MEDWIN PUBLISHERS
Committed to Create Value for Researchers

Epidemiology International Journal
ISSN: 2639-2038

Uncertainties in Preliminary Seroprevalence Estimation of Sars-Cov-2. Looking at the Whole Covid-19 Iceberg. Implications for General Medicine

Turabian JL*

Specialist in Family and Community Medicine, Regional Health Service of Castilla la Mancha (SESCAM), Spain

***Corresponding author:** Jose Luis Turabian, Health Center Santa Maria de Benquerencia. Regional Health Service of Castilla la Mancha (SESCAM), Toledo, Spain, Email: jturabianf@hotmail.com

Review Article

Volume 4 Special Issue 2

Received Date: September 01, 2020

Published Date: October 01, 2020

DOI: 10.23880/eij-16000S2-008

Abstract

A series of circumstances make it difficult to assess the preliminary results of seroprevalence of COVID-19: the methodological differences, the sampling biases, the problems of precision and reliability of the tests, the variation in prevalence according to the time phase of the outbreak, and the possible loss of antibodies over time since infection. Despite this, the first data indicate that the observed seroprevalence is quite similar in many countries and cities in the world, and can be between 2-3% and 10-15%. These figures indicate that, as expected, the actual number of people who have had COVID-19 is much greater than the number of cases confirmed with the Polymerase Chain Reaction test. However, the infections are not massive, and most of the populations do not have antibodies; herd immunity is far from being achieved, in the case that immunity is effective and long-lasting. So, the march of the coronavirus through the population has just begun.

Furthermore, regardless of doubts about the precision of the tests, with a probable low prevalence of COVID-19, the positive predictive value of the seroprevalence test decreases and there will be more false positives, which is erroneously increasing the prevalence value found. These data may indicate increased risks from the second wave of the pandemic. Currently, de-escalation of the containment measures will lead to new cases, outbreaks and contacts: only 5-10% of the SARS-CoV-2 iceberg has been made visible so far. This implies that general practitioners must be prepared to attend to new patients in these outbreaks: strong epidemiological information systems, tests, maintenance of telecare in consultations, use of personal protective equipment, contact tracing, etc., until the existence and availability of vaccines, in addition to maintaining care for new health problems and continued care for chronic non-COVID-19 problems.

Keywords: Coronavirus; COVID-19; SARS-CoV-2; General Practice; Epidemiology; Infectious Disease; Outbreak Modelling; Acute Respiratory Infections; Population Surveillance/methods; Public Health Practice

Introduction

In late December 2019, reports of a mysterious pneumonia emerged in Wuhan, China. 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). On March 11, the WHO declared the global pandemic. Since the start of the epidemic, on the date of this report (August 27, 2020), more than 24 million reported cases have been reached worldwide, more than 800,000 people have died worldwide and it has become the worst public health crisis in a century [1-4].

While the pandemic is declining in some countries that were first affected, the number of new cases is growing faster than ever worldwide. Hot spots are emerging in Latin America, Africa, Asia and the Middle East [5-7]. Outbreak was defined from the start by a series of changing epicenters, including Wuhan (China), Iran, north of Italy, Spain, and New York, now there are more risks ahead as these nations begin to reopen their economies; and some countries where the number of cases seemed to have decreased, such as Israel, Sweden and Costa Rica, are now seeing them increase again [8].

In the United States, Brazil and India (after the relaxation of a 3-month blockade, cases are increasing. But the pandemic also breaks out in Russia, forming a belt of infection that stretches across Central Asia and the Middle East and the Indian subcontinent. The increase in COVID-19 cases in South Africa means that the pandemic has a strong foothold in sub-Saharan Africa. During the first days of July 2020, Kazakhstan registered the second highest number of new cases in Europe after Russia. In Central and South America, in addition to Brazil, Mexico, Colombia, Peru, Chile and Argentina, they also have cases by the thousands [9].

There is a wide realization that public health and individual health are entangled: our individual health is entangled with those we live and work with, with people on the other side of the world and with our environment [10]. COVID-19 has catalyzed a revolution in research to understand the virus that causes it, its clinic and epidemiology [11].

In this situation, from an epidemiological perspective, conducting seroprevalence studies is really important. Serological testing can play an important role in the clinical and public health response to COVID-19. Seroprevalence studies can show results that allow estimating how many people have been infected at a certain level (for example, at the national level), identifying people who could possibly be protected from a subsequent infection, as well as people who have not had it and they may still be at risk for infection [12,13].

But antibody tests also face uncertainties: the problem of their precision and reliability, and the fact that the level of antibodies may disappear over time. Anyway, without testing there is no data. Serological testing, with its possible limitations, has many purposes and uses beyond the diagnosis and protection of people, since data are needed to manage all aspects of the pandemic. For example, morbidity data (prevalence and incidence) are the cornerstone of epidemic prediction models, which are highly needed to reveal future demand for care, including the timing of case waves and the magnitude of services required in emergency physicians, hospital staff, hospital beds, ventilation equipment, as well as primary care services where most patients will be cared for. Without good data, forecasters have to rely on guesswork and assumptions [14].

