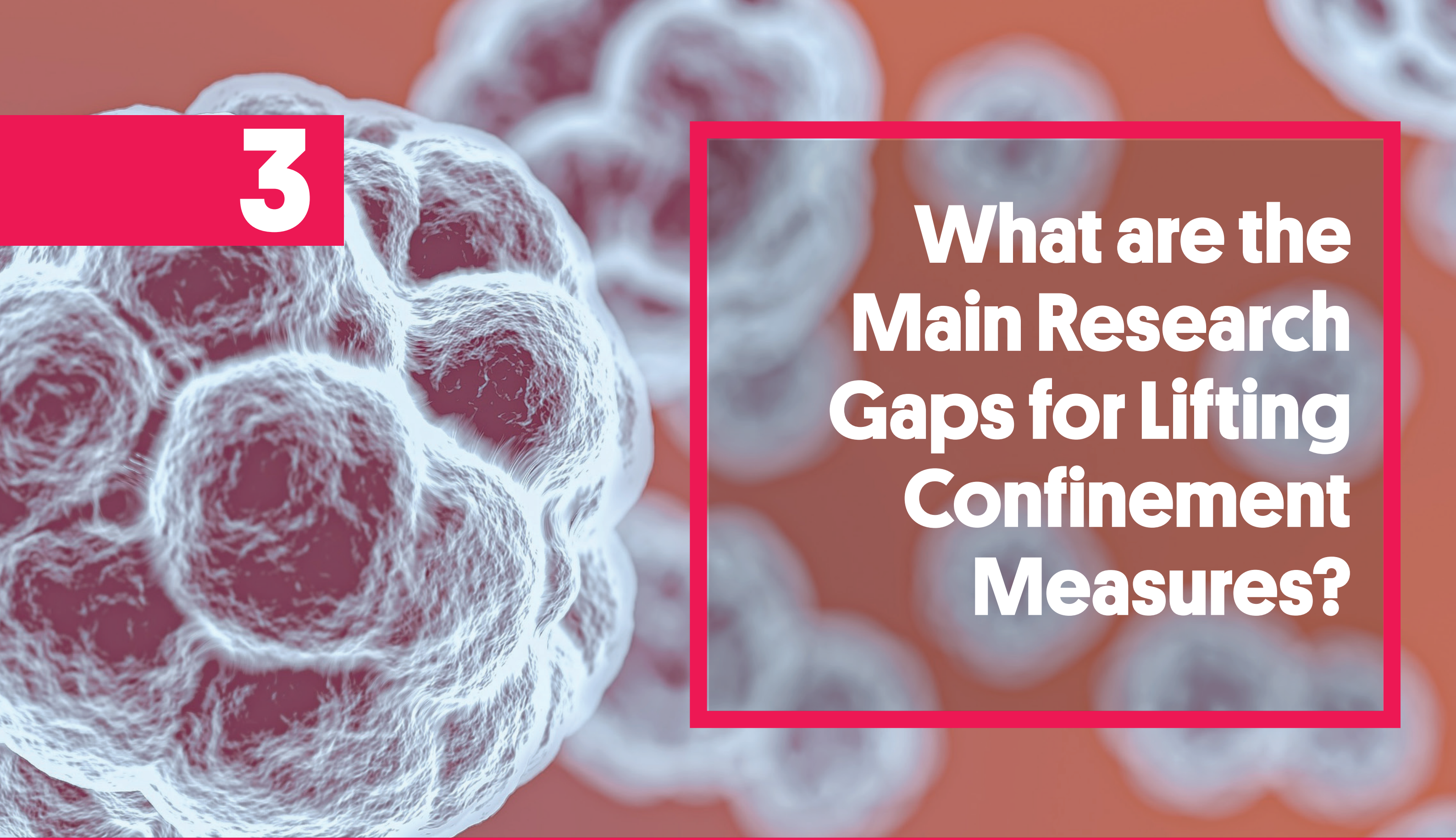

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What are the Main Research Gaps for Lifting Confinement Measures?

Series | COVID-19 & response strategy

ISGlobal Barcelona Institute for Global Health

Author: Adelaida Sarukhan, immunologist and scientific writer at ISGlobal

[This document is part of a series of discussion notes addressing fundamental questions about the COVID-19 crisis and response strategies. These documents are based on the best scientific information available and may be updated as new information comes to light.]

