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Mini Review

Covid-19 Serosurveillance. The map and the territory

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ABSTRACT

The spread of the COVID-19 epidemic is unprecedented. Community data on COVID-19 are urgently needed to understand the extent, dynamics of transmission, sociodemographic and environmental variables associated. Seroprevalence studies allow to know the frequency and distribution of the infection, regardless of the appearance of symptoms, as well as the evolution of the Serosurveillance by means of successive surveys. But serological tests for COVID-19 are characterized by high risk of bias and heterogeneity; estimates of sensitivity and specificity are unreliable and had limited generalizability to populations. Tests with low specificity give more false positives than true positives in low prevalence settings, resulting in unacceptably low positive predictive values. Furthermore, differences in study methodology, viral load, clinical severity, intrinsic health of the study population, and several other potential confounders likely explain the variability between populations. Distribution of seroprevalence is very uneven geographically. Although it seems evident that in general seroprevalence is not high (from 5% or less to a maximum that could be around 20%). Group immunity, with exceptions, seems to be far away. Population is still susceptible to infection, and that antibodies can decline quite rapidly. Periodic survey rounds should continue to monitor trends. Serosurveys are an indicator of a much broader response to infection that can lead to immunity; furthermore, they should serve to help develop and implement social measures on the living conditions to avoid the development of infections. In short, we began to have "maps" but we still do not know the "territory."

Keywords: COVID-19; SARS-CoV-2; Seroprevalence; Surveillance; Epidemiology; Public Health Practice.

Introduction

In late December 2019, reports of a mysterious pneumonia emerged in Wuhan, China, a city of 11 million inhabitants in the southeast province of Hubei. It was later determined that they were caused by a new coronavirus, the SARS-coronavirus-2 (SARS-CoV-2), a primarily zoonotic virus. The WHO announced on February 11, 2020 that the official name of the disease was coronavirus disease 2019 (COVID-19).Since the start of the epidemic on the date of this report, more than 21 million reported cases have been reached worldwide and more than 700,000 people have died, making it the worst public health crisis in a century [1-6].

Despite these, a number of important properties of the virus are still not well understood, and population or community data on COVID-19 are urgently needed to help understand the extent, dynamics of transmission, and effects of the pandemic [7]. Furthermore, even less analysis has been conducted on socio-demographic and environmental variables associated with the infection of COVID-19 [8].

The reverse transcription polymerase chain reaction (PCR) to detect viral RNA is the most sensitive method for early identification of COVID-19. However, it is not a suitable tool for use in retrospective mass screening [9]. Additionally, official data on the number of people who were infected has not been available, and the official estimates are severely limited by:

- Data is not collected uniformly at the national level and there are substantial delays in reporting and aggregation of data, as well as marked discrepancies in how cases and deaths are counted.

- The availability of diagnostic tests of PCR remains limited, being carried out in many places only in severe cases in hospital patients. Therefore, the confirmed incidence / prevalence based only on positive PCR tests for COVID-19 does not reflect the true underlying prevalence in a population [10-11].
- PCR clinical symptom-based do not identify asymptomatic or minimally symptomatic individuals who may not seek medical attention, and who may represent a significant proportion of community spread [12].

Thus, seroconversion is the preferred standard for retrospectively detecting SARS-CoV infection [13]. In this scenario, this article, which is a mini-review and a personal view, aims to reflect, conceptualize, and summarize the results of the COVID-19 Serosurveillance studies.

Methods

Literature revision was based on a non-systematic or opportunistic search for information, considering the bibliographic references of selected articles, reviews of books related to the topic and searches on the Internet. The comments in this article should be considered as a personal point of view, based on the author's experience and the review cited above.

Discussion

Serosurveillance Surveys

Serosurveillance surveys are cross-sectional descriptive studies in which blood is collected from a representative sample of the population, in order to estimate the seroprevalence of antibodies, antigens and / or immune complexes. Serosurveillance provides estimates of antibody levels against infectious diseases and is considered the gold standard for measuring population immunity due to infection. The seroprevalence studies allow knowing the frequency and distribution of the infection, regardless of the appearance of symptoms, as well as the evolution of the Serosurveillance by means of successive surveys. They also make it possible to identify population groups with a higher risk of becoming ill because they have a higher proportion of susceptible and generate hypotheses according to clinical-epidemiological and socio-demographic variables [14, 15]. In addition, they complement the notification, hospitalization, mortality, and immunization coverage data when it exists [16]. Consequently, it can be accepted that in order to understand the true incidence of SARS-CoV-2 infection, representative population studies of the community are required to allow a more accurate estimate of all infected persons.

However, serological tests for COVID-19 have been available a short time ago, including some marketed for use as rapid, point-of-care tests. Their pace of development has, however, exceeded that of rigorous evaluation, and important uncertainty about test accuracy remains. A recent systematic review and meta-analysis to assess the diagnostic accuracy of serological tests for SARS-CoV-2 infection found that these were characterized by high risk of bias, heterogeneity, and estimates of sensitivity and specificity were unreliable and had limited generalizability to populations [17].