In this scenario, this article aims to review, summarize and systematize the data provided by the seroprevalence studies of COVID-19 and reflect about the uncertainties and clinical-epidemiological implications of its results, focusing specifically on the level of primary care/general medicine.

Methods

The search for information was based on a non-systematic narrative review considered the bibliographic references of selected articles and opportunistic searches on the Internet, since January 2020, in English and Spanish.

Discussion

Serological tests use blood samples to identify antibodies and measure the body's immune response to foreign pathogens (that is, antigens). Samples are analyzed for the presence of immunoglobulin, Ig M, and IgG antibodies, indicating recent exposure to SARS-CoV-2 (early stage [IgM] and late stage [IgG] infection). There are different types of serological tests: neutralization tests, immunofluorescent tests, enzyme immunosorption tests (ELISA) and Western blot tests [15].

Reliability and Precision of Antibody-Based Tests for COVID-19

Although antibody-based tests are receiving increasing attention, it is not yet known how reliable and accurate they are, including whether or not positive results will indicate immunity to reinfection [16]. Seroprevalence surveys for anti-SARS-CoV-2 antibodies have faced considerable criticism from scientists, in part because the tests themselves have varied widely in the precision of their results. In some countries, health authorities (such as the U.S. FDA) allowed manufacturers to promote serological testing if they met certain criteria for accuracy and reliability, but were not required to have full approval. Currently, more than 70 tests are available under this policy [17,18].

The performance of a test depends on two measures: sensitivity and specificity. Sensitive tests generate few false negatives and specific tests lead to few false positives. A high-quality test should achieve 99% or more sensitivity and specificity. That means that testing should turn up only about 1 false positive and 1 false negative for every 100 true positive and true negative results. Without reliable tests, these can end up doing more harm than good [19]. In this regard, it has been reported that IgG/IgM antibody tests

against SARS-CoV-2 have a sensitivity of only 30% during the first week of symptoms, and increase to 91% during the third week, according to a review of 38 studies published by the Cochrane Library. Data beyond 3 weeks were limited. In general, the specificity of the test was greater than 98% [20]. However, the accuracy of a test should depend on what it is being used for. For seroprevalence studies, which seek to identify the proportion of a population that has been infected with the virus, more than 98 percent specificity and more than 90 percent sensitivity are desired [21].

But, in addition, it must be remembered an important fact: 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 high, the positive predictive value of the test increases, and as a consequence there are few false positives and more false negatives. When the prevalence is low, the opposite occurs: the positive predictive value of the test decreases, and there will be more false positives and fewer false negatives. For example, in a population where the prevalence is 5%, a test with 90% sensitivity and 95% specificity will yield a positive predictive value of 49%. In other words, less than half of those testing positive will truly have antibodies. Alternatively, the same test in a population with an antibody prevalence exceeding 52% will yield a positive predictive greater than 95%, meaning that less than one in 20 people testing positive will have a false positive test result [22-24].

Variation of Seroprevalence Results According To the Time of the Test

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 [25]. Antibodies to SARS-CoV-2 have been reported to demonstrate infection when measured at least 14 days after symptom onset [26]. Furthermore, antibodies can "disappear" in a certain number of people after infection (seronegativization). A large population study showed that 14% of people who tested positive for IgG antibodies in the first wave of the study, were tested negative in the third wave (21 days apart between each round). This seronegativization does not imply by itself that these people have lost their immunity to the coronavirus and in part may be due to a possible lack of sensitivity of the tests [27].

Bias in Sample Selection

In addition to reservations about the precision of the tests, the seroprevalence studies must be well designed and have no sampling biases [28]. These studies sometimes use randomly selected population samples, but other times opportunistic samples and refer to certain specific places, such as neighborhoods of a city, hospitals, etc., and sometimes with large losses of personnel in the samples, which makes it difficult to compare and reliability of the diversity of its results; That is, due to sampling bias, these studies are producing very different and sometimes, almost uninterpretable results [14].

Antibody Tests Are a Potentially Useful Tool in the Pandemic Response

The importance of antibody testing lies in providing information to help track the spread of the virus at the community level, particularly given the confusion over asymptomatic transmission, and assessing the impact of public health efforts. Knowing how widespread the infection has been in a population could guide research and possibly public health decisions, including reopen their economies [29-31]. Assessment of immunity at the population level (sero-surveillance) [32] can help to determine the level of antibodies required to achieve collective immunity, to identify groups of susceptible individuals ('immunity gaps') and to assess the persistence and the duration of protective antibodies. In the future, sero-surveillance could provide relevant information to plan vaccination strategies, avoiding the need to vaccinate those who already have immunity [33].

Seroprevalence Studies and Data

Without testing there is no data. But, as the duration of antibody elevations is currently unknown, there is no certainty about the usefulness of these tests for seroprevalence studies for public health management purposes [20]. In any case, immunological studies could give us an idea of the true infection rates in the community. But only very recently have general population tests been carried out in different places to detect the virus. Due to the high proportion of asymptomatic or mild infections (approximately 80%), data restricted to laboratory-confirmed cases do not capture the true extent of the spread or burden of the virus, or its infection-fatality ratio [34].

