TONY BLAIR INSTITUTE FOR GLOBAL CHANGE

Antibody Testing as a Tool of Pandemic Management

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Published at https://institute.global/policy/antibody-testing-tool-pandemic-management on July 22 2021

Introduction

Since December 2020, more than 3.69 billion Covid-19 vaccine doses have been administered globally. [1] Vaccines made by the following companies are currently being deployed at scale: AstraZeneca, CanSino Biologics, Johnson & Johnson, Moderna, Pfizer, Sinopharm, Sinovac Biotech and the Gamaleya Research Institute. (See **Table 1**). Canada, Chile, Israel, several Gulf countries, Mongolia, the US, the UK and a few others have partially vaccinated at least 50 per cent of their populations, while some countries have yet to report administering a single dose. Israel, the UK, the US and other countries with advanced vaccination programmes have released a number of studies and data points on vaccine effectiveness and the impact on new Covid-19 cases, hospitalisations and deaths. They all show steep drops among those who are fully vaccinated. However, the spread of variants of concern (VOCs) – specifically the Delta variant—is raising new questions about vaccines and the nature of the immune response to proliferating variants.

Various tests are in use to both diagnose active infections and generate surveillance data that policymakers use to guide how they manage the pandemic. The three types of testing option for SARS-CoV-2 are antigen tests, molecular tests and antibody tests. The first two are diagnostic, while antibody tests are used to detect the presence of antibodies specific to SARS-CoV-2 in the blood. Despite some limitations, antibody testing (also known as serological testing) is likely to become more prominent in governments' vaccination strategies and plans, especially with respect to questions around boosters. Antibody testing can provide answers to key questions:

- How much virus has been in circulation (termed "seroprevalence")?
- What is the balance of infection-induced immunity versus vaccine-induced immunity ("differentiation")?
- Do those who are vaccinated have enough antibodies to provide protection?
- What is the durability of that protection?
- How are the vaccines protecting against the VOCs? What is the timeframe before the vaccines becomes ineffective?
- How do the different vaccines compare in terms of efficacy?
- How do the different platforms employed to develop vaccines compare?

Answers to these questions are important. There are billions of people globally who have yet to receive a single dose of Covid-19 vaccine, and the existence of vast pockets of unvaccinated people is directly responsible for the proliferation of variants, some of which (like the Delta variant) are highly transmissible. Current vaccines vary with respect to their effectiveness against the original SARS-CoV-2

virus and emerging variants. While death and hospitalisation rates remain low among the fully vaccinated, infection rates are increasing, including among the fully vaccinated.

Some epidemiologists, particularly in countries such as the US, are suggesting two possible approaches to dealing with the challenge of variants and declining immunity. The first one rations vaccine doses and hinges on the strategic use of antibody testing. A spot antibody test would be administered to people six months post-initial vaccination (that is, after the first dose, or the second dose if it is a two-dose course). Those who show very reduced levels of antibodies would receive a booster shot. There would be another category: those aged over 80 who are known to have lower antibody levels, as well as the immunocompromised. These people would automatically receive a booster and not have to take the antibody test. A second approach is to provide a booster to people over 50, without administering an antibody test at all; this means that most people who may have lower antibody levels would be covered. Additional data would then be used to make recommendations for when booster shots should be given to other parts of the population. For those who are not covered by the approach but have access to private-sector medicine or insurance and want additional vaccination, a fee would be charged for the booster.

A variation of the first approach was just announced by Israel's Ministry of Health. It will provide third-dose booster shots to adults who are immunocompromised. The ministry cited data that such people do not develop a sufficient antibody response after two doses of vaccine – Pfizer, in the case of Israel. The decision has generated some controversy in light of the fact that the US's regulatory body, the Food and Drug Administration (FDA), has not approved booster shots. Children under the age of 12 with weak immune systems and background illnesses are also due to receive booster shots. The UK has a variation on these approaches, as well. The government's Joint Committee on Vaccination and Immunisation (JCVI) has issued recommendations for boosters along similar lines. Those prioritised for the first stage are people aged 70 and over, as well those who are immunosuppressed, frontline health- and social-care workers, care home residents, and clinically extremely vulnerable adults – in other words, those at highest risk of severe disease. [2] Target groups for the second stage are: adult household contacts of immunosuppressed individuals; people aged 50 and over; and adults aged between 16 and 49 who are in a Covid-19 or influenza at-risk group.