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The diversity of viruses on this planet is immense. It is estimated that mammals harbour some **320,000 different viruses** that we know nothing about[1]. The new coronavirus (**SARS-CoV-2**) was one of those until late last year, when it acquired the ability to jump from an animal species (probably a pangolin) to humans, and from there progressed to human-to-human transmission, causing an outbreak of cases of pneumonia of unknown origin in the city of Wuhan. The scientific community quickly realized that it was a new virus and, within a couple of weeks, scientists had managed to **isolate, sequence and classify** the culprit as a new coronavirus, similar to SARS. By January 13, a molecular diagnostic test was already available.

Just as the virus has spread rapidly from Wuhan City to the rest of the world, scientific knowledge about the virus and the disease it causes (COVID-19) is also moving forward at an unprecedented pace. In just over three months, **more than 2,000 scientific articles** have been published on the subject, open access **online platforms and other mechanisms have been set up to facilitate immediate sharing** of all the information being generated, **clinical trials** have been coordinated on a global scale to test existing drugs, and Phase 1 trials (the kind that test the safety of a treatment before clinical efficacy is tested in phase 2 and 3 trials) have already begun for three candidate vaccines. Nevertheless, **we still need answers to many questions** related to the transmission, pathology, and epidemiology of this new virus.

Some of these gaps in scientific knowledge are making it **very difficult for the authorities to take immediate policy decisions** on the best way to begin easing containment measures and reopen society with the least human, social and economic cost possible ●

[1] Anthony SJ, Epstein JH, Murray KA et al. A strategy to estimate unknown viral diversity in mammals. mBio. 2013. 4(5):e00598-13.

The following are the most urgent questions that we need to answer:

1. What Percentage of the Population Has Been Infected by the Coronavirus?

"The only way to know how many people have acquired immunity is to carry out serological studies that can detect antibodies against the virus in blood taken from a sample of the population."

This basic question remains unanswered, yet it is one of the pieces of information **most urgently needed** to guide strategies for de-escalating restrictions. The reason this percentage is still unknown is that infection with SARS-CoV-2 can result in a number of different presentations, ranging from asymptomatic, mild or moderate cases to severe, life-threatening disease.

We know that, 80% of people with a confirmed diagnosis present mild to moderate symptoms, 15% present severe symptoms, and the disease is critical in 6%[2].

However, it is thought that a significant percentage of those infected have no symptoms or symptoms that are so mild that they often go undetected. Some studies suggest that **between 17% and 30% of those infected do not develop any symptoms** but may, nonetheless, contribute to the spread of the virus[3,4].

We need to know what proportion of the population has been infected by the virus (whether symptomatic or not) for two important reasons:

1. To improve estimates of the fatality rate.

2. To get a better idea of what percentage of the population may have developed immunity to the virus. The proportion of the population with immunity is a vital indicator of the speed at which confinement measures can be eased.

A British study that used mathematical models to estimate the real number of infections in each European country calculated that the percentage of the **Spanish population infected could be as high as 15%**[5].

However, the only way to know how many people have acquired immunity is to carry out **serological studies** that can detect antibodies against the virus in blood taken from a sample of the population. Such studies have been started in some countries (Santa Clara County in California, the Heinsberg Region in Germany and the Oise Region in France, among others) and the WHO has launched an initiative (Solidarity II) to support the harmonised and coordinated collection of data from different countries in order to gain a global vision of seroprevalence.

To carry out these studies in Spain, we need to do three things:

a) Identify or develop a test that has been validated in terms of its specificity and sensitivity.

b) Acquire or produce a sufficient number of such tests.

c) Plan a sampling strategy in both the population at risk (for example, health workers, as is already being done at the Hospital Clínic in Barcelona) and in the general population in order to obtain statistically significant data

[2] Report of the WHO-China joint mission on coronavirus disease 19 (COVID-19), Feb 2020.

[3] Mizimoto K, Kagaya K, Zarebski A, Chowell G. Estimating the asymptomatic proportion of coronavirus disease 2019 (COVID-19) cases on board the Diamond Princess cruise ship, Yokohama, Japan, 2020. Eurosurveillance. 2020. 25(10).

[4] Nishiura H, Kobayashi T, Suzuki A. Estimation of the asymptomatic ratio of novel coronavirus infections (COVID-19). Int J Infect Dis. 2020 S1201-9712(20)30139-9.

[5] Wölfel R, Corman VM, Guggemos W. Virological assessment of hospitalized patients with COVID-2019. Nature. 2020. 10.1038/s41586-020-2196-x.

2. Do Infected People Develop Immunity to the Virus?

"It is not enough to know how many people have developed antibodies to the virus, it is also essential to make sure that these antibodies will protect them against future infection."