Therefore, serological detection of specific antibodies against SARS-CoV-2 can improve estimating the true number of infections. The first studies of the number of cases in the community of various European countries begin to be published. Now, several hospitals 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, knowing it or not [35]. Monitoring the COVID-19 epidemic is important. The only current rationale for testing large-scale SARS-CoV-2 antibodies is for research purposes, including public health surveillance to inform epidemiology.

But, this 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 [36].

Place	Seroprevalence (evidence of antibodies against SARS-CoV-2)
China	-In Wuhan it varied between 3.2% and 3.8%
U.S.	-In to Boston suburb, 33% -In Los Angeles, 4.65% -In New York City from 6.93% to 13.9% -In New York, 68% of people examined in an urgent care center in the Queens neighbourhood -In Missouri, 2.65% -In residents of Santa Clara County, California, 2.5 to 4.2%
Germany	-In Gangelt, Heinsberg district (North Rhine-Westphalia) 15.5% (95% CI: 12.3% -19.0%)
Switzerland	-In Geneva 10%
United kingdom	-Around 17% of people in London and 5% of people elsewhere in the UK -1% in Scotland
Spain	-5% of the Spanish population -20.18% of the population of Torrejón (Madrid) -At the Hospital of Alcorcón (Madrid), 31% -In Galicia, 1% -In Barcelona between 5% and 11%
Italy	-In Nembro and Alzano (Bergamo), 60% -In healthy blood donors in Milan, 4.6% -7.1%
Netherlands	-In Netherlands 3%
Denmark	-In Denmark 1.9%
Finland	-3.4% in Helsinki
Sweden	-7,3%
France	-In France 4.4% -In Oise (France) 3.2%
Russia	-5.7% of residents of Saint Petersburg
Japan	-In Tokyo, 3.83% -In Kobe, 3.3%
Hong Kong	-In Hong Kong 2.7%
India	-0.73% of population
Brazil	-Seroprevalence varied significantly across the country, from less than 1% in many cities in the southern and central-western regions to 25% in a city called Breves located in the Amazon. -In Sao Paulo 9.5% -Seroprevalence among blood donors in the State of Rio de Janeiro 4.0%
Latin America	-From 0.25 to 3.75%
African countries	-5% in 20 Kenya -12.3% of 500 asymptomatic healthcare workers in Blantyre, Malawi -3% to 10% in Nampula and Pemba, Mozambique

Table 1: Seroprevalence in Different Places.

There are many more studies in progress whose results will be known (in Canada they have launched one that will analyze a million blood samples over two years, in the United States it has announced the largest in the history of the country, with 50,000 participants and there is another one underway in several cities, including New York, the most punished, etc.) [37]. these data, usually, show the number of participants who have had COVID-19 (the prevalence). But reliable data is lacking for many 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). But it is impossible to measure the severity of contagion across the continent. Africa, with a population of 1.3 billion people, has more than 525,000 confirmed cases and almost 13,000 deaths. In comparison, Latin America, with half the population, has 2.9 million cases and 129,900 deaths [38]. Among the preliminary data known are the following (Table 1).

China

A study that evaluated the serological response of the host, measured by the levels of immunoglobulins M and G in 17,368 individuals, in the city of Wuhan, the epicenter of the COVID-19 pandemic in China and in other geographic regions of the country, from March 9, 2020 to April 10, 2020, it showed that seropositivity in Wuhan varied between 3.2% and 3.8% in different subcohorts. Seropositivity decreased progressively in other cities as the distance to the epicenter increased. Patients who visited a hospital for maintenance hemodialysis and healthcare workers also had a higher seroprevalence of 3.3% and 1.8%, respectively [39].

United States

An analysis of the SARS-CoV-2 antibody test results from nearly 12,000 serum samples suggests that the burden of COVID-19 in the U.S. may be more than 10 times greater than currently reported. The researchers tested samples collected as part of routine care (but not related to COVID-19) between March 23 and May 3 from six regions: Connecticut, South Florida, Missouri, the Metropolitan Region of New York City, Utah and Puget Sound from Washington State. In New York City, for example, the estimated seroprevalence (adjusted for test sensitivity and specificity) was 6.93%, 12 times higher than the prevalence based on reported cases. In Missouri, the estimated seroprevalence was 2.65%, 24 times higher than the reported prevalence [40,41].

3% of the Indiana population 12 years and older had current or prior SARS-CoV-2 infection as of late April, and in the Atlanta area in late April through early May, antibody seroprevalence was also about 3% [42].

Another study found nearly 14 per cent of New Yorkers may have been infected [43]. In a Boston suburb, a sample of people tested on the street showed that about a third of the 64 people tested were exposed to the virus (28). A study in residents of Los Angeles County, California found that about 4% tested positive; based on this prevalence, the authors estimate that approximately 367,000 county residents had antibodies to SARS-CoV-2 (the official number of confirmed infections was only 8,430) [44,45]. About 68% of people examined at an urgent care center in the Corona neighborhood of Queens, New York, had evidence of antibodies to SARS-CoV-2: in Jackson Heights and Queens, 56% tested positive; the percentages were lower in the wealthier neighborhoods [46]. A seroprevalence study in residents of Santa Clara County, California showed an infection rate of 2.5 to 4.2%, which was later adjusted to 1.3 to 4.7% [47].