The two approaches cited have implications for vaccine-production capacity, with evidence suggesting that early booster shots would require an additional 500 million doses this year in the US, Europe and some smaller countries, with low- and middle-income countries (LMICs) waiting longer for their share. Given current production capacity for mRNA vaccines (the category that includes the Pfizer and Moderna vaccines) of about 7 billion for 2022, the delay may not be more than about six weeks and may possibly be as few as two to three weeks, with the key factor the willingness of vaccine-rich countries to increase donations to LMICs. Such estimates, however, vary. One researcher in the field of immunology, endocrinology and vaccine development posits that giving boosters to people who are already immunised "could easily divert one to two billion doses of vaccines over the coming 12 months to boost people

already immunized that might otherwise go to developing countries where people have yet to receive their first immunization." [3] There will be a political debate about this, which could easily add to the amount of time that it takes for desperate governments to receive critical vaccine supply. A survey carried out by YouGov and Imperial College's Institute of Global Health Innovation (IGHI) shows that significant majorities of people in the US (69 per cent) and the UK (78 per cent) would be willing to donate their booster shots to poorer countries if they tested positive for antibodies. Using mRNA vaccination doses in LMICs would make more sense than using them as booster shots. [4] Moreover, 81 per cent of British people and 64 per cent of Americans expressed a willingness to take an antibody test at least once to ascertain their levels of protection from Covid-19. [5] In summary, there is strong public support in some quarters for using antibody testing to guide decisions about where vaccines are deployed. Political leaders will need to weigh up such issues, and take into consideration the reality that the circulation of the SARS-CoV-2 virus anywhere is a threat even to people in countries with high vaccination rates.

If doses are not distributed to countries experiencing severe outbreaks, then transmission and infection rates of SARS-CoV-2 will remain high in unvaccinated countries. This, in turn, will lead to new variants that will render current vaccines less effective. The new variants will spread even in those countries with vaccinated populations and the cycle will continue.

Determining who has some level of protective immunity and who does not, which groups should be prioritised for vaccination, and where pockets of infection have been all matter for making choices about how to deploy vaccines. While antibodies are not the only marker of immunity, testing for them is a useful tool to help political leaders make decisions about pandemic management. In a context of surging infections driven by variants and vaccine scarcity in LMICs, it will become a politically charged issue.

Key Messages

1. Political tensions will increase as rich countries race to provide booster shots to already-immunised populations while LMICs continue to be either largely unvaccinated or vaccinated with vaccines that do not provide sufficient protection against VOCs.

2. Serological testing is a valuable tool for understanding the prevalence of SARS-CoV-2 virus in the population and types of immunity (vaccinated immunity versus infection-acquired immunity). It can guide vaccination strategies, particularly for targeting hotspots and for settings where vaccine supply is limited, such as LMICs.

3. Serological testing is important for understanding the durability of protection provided by Covid-19 vaccines and natural infection, as well as how immune systems respond to emerging variants. Such

information will guide vaccine makers as they determine whether boosters and adapted vaccines are necessary. Political leaders need such data for planning and vaccine procurement.

4. Serological testing has its limitations, however.

- While it can measure antibodies, it is unable to measure the quality ("affinity" and "avidity") of those antibodies. This is crucial to understanding immunity from Covid-19 as well as whether vaccine failure is due to poor-quality antibodies and not merely the absence of antibodies.
- While it is known that neutralising antibodies are likely to be a critical part of our immune response to Covid-19, serological tests do not identify the level of antibodies needed for immunity. Biostatisticians are modelling how specific antibody levels translate to high levels of protection from disease.
- Another limitation is that antibody tests' performance negatively correlates with the number of acquired mutations and over weeks following infection/vaccination. This is due to antibody decay.

