Coronavirus disease (COVID-19): Serology

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The identification of any new pathogen, such as the COVID-19 virus, is accompanied by many unknowns, particularly its ability to spread in the human population and its virulence. Initial surveillance strategies focus primarily on the use of molecular testing (RT-PCR) to measure acute infection in patients with severe disease, as these are the individuals who seek and require health care. This may miss the fraction of mild or asymptomatic infections that do not require medical attention, and as such, the full spectrum of the disease is not known. The answers to the questions below are based on our current understanding of the COVID-19 virus and the disease it causes. WHO will continue to update these answers as new information becomes available.

What is serology?

Serologic tests measure the antibody response in an individual. Antibodies to COVID-19 are produced over days to weeks after infection with the virus. The presence of antibodies indicates that a person was infected with the COVID-19 virus, irrespective of whether the individual had severe or mild disease, or even asymptomatic infection.

To accompany COVID-19 surveillance, seroepidemiologic studies are conducted to measure the extent of infection in the population among people who did not seek health care and were missed by current surveillance efforts because they either had no or mild symptoms. With any novel virus, including the COVID-19 virus, initial seroprevalence in the population is assumed to be negligible due to the virus being novel in origin. Therefore, surveillance of antibody seropositivity in a population can allow inferences to be made about the extent of infection and

about the cumulative incidence of infection in the population.

What is the difference between molecular testing and serologic testing?

Molecular testing, or PCR testing, detects genetic material of the virus and so can detect if a person is currently infected with the COVID-19 virus (SARS-CoV-2). The full genomic sequence of the virus was shared by Chinese authorities in early January, which enabled many laboratories to develop PCR assays that are now used to detect cases all over the world.

Serological testing detects antibodies against the virus, and so can detect if a person had a recent (IgM) or past (IgG) infection with the COVID-19 virus. Serologic tests cannot be used to diagnose acute infection with the COVID-19 virus.

Does the presence of antibodies mean that a person is immune?

No - Currently, no study has evaluated whether the presence of antibodies to SARS-CoV-2 confers immunity to subsequent infection by this virus in humans.

The development of antibodies to a pathogen through natural infection is a multi-step process that typically takes place over 1-2 weeks, but the process to develop a full immunologic response may be longer. Most COVID-19 studies on the presence of antibodies to date show that people who have recovered from infection have antibodies to the virus. However, some of these people have very low levels of antibodies able to neutralize virus in their blood.

How is WHO using serology as part of its response?

WHO is providing a global platform for public health professionals and researchers on the use

of serology for public health purposes and research in the context of COVID-19.

WHO is working with collaborating laboratories and FIND to develop new and evaluate and validate available serologic assays for COVID-19. There are currently several hundred immunoassays marketed for COVID-19 including enzyme-linked immunosorbent assays (ELISA), rapid immunodiagnostic tests (RDT)s and high throughput automated platforms. The first validation data on ELISAs and RDTs have been published, but the results are based on limited datasets and not all have been conducted with well characterized samples from COVID-19 patients. Laboratories have also developed neutralization tests which require biosafety level 3 facilities.

Within WHO's Solidarity II global collaboration, WHO is working partners to facilitate accelerate the development the global sharing of well characterized panels of sera to enable standardization of serologic assays worldwide, and to develop standardized serologic assays for collaborators to use.

In addition, WHO in collaboration with technical partners, has adapted early epidemiological investigations protocols for COVID-19 from pandemic influenza and from MERS-CoV to better understand these characteristics and how they may be used to inform public health measures. These are called the Unity studies and WHO is currently working with more than 40 countries to implement these studies:

- First few X case and contacts
- Health worker seroepidemiologic investigation of risk factors for infection
- Household transmission study
- Age-stratified population based serologic study

What are the expected results from serologic studies?

The results from seroepidemiologic investigations, whether individually or pooled across study sites/countries, will help to understand and provide robust estimates of key clinical, epidemiological and virological characteristics of COVID-19 virus, including:

- Key epidemiological parameters, including: secondary infection rate and secondary clinical attack rate of COVID-19 infection among close contacts, asymptomatic fraction of infection, serial interval and incubation period of COVID-19, the basic reproduction number (R_0) and

R_t of COVID-19 virus.