Germany

According to the so-called Heinsberg study, the authors assume that up to 1.8 million people with the new coronavirus may be infected in Germany (an amount ten times greater than the 163,000 official records as of May 4). In Gangelt, Heinsberg district (North Rhine-Westphalia), a carnival event took place on February 15; the study of a random Gangelt sample resulted in 15.5% were infected. 22% of the patients who tested positive in the Heinsberg study were asymptomatic [48-50].

Switzerland

Nearly 2,800 people in Geneva, Switzerland underwent antibody tests between early April and early May. Using these results, the researchers estimated that the seroprevalence of the general population was 4.8% during the first week of testing, and increased to 10.8% during the fifth week. Children ages 5 to 9 and adults age 65 and older were less likely to test positive. Furthermore, the researchers estimated that for every confirmed case reported, there were 11.6 infections in the community [51].

United Kingdom

An antibody surveillance study led by the Office for National Statistics had found that around 17% of people in London and 5% of people elsewhere in the UK had tested positive for anti-SARS-CoV-2 antibodies [52]. Another study prevalence study in 885 people in England suggested that approximately 7% of the population had been infected with SARS-CoV-2 [53]. Another study showed a prevalence of 1% in Scotland in blood donors in March 2020 [54].

Spain

5% of the Spanish population has been infected with SARS-CoV-2, which represents around 2.3 million citizens (with "official" data of infected as of May 14, of 229,540 cases). However, the impact of the virus varies greatly according to the Spanish province, from Soria where the percentage of people who have been infected is 14.2%. Madrid 11.3%, Barcelona 7.1%, but in Huelva it is 1.5%, Murcia 1.4%, Tarragona 1.6% or La Corona 1.8%. Thus, it can be said regarding Spain, that the official data indicates that

they have barely detected around 10% of the total number of actual cases in the community. On the other hand, this study indicates that 33% of the respondents positive in SARS-CoV-2 are asymptomatic [47,53-57].

20% of the population of Torrejón de Ardoz city (Madrid) have antibodies against the coronavirus according to a massive voluntary study carried out between May 9 and June 3 (104,299 residents, 74,79% of the total population older than one year). The first cases occurred in this city during the 15 days prior to the approval of the state of alarm in Spain, and there was probably a greater community spread than in other cities in Spain [58].

In Galicia, a seroprevalence study is underway with a sample of 100,000 people, of whom more than 2,000 tests have been carried out, with just 1% positive [59]. A study among professionals at the Hospital Clinic de Barcelona (578 people who work at the Hospital) prevalence was 11.2% [60]. In another study also in Barcelona, at the Sardenya Health Center, in Horta-Guinardó, based on a sample of their patients, found a 5.47% prevalence; the group of men gave 4.4% and the group of women 6.4% [61]. In another study, in workers at the Hospital Fundación de Alcorcón (Madrid) with 2,625 workers included (more than 90% of the total), 31% showed antibodies against COVID-19 at the time of the test. The hospital was considered one of the foci of contagion of coronavirus in March [35,62].

Italy

In a study in residents of Nembro and Alzano (Bergamo) 6 out of 10 people would have passed the disease [63]. Another study reported the results of a randomized trial of 789 healthy blood donors in Milan, Italy, from the end of February, when the outbreak began in the region, until the end of April; these individuals had to be free of COVID-19 symptoms and had not had contact with infected individuals in the previous two weeks, and samples were taken at 20 per day. At the start of the study, the first two weeks of sampling, the researchers found that the prevalence of positive SARS-CoV-2 serology was 4.6%. But this increased to 7.1% in the last three weeks of the study, which was a significant change over time. The authors calculated that these estimates translated into around 231,000 undiagnosed cases in Milan as of April 8, meaning that only about one in 20 individuals with the virus were actually diagnosed [64].

Other European countries

The European Center for Disease Control has compiled the first seroprevalence studies published in Europe, and by now almost all are below 5%: A study in the Netherlands with 7,000 people recorded a 3% prevalence [37], 3% also reported in France and 4.4 %, in Oise (France) [65], 1.9% in Denmark, 3.4% in Helsinki [66], and Sweden reported a prevalence of 7.3% in late April [67].

Japan

A seroprevalence survey in the city of Kobe put the figure at 3.3% [37]. Seropositivity for the SARS-CoV-2 IgG between April 21 and May 20, 2020, at two primary care clinics in Tokyo, Japan was 3.83% [68].

Hong Kong

Among the Hong Kong general population 2.7% were positive. Among asymptomatic Hubei returnees 4% were seropositive [69].

India

The first government serological survey estimated that approximately 0.73% of India's population had antibodies. If that percentage is applied to the population in rural India, excluding tribal areas, some 750 million people, that means that around 5 million people have been infected and recovered in these areas [70].