5. Companies and research institutions will need to invest in improving their antibody-testing capabilities in order to keep pace with the evolution of the virus. Correlates of immunity must be established by these tests. We will also need additional platforms to overcome challenges related to sensitivity levels of antibody tests.

What Are Antibody Tests?

Antibodies (and T-Cells)

Antibodies are proteins created by the body's immune system soon after a person has been either infected or vaccinated. Antibodies help the body fight off infections and can protect a person from contracting that disease again. How long this protection may last varies from person to person and for different diseases. [6] T-cells are also important as they raise alarm bells or kill cells that are infected. Antibodies and T-cells together fight the virus and then assist the immune system in creating a memory of the pathogen that is important for protecting a person if they are re-exposed to the virus.

Antibody Tests

Antibody or serology tests look for specific antibodies in the blood to determine whether a person has previously been infected with SARS-CoV-2, the virus that causes Covid-19. [7] They can also be used to understand whether a Covid-19 vaccine has induced an immune response. There are several types of antibody tests. (See Annex A for more on antibodies, T-cells and serological testing.)

- A nucleocapsid protein IgG antibody test is a blood test that detects IgG antibodies specific to the nucleocapsid protein of the SARS-CoV-2 virus. [8]
- The spike protein IgG antibody test detects IgG antibodies specific to the virus spike protein that develops after someone receives a Covid-19 vaccine. [9] The test can also indicate infection and exposure at a later stage.
- Finally, the spike protein IgM antibody test detects IgM antibodies, which are the first antibodies that the immune system produces following infection. IgM tests may show infections that are either recent or current.

How Is Serological Testing Done?

Serological testing can be done through either rapid diagnostic tests or laboratory-based assays that require drawn blood. [10] The former are useful for maximising patient access but results are qualitative only and may need further confirmation. [11] The latter are useful for high-throughput testing of high-risk groups, such as frontline health-workers and others who provide essential services, allowing them to keep

working or return to work. [12] Moreover, they provide both qualitative and quantitative information as well as more accurate results. The lab-based test (neutralisation assay), while more expensive and requiring a biosafety level 3 laboratory, provides a range of valuable insights. It can be used to find eligible donors for convalescent plasma; evaluate vaccine effectiveness and understand immunity; and find the specific number of infections by strengthening the serological diagnosis of infections that are asymptomatic. New, advanced point-of-care tests now provide a numerical result that indicates the level of Covid-19-specific antibodies in the blood. They show the level of a person's antibody response by measuring the quantity of antibodies in the blood sample. The test gives answers about the body's immune response to the SARS-CoV-2 virus, either post-vaccination or following a previous Covid-19 infection.

A positive test result shows that the person has antibodies from either a past infection with the SARS-CoV-2 virus or an immune-system response to a Covid-19 vaccination. A person who tests positive may still be infected or may have recovered from being infected with the virus. It is possible, however, that the antibodies detected could be from an infection from the coronavirus family of viruses, but not the SARS-CoV-2 virus. What is not clear from a positive test is how much protection the antibodies provide, or the durability of such protection. A negative test result means that a person's immune system has not developed antibodies in response to the virus, which could be for several reasons. First, it could be a true negative result. Second, a negative result could mean that a person was exposed to the virus but their immune system did not produce antibodies (false negative). This could be because either the test was performed too soon after the onset of the infection or because the person's immune system did respond to the virus but did not produce IgG antibodies. [13] A negative test can also mean that the person was infected but the antibody levels have declined with time and are no longer detectable by current assays.

