it is crucial for researchers and political leaders to develop clear communication strategies to deliver accurate interpretation of results. Communications strategies should contextualize the seroprevalence and seroincidence results, describe how the results can and cannot answer certain questions, and include appropriate language to convey potential biases.

How can political leaders promote meaningful serosurveys in their communities?

Political leaders must become public health advocates as the pandemic continues to affect the nation. Given the multiple considerations for choosing serology tests, designing serosurveys, collecting data, and engaging with communities, the following steps are recommended:

The US government should create a central repository for serosurveys.
Given the demand for serosurveys for COVID-19, transparency and availability of data should be a priority. For studies important to public health, such as clinical trials, the research proposals and funding information are often available. This includes sites such as ClinicalTrials.gov, which provides essential information about study design, recruitment, and organizations performing the research. Having a clear repository such as this for SARS-

CoV-2 serosurveys would improve the current landscape of conducting such studies. While certain details regarding ongoing serosurveys can be made available through press releases, most are announced when the studies are already completed. In addition, only the results are announced without much methodological detail. Providing information in this way deprives opportunities for 1 state, for example, to learn from ongoing studies in another state. This can lead to overlapping studies that may be answering the same question or examining the same population. Such overlap would waste precious resources and the time of researchers and participants.

A central repository, similar to that found in ClinicalTrials.gov, would be a valuable resource to include all serosurveys, including their methodology, timelines, and purpose. A systematic method of entering data on serosurveys would then allow studies to be easily compared and could also allow individuals to access serosurveys in their area. It could also identify research gaps, such as a lack of longitudinal studies in a particular region. This could inform local research decisions on study design. It may also provide federal funding sources, such as the NIH, a clear list of current research to enable decisions on grant distribution. Like ClinicalTrials.gov, such a repository could also be an international resource and could provide connections for others interested in initiating their own similar studies. The CDC or another HHS agency could host such a site.

The CDC should lead a consistent, standardized effort to perform serosurveys nationwide.

Right now, states are designing and initiating their own studies, but having a consistent protocol for carrying out serosurveys would make findings more valuable. The benefit of a shared protocol is in comparable results; taking similar steps to stratify demographic information, using similar serology tests, or using similar sampling methods will allow results of different studies to be more accurately compared. Steps can be followed that give the study more statistical power and meaning. The WHO has already published a guidance document on sero-epidemiologic studies, including study design and reporting of results. The CDC should provide such guidance in the United States.

The CDC has the ability to guide the public health system response in state and local health departments. This should be a published, standardized approach that could be shared across health departments throughout the country. While the CDC currently provides a standardized reporting method for SARS-CoV-2 diagnostics, there is no consistent, clear guidance on how this testing is occurring. National coordination of serosurveys would better utilize resources, improve efficiency, and foster data harmonization. Further, the CDC should provide funding to state and local health departments to perform these serosurveys. The CDC could provide financial support for initial cross-sectional studies. As resources become available, the NIH should also help fund longitudinal cohort studies that will inform understanding of serology over time. These time- and resource-intensive longitudinal

studies could be led in select representative states, potentially in collaboration with academic institutions.

The CDC has already begun community and large-scale serosurveys and would be an excellent resource for such protocols. This would allow state and local health departments to consistently collect data associated with serology tests. The CDC is currently working with many state health departments; consequently, providing a common protocol now would provide the CDC with more translatable data in the future. In addition, states could coordinate with local health departments to provide clear guidance on serological testing methods, as well as handling local citizens' questions regarding the purpose of the studies. Maintaining clear messaging that these studies provide information about past infection and the spread of the virus, rather than providing individual information on immunity status, is important in moving forward with these studies at the state and local levels.

The FDA, NIH, CDC, and NCI should release the results of their antibody test validation study.