Brazil

Seroprevalence of SARS-CoV-2 antibodies varied significantly across the country, from less than 1% in many cities in the South and Central-West regions to 25% in one city called Braves located in the Amazon. Of fifteen cities with the highest incidence, eleven were in northern Brazil, including six located along a 2,000-kilometer portion of the Amazon River. Overall, the incidence of the SARS-CoV-2 antibody across the 90 cities where people were tested on the last 200 was 1.4%. The authors say this extrapolation of 1.4% to the total populations to the cities; give rise to estimated 760,000 cases of the infection, compared to the 104,782 officially reported. The highest incidence, of 3.7%, was observed among indigenous people, and the lowest incidence, of 0.6%, was observed among white people [71].

Another study in the city of Sao Paulo, the most populous in South America, showed 9.5% [72]. Seroprevalence of antibodies to SARS-CoV-2 among blood donors in the State of Rio de Janeiro was 4.0%; further adjustment by test sensitivity and specificity produced lower estimation of 3.6% [73].

Latin America

In some cases the data is of poor quality and the prevalences are obtained through mathematical models; the

figures range from 0.25 to 3.75% [74]. Ecuador and Brazil are the most affected countries, with approximately 3% of the infected population [75]. An investigation to determine seroprevalence has begun in Cuba [76].

African Countries

One in 20 Kenyans between the ages of 15 and 64, or 1.6 million people, has antibodies to SARS-CoV-2 in Kenya. 12.3% of 500 asymptomatic healthcare workers in Blantyre, Malawi, had been exposed to the SARS-CoV-2; 3% to 10% of survey participants in Nampula and Pemba, Mozambique had antibodies to SARS-CoV-2. On the other hand, several more studies are under way: a study funded by France will analyze thousands of antibodies in Guinea, Senegal, Benin, Ghana, Cameroon and the Democratic Republic of the Congo; and 13 laboratories in 11 African countries are participating in a global survey of antibodies against SARS-CoV-2 coordinated by the World Health Organization [77].

Other Countries

Australia is conducting a seroprevalence survey conducted by the National Center for Immunization Research and Surveillance and the Kirby Institute [78,79]. Likewise, in Canada, the Canadian Blood Services has formed a research partnership with the COVID-19 Immunity Task Force to determine the prevalence of COVID-19 antibody in the blood serum of Canadians [80]. Similarly, in St Petersburg, Russia, another seroprevalence study has begun; preliminary results show that 5.7% of Saint Petersburg residents have had Covid-19 [81,82].

Prevalence of Asymptomatic Disease

Data on the transmission of COVID-19 on the Diamond Princess ship, with more than 3,700 people on board, showed that there were a total of 712 confirmed cases between passengers and crew, about half of which were asymptomatic at the time of the test, and it was estimated that 18% of the positive cases were "true asymptomatic", people who never developed symptoms despite being infected [83]. It is estimated that 40-45% of people who test positive for SARS-CoV-2 have no symptoms at the time of the test. This data suggests that it is a significant factor in the rapid progression of the COVID-19 pandemic [84].

How Will The Role Of General Practitioner (GP) Be Affected By Variations In The Prevalence/Incidence Of COVID-19?

General medicine is the cornerstone on which the entire healthcare system rests, continuing care for people and the community being part of its essence [85]. The 80-85% the COVID-19 is mild [34]. And so it is very important how to deal with infection in primary care and in the community [86], since most infections will be attended by the GP, which means attending to most cases [87]. The GP, in addition to recovering all previous assistance to all health problems, have to maintaining telephone triage/video consultations, not over prescribing, and using preventive measures for himself and for patients [88]. Nowadays, herd immunity is far from being achieved (would a figure of 50% be acceptable?) (Supposing immunity will be effective and long-lasting, what is not yet clarified), and when restrictive measures are limited, outbreaks are to be expected. Although there is wide geographic variability with much higher rates in urban centers than in rural areas [89], and also, it has been reported, using a mathematical model, that population heterogeneity can significantly affect disease-induced immunity, because the proportion of infected individuals in the groups with the highest contact rates is higher than in the groups with rates of contact low contact; thus, in an age-structured community with mixing rates fitted to social activity, then the disease-induced herd immunity level can be del 40%, which is substantially less than the classical herd immunity level of 60% obtained through homogeneous immunization of the population [90].

In this context the GP will have a key role in the control of outbreaks of the COVID-19 pandemic: detect suspicious cases as soon as possible and carry out tests to confirm new infections so that transmission chains can be shortened [91]. Therefore, it will be affected in the near future by the epidemiological situation of COVID-19, probably to a greater degree than hospital care.

Conclusions of Covid-19 Seroprevalence Studies and Its Implications for General Medicine

- 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.
- Due to the dynamics of increasing seroprevalence during the first phase of the pandemic, these studies are only snapshots in time and space, and reflect the circumstances of the period in which they were made.
- 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.
- The first results indicate that the observed seroprevalence seems very variable, from 1% to 60%, but if extreme data

(from places or special samples) are not considered, it is actually quite similar in many countries and cities around the world, which can be between 2-3% and 10-15%; more likely between 3-10%.