Testing at Scale

Serological testing can be done in large numbers, which allows the identification of seroprevalence in the general population. It can also be more targeted and used to test specific demographic groups, such as health-care workers, adolescents or residents of care facilities. Such large-scale testing is facilitated by the enzyme-linked immunosorbent assay (ELISA), which is a sensitive and reproducible technology. "An ELISA is a set of standardized reagents and microwell plates manufactured … in batches or lots … and used for detecting and quantifying antibodies or antigens against viruses, bacteria, and other materials." [14] ELISAs make it possible to test many samples at the same time, automate the process through equipment or robotics, and computerise the calculation and reporting of results. [15] The test is done in one well or tube and involves mixing patient samples, antibodies, enzymes and antigens along with a colour-changing molecule. [16] If the colour changes then the result is positive, while no colour change means a negative result. The testing procedure is outlined below. [17]

1. "A patient sample of blood or serum (which may contain antibodies to SARS-CoV-2) is added to a well containing SARS-CoV-2 specific antigen.
2. The patient antibodies to SARS-CoV-2 stick to the SARS-CoV-2 proteins coated on the bottom of the well and the rest of the liquid sample is washed off.
3. Other laboratory-produced antibodies with enzymes attached are added and stick to patient antibodies present in the well as a 'second layer.' Excess antibody with enzyme attached is washed off, so enzyme is only present in wells when a patient has produced antibodies to Covid-19.
4. A special colourless molecule is added to the well.
5. In wells containing samples from patients who have been infected with Covid-19 and so have antibodies to the virus, the 'second layer' antibodies with enzyme act on the colourless molecule causing it to rapidly change colour, indicating a positive test.
6. This colour change can be read either by eye or by a machine called a spectrophotometer.
7. If the patient had not been infected with Covid-19, the enzyme-linked antibody would not stick to anything in the well and the colourless molecule would not change colour. This would be a negative test." [18]

ELISAs are done in "standard batches of up to 96 assays completed at the same time, allowing cheap and time-effective method for batch testing of large numbers of patient samples at the same time." [19]

Critiques of Serological Testing

Antibody testing has its share of detractors. First, some critics argue that many tests – specifically lateral-flow tests – are neither precise nor sensitive enough to generate results that can be meaningfully interpreted. Because the tests received emergency-use authorisation (EUA) as a result of the pandemic, there is limited evidence to understand how they might correlate to protection. This remains the most significant challenge. Second, for LMICs, the use case for serological testing seems to be stronger but faces some challenges. The lateral-flow tests remain inaccurate, which boosts the argument for using blood tests. However, such tests require trained phlebotomists and labs to process them. Furthermore, blood tests are more expensive than vaccine doses. Why waste scarce financial resources on antibody tests when vaccines can be purchased for less money? However, not all LMICs are the same and some do have both the human and financial resources to test. Even poor countries such as Liberia and Sierra Leone are using antibody testing. Third, there can be a mismatch between the test and what the antibodies measure. The "information that can be inferred from a positive antibody test may depend on the specific antibodies that the test detects. Some detect the presence of antibodies against the spike (S) protein, while others detect antibodies against the nucleocapsid (N) protein." [20] While many antibody tests detect the N-protein, it is not found in most Covid-19 vaccines. This means that after

receiving a Covid-19 vaccine in most cases there will not be an antibody response against the N-protein, resulting in a negative antibody test.

What Can Be Learned From Serological Testing?

While antibody testing has limitations, it can still be useful. First, from a medical diagnostic perspective there is a case for testing to ascertain a person's sero-status. There is value in establishing whether someone has antibodies when doctors want to rule out the possibility of a Covid-19 infection and, for certain reasons, it is unclear what the person's vaccine status is, or it is unclear whether there is an instance of vaccine failure. If a person is vaccinated yet tests positive for Covid-19 then an antibody test can be useful in assessing the possibility of vaccine failure to determine whether the vaccine actually triggered an immune response. Some tests can distinguish between infection-generated immunity and vaccinated immunity. With respect to the latter, there are various reasons why failure may occur. Where it does, such information is important in determining other courses of action. For example, some of these people may be suitable candidates for antibodies, which can provide protection for a period of months, depending on what antibodies are administered. [21] Also, antibody tests play a role in identifying candidates to donate plasma for use in convalescent plasma therapy.