Validation of serological tests is critical to ensuring that the tests perform as they are intended, and a lack of validation has led to a patchwork of false positives and false negatives across the country, interfering with estimates of seroprevalence. Currently, tests need to be internally validated for EUA submission. Upon EUA submission, the manufacturer now must also submit the test for independent validation through institutes such as the NCI. Currently approved tests must also submit their kits for independent validation. Outside studies, typically in academic settings, have found discrepancies between the accuracy claimed by the manufacturer and their independent tests.

On May 4, 2020, it was announced that the NCI would be initiating such independent validation studies, but no results have thus far been made public. While the FDA has posted selected results on their serology testing website, it is not clear if these results are from the manufacturer or from the NCI. The FDA recently listed a select number of these independent validation results, although only 2 of the 18 EUA tests are listed.[59] This is an important first step in organizing and publishing these data. Some results have begun to be listed in the package inserts for various antibody tests, but it is not easy for the purchasers of tests nor the individuals who have received tests to see which tests have been independently validated. The benefit of publishing these results would far outweigh the effort needed to add this data to the website. The NCI is generating this valuable data, which could be useful in determining the dependability of tests when designing serosurveys. Therefore, it would be reasonable and beneficial for the FDA to add a separate column or website for the values generated by the independent validation studies. Given the variable quality of antibody tests, such independent validation is critical.

***Large employers and universities using antibody tests should be strongly
encouraged to register their studies in the central repository.***
There is potential for test results to inappropriately inform decision making by and about
individuals. This is particularly fraught because there is insufficient information available
about how long immune protection may last, and the quality of antibody tests may lead to
many false positives and false negatives. The potential for long-term medical sequelae from
COVID-19 disease adds to this concern. Additional protective measures may need to be taken
if discrimination based on SARS-CoV-2–specific antibody status occurs, but the first step is
to have transparency that these tests are being used. Guidance should be released for large
employers and universities using antibody tests, including how such studies should and
should not be interpreted.

Beyond these high-level recommendations, political leaders and public health authorities
should focus on quality study design, continuing research into the immune response in
SARS-CoV-2 infections, and working with vulnerable populations.

***State and local health departments should first focus on serial, cross-sectional
serosurveys, followed by longitudinal cohort studies.***
Because of budget, time, and resource limitations, cross-sectional studies are likely the most
accessible in these initial serosurveys. While a single cross-sectional study provides only a
snapshot of a population, serial cross-sectional studies provide a way to monitor populations
over time. Importantly, state and local public health departments should coordinate to
simultaneously conduct cross-sectional evaluations. Each evaluation across the country
should be conducted within the same time period, with careful sampling parameters to
ensure population representation. The serial evaluations should be scheduled in waves to
provide snapshots over time while balancing budgetary and resource constraints.

These initial studies should be followed by longitudinal cohort studies to better characterize
the spread of SARS-CoV-2, with representative sampling of populations and in-depth
data collection of cohorts over time. This will better inform understanding of antibody
dynamics and sequelae of SARS-CoV-2 infection. The NIH should provide funding support
and guidance for such studies, as it has with other disease studies. These studies may be
performed by academic institutions, which have experience in such time- and resource-
intensive studies. Questions related to serology to be addressed include the rate of false
positives of individual tests, antibody neutralization capacity, the possibility of reinfection,
and duration of immunity. The research strategy should include longitudinal studies to follow
SARS-CoV-2 infection survivors and people who are seropositive but never develop disease.
These questions are currently under study by various laboratories or groups, but there is a
lack of coordination and national leadership directing the research. Guidance from the NIH
would be valuable in systematizing the methods and data collected from each study across
the country.

Conclusions

This document describes the importance of performing serosurveys for SARS-CoV-2 infections as a tool for public health and provides information on the resources needed for these studies and how the US government can effectively implement serosurveys. Serosurveys can generate valuable data on the true prevalence of SARS-CoV-2 infection that can better inform public health decisions at a population level, such as PPE allocation. The US government should take this opportunity to lead these serosurveys to ensure that resources are used efficiently, and the data collected can be used to improve the public health of Americans in the future.

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