- Regardless of the doubts about the precision of the tests, with a probable low prevalence of COVID-19 (for example 5%), the positive predictive value of the seroprevalence test decreases and there will be more false positives (and fewer false negatives); this may erroneously increase the prevalence value found, which in reality will be even lower than the reported seroprevalence figure.
- These figures indicate that, as expected, the actual number of people who have had COVID-19 is much greater than the number of confirmed cases with PCR.
- However, these first data indicate that SARS-CoV-2 infections are many, but not massive, and most of the population do not have antibodies. This could indicate increased risks from the second wave of the pandemic since most people have not contracted the virus. The march of the coronavirus through the population has just begun.
- More antibody studies may help complete the picture, but given its limitations, it could currently be dangerous to base only COVID-19 policies on antibody surveys.
- Nowadays, herd immunity is far from being achieved (would a figure of 50% be acceptable?) (Supposing immunity will be effective and long-lasting, what is not yet clarified), and when restrictive measures are limited, outbreaks are to be expected. This implies that the GPs must be prepared to attend to the patients of the outbreaks: realization of PCR, contact tracing, epidemiological information systems, maintenance of the telecare in the consultations, use of Personal Protective and Safety Equipments, etc., until the existence and availability of vaccines, in addition to maintaining care for new health problems and continued care for chronic non-COVID-19 problems.

References

1. (2020) Archived: WHO Timeline-COVID-19. WHO.
2. Coronavirus COVID-19 Global Cases by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins. The Center for Systems Science and Engineering (CSSE) at JHU.
3. Gupta SD (2020) Coronavirus Pandemic: A Serious Threat to Humanity. J Health Manag 22(1): 1-2.
4. Russell P, Locke T (2020) PM: COVID-19 Worst Public Health Crisis in a Generation. Medscape.
5. Dyer O (2020) Covid-19 hot spots appear across Latin America. BMJ 369: 2182.
6. (2020) Africa records over 200 000 COVID-19 cases. WHO.
7. Shuchman M (2020) Low- and middle-income countries face up to COVID-19. As cases of COVID-19 are being declared the Global South, low- and middle-income countries brace themselves for the pandemic. Nat Med.
8. (2020) The outbreak is surging, with clusters on several continents. The New York Times.
9. (2020) COVID-19: the worst may be yet to come. Lancet 396(10244): 71.
10. Williams S, Tsiligiann I (2020) COVID-19 poses novel challenges for global primary care. npj Prim Care Respir Med 30(30).
11. Callaway E, Ledford H, Mallapaty S (2020) Six months of coronavirus: the mysteries scientists are still racing to solve. Nature.
12. (2020) Coronavirus disease 2019 (COVID-19). Serology testing for COVID-19. Centers for Disease Control and Prevention.
13. Hahn SM (2020) Coronavirus (COVID-19) update: serological tests. FDA.
14. Schneider EC (2020) Failing the Test-The Tragic Data Gap Undermining the U.S. Pandemic Response. N Engl J Med 383: 299-302.
15. (2020) Serology-based tests for COVID-19. Johns Hopkins University.
16. (2020) Coronavirus Disease 2019 (COVID-19) Test for Past Infection (Antibody Test). CDC.
17. (2020) EUA authorized serology test performance. FDA.
18. Vogel G (2020) Antibody surveys suggesting vast undercount of coronavirus infections may be unreliable. Science.
19. Mallapaty S (2020) Will antibody tests for the coronavirus really change everything?. Nature.
20. Deeks JJ, Dinnes J, Takwoingi Y, Davenport C, Spijker R, et al. (2020) Antibody tests for identification of current and past infection with SARS-CoV-2. Cochrane Database of Systematic Reviews.
21. Kwon D (2020) Why the Accuracy of SARS-CoV-2 Antibody Tests Varies So Much. The Scientist.
22. (2020) Interim Guidelines for COVID-19 Antibody Testing in Clinical and Public Health Settings. Centers for

Disease Control and Prevention.

23. Woloshin S, Patel N, Kesselheim AS (2020) False Negative Tests for SARS-CoV-2 Infection-Challenges and Implications. N Engl J Med 383: 38.

24. Levesque J, Maybury DW (2020) A note on COVID-19 seroprevalence studies: a meta-analysis using hierarchical modelling. MedRxiv.

25. (2020) Important Information on the Use of Serological (Antibody) Tests for COVID-19-Letter to Health Care Providers. U S Food & Drug Administration.

26. Caturegli G, Materi J, Howard BM, Caturegli P (2020) Clinical Validity of Serum Antibodies to SARS-CoV-2. Ann Intern Med.

27. Ibañes LG (2020) Conclusions of the seroprevalence study. Antibodies 'disappear' in 14% of Spaniards. El Mundo.

28. Lopatto E (2020) The disappointing truth about antibody testing. There's still a lot we don't know about COVID-19. The Verge.