Second, such testing is of value in understanding the seroprevalence of virus in the country's population as a whole. This would provide insight into how much virus was in circulation and, therefore, how far a country is from reaching population immunity, which scientists estimate to be in the range of 60–70 per cent of a given population either vaccinated or already exposed to the virus. This outcome is more likely to be viable in countries with high vaccination rates but is seen as increasingly unlikely as a result of ongoing challenges such as the rise of variants, vaccine hesitancy and the delay of vaccinations for children. [22] A related, yet analytically distinct, use for serological testing is determining prioritisation for vaccination. For example, some data show that people who had Covid-19 were essentially fully protected by just one dose of the Moderna and Pfizer vaccines. [23] Such a finding is useful for making the most efficient use of available vaccine supply while still ensuring that those in high-priority groups are protected. [24] Testing can help identify those with partial versus no immunity and guide deployment of vaccine supply. However, while useful, seroprevalence surveys are limited by antibody decay.

Third, serological testing has played a crucial role in helping scientists understand the extent to which current Covid vaccines are effective against VOCs, as well as their effects on immunity (see **Table 2** and **Annex B** for details on specific vaccines and VOCs). There are now several VOCs: Alpha (first detected in the UK), Beta (South Africa), Gamma (Brazil) and Delta (India). We know that the VOCs are more transmissible than the original virus and that there is some evidence that increased disease severity appears to be linked to at least a few of them. In the cases of Beta and Delta, efficacy rates are lower than against the original strain, but the vaccines still provide strong protection against death and severe

disease. Declines in antibody levels are associated with declines in protection but this does not necessarily render vaccines completely ineffective. It remains unknown how long the antibodies last.

Fourth, serological tests allow for monitoring of antibody levels, which can help in determining the length of vaccinated immunity (see **Table 3** and **Annex C** for what is known about Covid-19 vaccines and durability). This is important for understanding if and when boosters or full revaccination may be necessary. Ultimately, only testing over a period of months and years can determine length of vaccinated immunity as most tests are unable to predict when vaccinated immunity will cease. What we do know is that research shows that the length of immunity can be limited in the very young and very old. We also know that the duration of immunity that vaccines provide depends on a number of factors, including the vaccine itself. For example, in general, subunit vaccines offer shorter durability than live vaccines. [25] Subunit vaccines often require primary courses and boosters. This finding can help political leaders in resource-constrained settings make decisions about which vaccines to purchase. Serological testing can shed light on which vaccines are best in terms of creating the strongest titers [26] and which are the weakest. A recent study that analysed immunity levels to Covid-19 used data from antibody tests and showed that titers decline at least by half (and up to 80 per cent) within six months of recovery from Covid-19; models for the reduction of neutralisation titers also show a major loss in protection from Covid-19. [27] The study also found that, in people who had been vaccinated, the decline of neutralisation titers over the first three to four months after vaccination is at least as fast as the decline seen in those recovering from natural infection. [28] Such information is useful in understanding how declining immunity and antigenic variation could influence vaccine efficacy. [29] It can also be useful for generating evidence-based analyses of protection to inform vaccine strategies that can influence how the pandemic evolves over time. [30]

How Is Serological Testing Being Used?

The UK

The deployment of serological testing varies by country. For example, the UK government has a mass-testing programme comprising four pillars. The first two pillars involve virus testing. Pillar 3 uses serological testing to identify the people who have antibodies as a result of having been exposed to the virus (in place since 1 June 2020). [31] Pillar 4 comprises surveillance testing and uses virus and serological testing to understand both the spread and prevalence of the virus in the population, as well as to understand the accuracy and ease of use of home testing. [32] "Blood samples are tested for antibodies using an assay for IgG immunoglobins against the spike (S) protein, which are produced to fight the virus, irrespective of symptoms. Since March 2021, the process has involved testing samples for IgG immunoglobulins against the nucleocapsid (N) protein as well." [33] Testing is highest in England, which makes sense because it has the largest population; Northern Ireland, Scotland and Wales are all testing their populations as well. From last March until the present, weekly testing levels have been between just under 15,000 adults (from 16 to over 80 years of age) to over 23,000, with antibody levels increasing to over 86 per cent. [34] The survey does not distinguish between infection-acquired and vaccination-acquired antibodies. Finally, the UK has also used serological surveys to help prioritise groups for vaccination.