A first prerequisite for the use of serology to measure the extent of the COVID-19 circulation is to understand the kinetics of antibody development in people infected with SARS-CoV-2. Antibody tests are likely to have a useful role in detecting a previous SARS-CoV-2 infection if used 15 or more days after the onset of symptoms. Therefore, there is no absolute certainty about the usefulness of these tests for seroprevalence studies for public health management purposes [18]. Tests measure IgM or IgG antibodies, but IgM antibodies may not develop at all, and IgG antibodies generally do not develop until later in the disease process. Therefore, the use of such tests to diagnose COVID-19 will bypass some infections, depending on when the test is performed [19]. Furthermore, antibodies can "disappear" in a certain number of people after infection (seronegativization) [20]. On the other hand, although antibody-based tests are receiving increasing attention, it is not yet known whether or not positive results will indicate immunity to re-infection [21, 22].

In addition, it must be remembered that sensitivity and specificity are not intrinsic characteristics of the test. Sensitivity and specificity also depend on the prevalence of the disease; when the prevalence is low, the positive predictive value of the test decreases, and there will be more false positives and fewer false negatives [23].

It should be considered that asymptomatic cases are also contagious, so detection of asymptomatic or subclinical SARS-CoV-2 infection is critical to understanding the overall prevalence and potential for COVID-19 infection. This is one of the arguments for conducting seroprevalence surveys [24]. But it is suggested that asymptomatic individuals have a weaker immune response to SARS-CoV-2 infection. The reduction of IgG and neutralizing antibody levels in the early convalescence phase could have implications for immunity strategy and serological studies [25]. All these factors make it uncertain the usefulness of seroprevalence studies for public health management purposes. In any case, immunological studies could give us an idea of the true infection rates in the community.

Preliminary data from Serosurveillance studies

The first studies of the number of cases in the community of various European countries begin to be published. Now, several hospitals, health institutions and regional governments around the world have launched studies to find out what part of their populations or professionals have been able to pass COVID-19. Here, it is necessary to remember that the only current rationale for testing large-scale SARS-CoV-2 antibodies is for research purposes, including public health surveillance to inform epidemiology, not for individuals considered independently. However, such epidemiological surveys of seroprevalence should be done through carefully designed studies with clear objectives, sampling frames, inclusion criteria, and consent procedures. Without this framework, it will be difficult to interpret the results and its applicability will be uncertain [26].

These data, usually, show the number of participants who have had COVID-19 (the prevalence) and are becoming available in many developed countries. But reliable data is lacking for many places, like African nations (some governments are reluctant to recognize epidemics or expose their ruined health systems to external scrutiny; other nations simply cannot perform meaningful tests because they are so devastated by poverty and conflict) [27].

The results of the seroprevalence studies (evidence of antibodies against SARS-CoV-2) carried out so far, show variable results according to the geographical location, the population included (general population, health center workers, etc.) and the time phase of the COVID-19 outbreak. Additionally, many seroprevalence

studies are preliminary, unpublished in journals where they undergo scientific reviews, and have differences between methodologies and approaches. Consequently, no definitive conclusions should be drawn hastily. It could be said that these studies show a "map" of the pandemic that, although in some way it is a representation or translation of the true "territory", it can cause some confusion.

In this way, some data referring to the start of the pandemic (since some countries, after the initial outbreak and the suspension of the confinement measures imposed, are currently facing news outbreaks or directly a second wave of infections) are: In Wuhan the prevalence varied between 3% -4%; in Los Angeles, 5%; in New York City from 7% to 14%; in Maryland (USA) 4.2%; in Indiana (USA) 2.8%; in Gangelt (Germany) 16%; in Geneva (Switzerland) 10%; , the 17% of people in London and 5% of people elsewhere in the United Kingdom; in Spain 5%; in Nembro and Alzano (Bergamo, Italy) 60%; in healthy blood donors in Milan 5% -7%; in northern European countries from 2% -7%; in France 4%; the 6% of residents of Saint Petersburg (Russia); in Tokyo (Japan) 4%; In India the 1% of population; in Brazil from less than 1% in many cities in the southern and central-western regions to 25% in the Amazon. Etc. [28-30].

On the other hand, randomized tests yield much higher prevalence estimates than estimates based on non-randomized tests or on reported cases; some prevalence studies have used select subpopulations or non-random samples, both of which have limitations with respect to generalizability. Although, it is probably that random and non-random sampling provide important information on the prevalence of the disease [30].

Within the confusion of these figures, justified by all the aforementioned confounding factors, it could be said that they indicate, as expected, an actual number of people who have had COVID-19 that is much greater than the number of confirmed cases with PCR. Actual cases may be between 6 and 24 times higher than reported, but we are still a long way from herd immunity (28, 31). Although some experts have pointed out that there are certain areas of the world that would be awfully close to achieving group immunity or herd immunity. This is the case of certain neighbourhoods in Madrid (Spain), northern Italy or New York City (USA), where it is estimated that "there are immunology studies that suggest the existence of a natural immunity to SARS-CoV- 2 in many people "[32].