29. Madrigal AC, Meyer R (2020) How Could the CDC Make That Mistake?. The Atlantic.

30. Johnson K (2020) COVID-19 antibody tests proliferate: what do they show?. Medscape.

31. Baraniuk C (2020) Covid-19 antibody tests: a briefing. BMJ 369: 2284.

32. Wilson SE, Deeks SL, Hatchette TF, Crowcroft NS (2012) The role of seroepidemiology in the comprehensive surveillance of vaccine-preventable diseases. CMAJ 184(1): 70-76.

33. (2020) OECD Policy Responses to Coronavirus (COVID-19) Testing for COVID-19: A way to lift confinement restrictions.

34. Wu Z, McGoogan JM (2020) Characteristics of and Important Lessons from the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases from the Chinese Center for Disease Control and Prevention. JAMA 323(13): 1239-1242.

35. Viciosa M (2020) First indications: SARS-CoV-2 infections are many more but not massive. Newtral.

36. Andersson M, Low N, French N, Greenhalgh T, Jeffery K, et al. (2020) Rapid roll out of SARS-CoV-2 antibody testing-a concern. BMJ 369: 2420.

37. Fuentecilla JL, Lillo D (2020) What is a seroprevalence study. NIUS Diario.

38. Hierra L (2020) The coronavirus in Africa. One hundred thousand more infections this week. El País.

39. Xu X, Sun J, Nie S, Li H, Kong Y, et al. (2020) Seroprevalence of immunoglobulin M and G antibodies against SARS-CoV-2 in China. Nat Med 26: 1193-1195.

40. (2020) Commercial Laboratory Seroprevalence Survey Data. Coronavirus Disease 2019 (COVID-19). CDC.

41. Havers FP, Reed C, Lim T, Montgomery JM, Klena JD, et al. (2020) Seroprevalence of Antibodies to SARS-CoV-2 in 10 Sites in the United States, March 23-May 12, 2020. JAMA Intern Med.

42. Menachemi N, Yiannoutsos CT, Dixon BE, Duszynski TJ, Fadel WF, et al. (2020) Population Point Prevalence of SARS-CoV-2 Infection Based on a Statewide Random Sample-Indiana, April 25-29, 2020. MMWR Morb Mortal Wkly Rep 69(29): 960-964.

43. (2020) Study finds nearly 14 per cent of New Yorkers may have been infected. The Sydney Morning Herald.

44. Sood N, Simon P, Ebner P, Eichner D, Reynolds J, et al. (2020) Seroprevalence of SARS-CoV-2–Specific Antibodies Among Adults in Los Angeles County, California, on April 10-11, 2020. JAMA 323(23): 2425-2427.

45. Crist C (2020) WebMD Poll: 93% With COVID-19 Symptoms Didn't Get Test. Medscape.

46. Goldstein J (2020) 68% Have Antibodies in This Clinic. Can a Neighborhood Beat a Next Wave?. New York Times.

47. Yasinski E (2020) Researchers Applaud Spanish COVID-19 Serological Survey. The Scientist.

48. van den Heuvel M (2020) Heinsberg study in "preprint": high number of unreported infections, death rate only 0.36% - does this apply to the whole of Germany?. Medscape.

49. Streeck H, Schulte B, Kümmerer B, Richter E, Hoeller T, et al. (2020) Infection fatality rate of SARS-CoV-2 infection in a German community with a super-spreading event. MedRxiv.

50. (2020) Germany ramps up antibody tests to determine coronavirus immunity. The Local.

51. Stringhini S, Wisniak A, Piumatti G, Azman AS, Lauer SA, et al. (2020) Seroprevalence of anti-SARS-CoV-2 IgG antibodies in Geneva, Switzerland (SEROCoV-POP): a

population-based study. Lancet 396(10247): 313-319.

52. Burki TK (2020) Testing for COVID-19. Lancet Respir Med 8(7): 63-64.

53. Roxby P (2020) About 7% have had coronavirus, says ONS survey. BBC News.

54. Thompson C, Grayson N, Paton R, Bolton JS, Lourenço J, et al. (2020) Detection of neutralising antibodies to SARS coronavirus 2 to determine population exposure in Scottish blood donors between March and May 2020. MedRxiv.

55. Instituto de Salud Carlos III (2020) ene-covid19 study: first round national sero-epidemiology study of sars-voc-2 infection in Spain. Preliminary Report.

56. Pollán M, Gómez BP, Barriuso RP, Oteo J, Hernan MA, et al. (2020) Prevalence of SARS-CoV-2 in Spain (ENE-COVID): a nationwide, population-based seroepidemiological study. Lancet 396(10250): 535-544.

57. Wise J (2020) Covid-19: Surveys indicate low infection level in community. BMJ 369: 1992.

58. Madrid EFE (2020) 20.18% of the population of Torrejón has antibodies against the coronavirus. El Mundo.

59. López P (2020) The disturbing result of the massive test in Galicia with only 1% positives. El Confidencial.

60. Garcia-Basteiro AL, Moncunill G, Tortajada M, Vidal M, Guinovart C, et al. (2020) Seroprevalence of antibodies against SARS-CoV-2 among health care workers in a large Spanish reference hospital. MedRxiv.