In the UK, antibody testing kits are not widely available. Tests are provided by the government to care-home residents, NHS and social-care staff and hospital patients. Blood samples must be analysed in a laboratory. There are commercial test kits that can be purchased and used for private use, but they are of varying degrees of quality, meaning that care must be taken when interpreting results. The UK regulatory body, the Medicines and Healthcare products Regulatory Agency (MHRA), has specified two criteria for serology tests: they must be at least 98 per cent accurate for both clinical sensitivity and specificity (see **Annex A** for more). The government has set up a process to independently evaluate Covid-19 antibody tests; none have reached completion, although five companies are registered at the time of writing. [35]

The US

The sheer size of the US population (over 330 million people) necessitates a different approach. The US Centres for Disease Control (CDC) is responsible for serological testing, and is working with both

public-health institutions and private-sector partners on a range of seroprevalence surveys of varying sizes, populations and locations. [36] Three types of serological surveys are being carried out:

- "Large-scale geographic seroprevalence surveys, which have been conducted across the US and initially focused on locations severely affected by Covid-19.
- Community-level seroprevalence surveys "cover smaller areas than a 'large-scale geographic survey.' They sample from select counties, and within this area, the selection of participants is completed in a systematic way. This allows for a more representative population to be tested where results might apply to other similar populations. CDC is working with state and county health departments to learn more about how Covid-19 is spreading in communities by performing serology tests in households in various communities." [37]
- Special populations seroprevalence surveys "answer questions about specific populations, such as health-care workers or pregnant people. Because they examine samples from a specific population, their findings cannot necessarily be applied to other populations. However, such surveys can help answer important questions about the risk of infection within specific populations." [38]

There are 84 antibody tests that have received EUA from the FDA. [39]

European Union

The EU issued a technical note on the use of serological testing as input into ongoing discussions about how Digital Green Certificates could be used to facilitate free movement within the EU during the pandemic. [40] The tests are being used "in sero-epidemiological studies to monitor the prevalence of SARS-CoV-2 in different population groups and areas. Such sero-epidemiological studies are performed in EU/EEA countries; the sero-epidemiological study network in the WHO European Region is coordinated jointly by the WHO Regional Office for Europe and ECDC. Studies are ongoing, but results are not yet available." [41] Serological testing in the region is challenged by the fact that the tests are not standardised or harmonised, which means that results are not comparable.

Over the course of 2020, the European Commission (EC) encouraged serological surveys to facilitate pandemic management, with a focus on understanding how quickly immunity was being developed during outbreaks. Such data proved useful to guiding vaccination and de-escalation strategies. In short, serological testing was important for both planning and surveillance. The European Centre for Disease Prevention and Control (ECDC) also pushed for serological surveys to understand age-specific population immunity, as well as to help decision-making on vaccination and prioritisation strategies against Covid-19. [42] Such studies also contributed to identifying demographic groups that are highly exposed to SARS-CoV-2 in order to focus vaccination efforts on them. Serological testing has been recommended for other uses, as well: to determine seroprevalence in a population and specific settings;

to research correlates of protection; to understand durability of immunity; and to understand vaccine efficacy in the real world after rollout. [43]

In addition to informing EU-level recommendations, serological testing has also been used by individual countries to help guide their vaccination policies. For example, France and Spain are using testing data to help prioritise groups for vaccination, while Italy is using serological surveys to understand the vaccine-induced immune response, better specify that response, measure the length of immunological memory and identify correlates of protection. [44] Neighbouring Spain is leveraging the test to estimate the prevalence of IgG antibodies against the virus. [45] Several countries are using serological testing to determine levels of the virus over time. Italy is examining the size and extent of the virus in addition to its frequency in different demographic groups; Germany is surveying its general population as well as critical groups such as health-care workers. [46]