Furthermore, the herd immunity threshold required to prevent a resurgence of SARS-CoV-2 is widely believed to be greater than 50% for any epidemiological setting. But herd immunity can be greatly reduced if a fraction of the population is unable to transmit the virus due to innate resistance or cross-protection from exposure to the effects of seasonal coronaviruses.

This help explain the large degree of regional variation observed in seroprevalence and suggest that sufficient herd immunity may already exist to substantially mitigate a potential second wave [32].

The "Map and the Territory"

Map-territory relationship describes the relationship between an object and the representation of that object, similar to the relationship between a geographic territory and a map of it. And it should be noted that "the map is not the territory" [33]. In addition, moving a little beyond the "map" of the seroprevalence survey figures and their methodological limitations, there are other limitations. The "territory" is not only an environment characterized by its physical geography, the landscape, and the biotic and abiotic elements of nature present in it. It is a scenario that is built from historical, social, cultural, economic, political, and environmental relationships, configuring a context where life, health, disease, and death beats and where contradictions and conflicts are expressed [34]. The map is a bird's eye view: it allows us to see the populations or communities we need to focus on, the gaps in healthcare, and the effects of programs instituted to address them. The territory is the lived experience of illness of the individual. If we are to be healers as well as technicians, at some point we have to put aside our maps and walk hand in hand with our patients through them [35, 36].

So, some, if not all, minorities are more negatively affected than the general population, although this higher overall infection rate can be multifactorial and difficult to understand and resolve precisely [30]. Risk of COVID-19 infection is higher among groups already affected by health disparities across age, race, ethnicity, language, income, and living conditions. Health promotion and disease prevention strategies should prioritize groups most vulnerable to infection and address structural inequities that contribute to risk through social and economic policy [8].

Conclusion

The spread of the COVID-19 epidemic is unprecedented; the pandemic has spread at high speed throughout the world in a short period of time. Unfortunately, there is no medical treatment or vaccine available against coronavirus infection. It can only be mitigated and so, epidemic curve flattens out. Only public health measures proven over time can help prevent the spread of the virus. Contain the source of infection, block transmission channels, and protect the susceptible population [37]. Furthermore, it is likely that the world is in the early stages of this pandemic, that the majority of the population is still susceptible to infection, and that antibodies can decline quite rapidly. Periodic survey rounds should continue to monitor trends [38].

Despite different approaches to acquiring herd immunity (for example in Sweden), however, until now, levels of exposure and immunity have been difficult to determine. What is evident from measurements taken in different populations is the geographically "highly uneven distribution", with exposure levels ranging from a small percentage to around 30% or more. Any measurement that we try to take by taking a random sample of the population is very easily biased in one way or another [39].

It is clear that nowhere is the prevalence of IgG seropositivity high (the maximum is around 20%) or convincingly increasing over time. This is especially clear in Sweden, where the authorities publicly predicted a 40% seroconversion in Stockholm by May 2020; the true seroprevalence of IgG was around 15%. Differences in testing methodology, viral load, clinical severity, intrinsic health of the study population, and several other potential confounders likely explain the variability between populations [40].

In any case, Serosurveys is an alternative way of estimating the population of individuals infected during a recent outbreak, and although these have provided a tentative "map" of the possible scale of the outbreak, there is still much uncertainty about the true number of COVID-19 infections, and the information they have given is partly confusing, its validity is not really known, and finally it has limited usefulness regarding the knowledge of the "territory"

of COVID-19. Caution is required if serological tests for COVID-19 are used for clinical decision-making, epidemiological surveillance, or public health [17].

Unfortunately, we do not yet know what the presence of detectable antibodies means, either for an individual or for a population, how long it will last or how much serological variation to expect between different groups, such as those who had an asymptomatic infection. A single serological test is unlikely to provide the kind of reliable and accurate information needed to fully understand the current pandemic. Tests with low specificity give more false positives than true positives in low prevalence settings, resulting in unacceptably low positive predictive values. To overcome the poor performance of a single serological test, an algorithm combining two or more tests should be considered. For example, in a 5% prevalence setting, screening with one of the more sensitive test (96.0% sensitivity, 99.2% specificity) and then using a more specific test (85.0% sensitivity, 100% specificity), the confirmatory test would increase the positive predictive value from 55% to 100%. Such an algorithm would still not identify antibodies in samples collected within the first 14 days of onset of symptoms and would require follow-up testing at a later date (more than three weeks after onset of symptoms) [41].

In the context of immunity, Serosurveys skim the surface; they are an indicator of a much broader response to infection that can lead to immunity. A full understanding of immunity requires knowledge about the differences in susceptibility to infections, innate immunity, the quality and functionality of antibodies, and the involvement of B cells and T cells in people with different degrees of disease, sex, ethnicity and ages. The key outstanding questions are the longevity of immune responses, the role of pre-existing immunity from exposure to seasonal coronaviruses, and whether or not there is potential for escalation of antibody-dependent disease. The surveys here provide only a start to answering these questions [8]. Furthermore, Serosurveillance studies should serve to help develop and implement social measures that have to do with interventions on the living conditions that favour the development of infections. In short, we began to have "maps" but we still do not know the "territory."

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