The findings of a number of studies indicate that patients with COVID-19 **develop immunoglobulin (Ig) M antibodies to the virus** about six days after infection, followed by IgG antibodies at a later stage[5]. However, it is still unclear whether:

a) All infected individuals (including those who are asymptomatic) generate sufficient antibody levels.

b) Whether these antibodies are protective (i.e. able to effectively neutralize a future SARS-CoV-2 infection).

This means that it is not enough to know how many people have developed antibodies to the virus, it is also essential to make sure that these antibodies will protect them against future infection.

That is a question that can only be answered by **laboratory studies** that determine whether the antibodies generated in each type of case (asymptomatic, mild or moderate symptomatic, severe symptomatic) are **capable of neutralizing the virus.**

The methodology for this type of *in vitro* assay already exists. It is relatively easy to adapt for SARS-CoV-2 and requires a relatively small number of samples •

3. How Long Does Immunity Last?

"It will be important to see how long the immune response persists in the different types of cases: asymptomatic, mild or moderate symptomatic, and severe symptomatic."

Once the population that may have protective antibodies against the virus has been identified or estimated, it is also important to determine how long this immunity might last. It could be a **few months** (as is the case with immunity to the coronaviruses that cause the common cold), or it could be a **couple of years** (as seen with SARS).

The answer to this question will be important in **guiding measures to contain future waves of infection until we have a vaccine**, which will not be available for at least 12 months.

To answer the question, we need to carry out **longitudinal serological studies**. This means monitoring the blood of people who have overcome the infection over a period of several months, taking samples at regular intervals to measure the amount, type and persistence of the virus-specific antibodies.

Once again, it will be important to see how long the immune response persists in the **different types of cases**: asymptomatic, mild or moderate symptomatic, and severe symptomatic •

[5] Wölfel R, Corman VM, Guggemos W. Virological assessment of hospitalized patients with COVID-2019. Nature. 2020. 10.1038/s41586-020-2196-x.

4. How Fast is the Virus Mutating?

"At the moment, genetic analyses carried out on samples obtained from patients around the world indicate that the virus is mutating very little."

The answer to that question will play an important role the answer to the previous question. **If the virus mutates quickly**, the antibodies we make today **may not be able to recognise the virus we are exposed to next year**. Any mutation could also compromise the efficacy of a vaccine created today, which will only induce the production of antibodies that recognise the current strain of the virus.

At the moment, genetic analyses carried out on samples obtained from patients around the world indicate that the **virus is mutating very little**[6], especially in terms of the surface protein (called the *Spike protein*), which is the mechanism that allows the virus to enter the cell.

Our body generates antibodies against this protein, which neutralize the virus, preventing infection. However, over time, the selective pressure on the virus (exerted by the growing immunity in the population) could lead to the emergence of strains that escape that immunity.

To answer this question, it is essential to set up **genetic surveillance mechanisms to monitor the virus**, that is, to regularly sequence viruses obtained from patients around the world and publish them for analysis on an open platform.

A global platform has already been set up for this purpose (www.nextstrain.org) and an similar platform has been created in Spain (www.NextSpain.uv.es). The Spanish tool was created by FISABIO and the University of Valencia in order to share and visualise the genomic data from virus samples collected in Spain

[6] https://www.livescience.com/coronavirus-mutation-rate.html

5. Why Are Children Less Susceptible to the Disease and What Role do They Play in the Transmission of the Infection?

"it will be necessary to actively monitor the paediatric population to detect active infections in children (even without symptoms), to measure the presence of active virus in their respiratory secretions or faeces, and to test the closest contacts of positive cases."

Data from Europe and the USA confirm what statistics in China already indicated: **children are much less susceptible to developing severe forms of the disease**, even though **they do appear to be infected**[2]. The reasons for this are not yet known and need to be investigated.

However, an even more urgent question at this time is to understand **what role children may play in the transmission of the virus**. This information will be essential in guiding decisions on reopening schools and recommendations on whether minors should be living with or in contact with older adults.

To answer this question, it will be necessary to **actively monitor the paediatric population** to detect active infections in children (even without symptoms), to measure the presence of active virus in their respiratory secretions or faeces, and to test the closest contacts (family members, teachers and out-of-school friends) of positive cases ●

TO LEARN MORE

- http://www.isglobal.org/en/coronavirus
- http://www.isglobal.org/en/covid-19-novedades-cientificas
- http://coronavirus.jhu.edu
- http://www.statnews.com

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[2] Report of the WHO-China joint mission on coronavirus disease 19 (COVID-19), Feb 2020.