61. Fernández C (2020) A study done in Barcelona shows that only 5% of the population has passed the Covid-19. El Mundo.

62. Torres Benayas V (2020) A hospital in Alcorcón, a new focus of the coronavirus in Madrid. El País.

63. Di Landro A (2020) Serological tests Bergamo, the results of Nembro and Alzano arrive: 61% positive. Bergamo Corriere Della Sera.

64. Valenti L, Bergna A, Pelusi S, Facciotti F, Lai A, et al. (2020) SARS-CoV-2 seroprevalence trends in healthy blood donors during the COVID-19 Milan outbreak. MedRxiv.

65. Salje H, Kiem CT, Lefrancq N, Courtejoie N, Bosetti P, et al. (2020) Estimating the burden of SARS-CoV-2 in France. Science 369(6500): 208-211.

66. Linde P (2020) Group immunity is far away. Several studies place seroprevalence below 15%. Epidemiologists ask not to let your guard down with surveillance. El País.

67. Eckerle I, Meyer B (2020) SARS-CoV-2 seroprevalence in COVID-19 hotspots. Lancet 396(10250): 514-515.

68. Takita M, Matsumura T, Yamamoto K, Yamashita E, Hosoda K, et al. (2020) Geographical Profiles of COVID-19 Outbreak in Tokyo: An Analysis of the Primary Care Clinic–Based Point-of-Care Antibody Testing. Journal of Primary Care & Community Health 11: 1-5.

69. Wang To KK, Cheng VCC, Cai JP, Chan KH, Chen LL, et al. (2020) Seroprevalence of SARS-CoV-2 in Hong Kong and in residents evacuated from Hubei province, China: a multicohort study. Lancet 1(3): 111-118.

70. Pulla P (2020) The epidemic is growing very rapidly: Indian government adviser fears coronavirus crisis will worsen. Nature.

71. Hallal P, Hartwig F, Horta B, Victora GD, Silveira M, et al. (2020) Remarkable variability in SARS-CoV-2 antibodies across Brazilian regions: nationwide serological household survey in 27 states. MedRxiv.

72. (2020) A study calculates that 1.16 million people had COVID-19 in Sao Paulo. EFE.

73. Filho LA, Szwarcwald CL, Garcia Mateos SO, Ponce de Leon ACM, Medronho RA, et al. (2020) Seroprevalence of IgG and IgM anti-SARS-CoV-2 among voluntary blood donors in Rio de Janeiro, Brazil. SciELO.

74. Pérez P (2020) Covid-19 in South America: European prevalence, but with more cases. El Mundo.

75. Matabuena M, Mier PR, Garcia CM, Leboran V, Gude F (2020) Mathematical estimation of COVID-19 prevalence in Latin America. MedRxiv.

76. (2020) Study of seroprevalence and prevalence of COVID-19 begins in Cuba. Cnicm-Infomed.

77. Nordling L (2020) Africa's pandemic puzzle: why so few cases and deaths?. Science 369(6505): 756-757.

78. (2020) COVID-19 response support. National Centre for Immunization Research and Surveillance.

79. Snow D, Aubusson K, Geraghty K (2020) The small steps Australia will take towards the goal of easing the lockdown. The Sydney Morning Herald.

80. (2020) New study to determine how widespread COVID-19 antibody is among Canadians. Canadian Blood Services.

81. (2020) Study of the spread of COVID-19 in St Petersburg, Russia. ISRCTN.

82. (2020) Researchers from European University at St. Petersburg and Scandinavia clinic are conducting the first representative Sars-Cov-2 serological survey in Russia. Preliminary results show that 5,7% of St. Petersburg residents have had Covid-19. European University at St Petersburg.

83. Baraniuk C (2020) What the Diamond Princess taught the world about covid-19. BMJ 369: 1632.

84. Oran DP, Topol EJ (2020) Prevalence of Asymptomatic SARS-CoV-2 Infection. Ann Intern Med.

85. Turabian JL (1995) Cuadernos de Medicina de Familia y Comunitaria. Una introducción a los principios de Medicina de Familia. Notebooks of Family and Community Medicine. An introduction to the principles of Family Medicine. Madrid: Díaz de Santos.

86. Smith J, Sears N, Taylor B, Johnson M (2020) Serious games for serious crises: reflections from an infectious disease outbreak matrix game. Global Health 16: 18.

87. Lorenzo SM (2020) Against coronavirus, more Primary Care than ever. AMF.

88. Leach J (2020) COVID-19 -Practical things for general practice to do. RCGP.

89. Eckerle I, Meyer B (2020) SARS-CoV-2 seroprevalence in COVID-19 hotspots. Lancet 396(10250): 514-515.

90. Britton T, Ball F, Trapman P (2020) A mathematical model reveals the influence of population heterogeneity on herd immunity to SARS-CoV-2. Science 369(6505): 846-849.

91. de Sutter A, Llor C, Maier M, Mallen C, Tatsioni A, et al. (2020) Family medicine in times of COVID-19: A generalists voice. Eur J Gen Pract 26(1): 58-60.