- Clinical presentation of COVID-19 infection and course of associated disease
- Risk factors for transmission and infection and identification of possible routes of transmission
- Impact of infection prevention and control measures in health care settings
- Serological response following symptomatic COVID-19 infection.
- Age-stratified seroprevalence of COVID-19 virus
- Cumulative incidence of infection, including extent of age-specific infection
- Infection and disease-severity ratios (case–hospitalization ratio [CHR] and case-fatality ratio [CFR]).

When can we expect results?

WHO is in regular contact with countries that are implementing the Unity studies, participating in the Solidarity II study, or that are conducting seroepidemiologic studies using their own study protocols. We have established communication between partners in countries to carry out studies to share experiences, challenges and successes and discuss results as they become available.

Early results from population based serologic studies are becoming available now, with more expected across the weeks to follow.

What are the limitations of serology for a novel pathogen?

As early results become available, it is important to understand the population involved in the study, what samples were tested, how and when samples were collected, which serologic assay(s) were used and how the authors interpreted the results.

At the current time, the biggest uncertainty remains the performance of serologic tests in terms of sensitivity and specificity, which should also assess cross-reactivity with other coronaviruses such as human coronaviruses, SARS-CoV and MERS-CoV, as well as how well the correlate with protective immunity (protection against re-infection).

What are the results of seroepidemiology studies?

Early results from Germany, the Netherlands, the United Kingdom, France, Denmark, the United States of America, Switzerland, Finland, Japan, Italy, China, Spain, Brazil, Croatia, Andorra and Luxembourg have shown that for most populations under study, the extent of infection is below 10%, with the exception of: one German study (14%), a report among first responders in New York State (10-17%), and two pre-print papers from Trieste, Italy (17.2%) and blood donors and children in London (11.3%). There are now four peer-reviewed publications online: one from non-COVID-19 patients in Wuhan, China,[1] one in community and hospital settings across different regions in China,[2] one in the general population in Boise, Idaho,[3] and one among residents of Hong Kong.[4] The remaining studies have not yet completed the peer-review process and some are only available on pre-print servers with the rest reported as press releases with minimal information.

These results will be updated as more results become available. WHO has not yet conducted a detailed review of each study results as full papers are not yet available.

[1] Wu X, Fu B, Chen L, Feng Y. Serological Tests Facilitate Identification of Asymptomatic SARS-CoV-2 Infection in Wuhan, China. *J Med Virol* 2020;10.1002/jmv.25904.

[2] Xu X, Sun J, Nie S et al. Seroprevalence of Immunoglobulin M and G Antibodies Against SARS-CoV-2 in China. *Nat Med* 2020. doi: 10.1038/s41591-020-0949-6.

[3] Bryan A, Pepper G, Wener M et al. Performance Characteristics of the Abbott Architect SARS-CoV-2 IgG Assay and Seroprevalence in Boise, Idaho. *J Clin Microbiol* 2020;JCM.00941-20.

[4] To KK, Cheng V, Cai JP et al. Seroprevalence of SARS-CoV-2 in Hong Kong and in residents evacuated from Hubei province, China: a multicohort study. *Lancet* doi: 10.1016/S2666-5247(20)30053-7

What do these results mean?

The results from the early seroepidemiologic studies, acknowledging the limitations described above, indicate that few people have evidence of infection thus far. This suggests that many

people remain susceptible to infection, which is important in planning for subsequent resurgence in infection.

What is herd immunity?

Herd immunity is the indirect protection from an infectious disease that happens when a population is immune either through vaccination or immunity developed through previous infection. This means that even people who haven't been infected, or in whom an infection hasn't triggered an immune response, they are protected because people around them who are immune can act as buffers between them and an infected person. The threshold for establishing herd immunity for COVID-19 is not yet clear.

What is an immunity passport or a risk-free certificate and what is WHO's view of this?

Some governments have suggested that the detection of antibodies to the SARS-CoV-2, the virus that causes COVID-19, could serve as the basis for an "immunity passport" or "risk-free certificate" that would enable individuals to travel or to return to work assuming that they are protected against re-infection. At this point in the pandemic, there is not enough evidence about the effectiveness of antibody-mediated immunity to guarantee the accuracy of an "immunity passport" or "risk-free certificate." That is, there is currently no evidence to determine whether or not people who have recovered from COVID-19 and have antibodies are protected from a second infection.

WHO view on the use of an "Immunity passports" in the context of COVID-19 is available here: https://www.who.int/news-room/commentaries/detail/immunity-passports-in-the-context-of-covid-19

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