Israel

The use of serological testing in Israel has evolved over time and is no longer done on a mass scale. Serological testing had been administered in hospitals or by health providers and was available to anyone. A positive test for antibodies allowed unvaccinated people to secure a Green Pass, which allowed people who recovered from Covid-19 – as well as those who had been vaccinated – to participate in various activities, such as going to synagogues and gyms, dining indoors at restaurants and attending events such as concerts. But the policy generated a surge in demand for serological testing, particularly among ultra-Orthodox and young Arab communities where vaccine hesitancy is high. [47] In the absence of proof of vaccination, people had to prove that they had recovered from Covid-19, evidenced via a serology test and issued according to guidelines from the Ministry of Health. The rising demand for testing led to a reversal of the policy, as the government wants to encourage vaccination. Serological testing is currently available for only a few groups. It is offered to pregnant women who think they may have had Covid-19 and want to be tested prior to getting vaccinated, and people with medical issues, such as those who are immunocompromised. [48] It is mandatory only for non-Israelis who want to enter the country, as well as for Israelis who were vaccinated abroad. Israel no longer has a Green Pass, thanks to very low infection rates. All restrictions have been cancelled, including mask mandates. As a result, there is no longer a need to prove antibody status (via either vaccination or a serological test). There are, however, discussions ongoing about changing the policy in light of breakthrough infections arising from the fast-spreading Delta variant.

Low- and Middle-Income Countries

The use of serological testing in LMICs requires a differentiated approach. For countries with weak health infrastructure and few financial resources, serological testing may not make sense when the priority is securing vaccines and supporting infrastructure such as syringes, needles, trained health workers, and cold and ultra-cold chain equipment if required. For LMICs with more resources, serological testing can be beneficial. Take, for example, the case of India, where it proved invaluable for the government with respect to informing public-health officials about which groups were most vulnerable, the dynamics of transmission and how to enact control measures. [49] Serological testing first took place in Mumbai in 2020, with results showing that 16 per cent of residents in high-rises had antibodies compared to 57 per cent of the slum populations, meaning that the former population were more vulnerable to the virus. [50] Confirmation of this finding came from the Mumbai Municipal Corporation that showed that 90 per cent of second-wave infections were in high-rises. [51] Testing of various groups and settings could be carried out to inform vaccine-distribution strategy as well as deploying measures such as mask-wearing and hygiene campaigns. India has found itself short of Covid-19 vaccine supply to the point that it stopped vaccine exports in March in order to supply its huge domestic population. A data-driven strategy would suggest that vaccinations be provided to those without infection-acquired immunity and those most susceptible to infection.

Lithuania also embraced serological testing, largely as a result of having scant Covid-19 vaccine supply. As a result of not being able to cover the whole population, the government has been forced to prioritise those most at risk. This is accomplished by assessing the levels of neutralising antibodies. According to the country's Ministry of Social Security and Labour, there are approximately 13,000 people living in care facilities, which have a staff of more than 8,000; about 40 per cent of the patients and staff have already had Covid-19 and will be excluded from the vaccination programme. [52] Rapid antibody tests will be done before administering a vaccine shot in order to determine whether a person has already been infected with Covid-19. [53] The ones who test positive will also be excluded from vaccination. In the context of scarcity, there is a use case for serological testing for countries with the resources to carry it out.

It was serological testing in Lagos, Nigeria, that first gave public-health authorities actual data on the prevalence of the virus in Africa's most populous country. Testing showed that more than 20 per cent of Lagos residents had antibodies for the virus. The findings indicated that the levels of infection were much higher than previously understood (confirmed infections at that point were only in the tens of thousands). More specifically, the results showed the prevalence of antibodies was 9 per cent in Gombe state, 19 per cent in Nasarawa state and 23 per cent in Lagos state, where more than 16 million people live. [54] A number of African countries committed to using serological testing to understand the extent of infection in their populations. Among them are Liberia, Sierra Leone, Zambia, Zimbabwe, Cameroon and

Morocco. Test results can be a central part of vaccination-prioritisation strategies given how little vaccine is available on the continent.

The Serological Test Kit Landscape

A range of institutions have been involved in developing serology tests, including research organisations, commercial entities and national governments. Test designs vary according to how they will be used. For example, the US CDC developed a serological test to support its national surveillance and research programmes. Regulatory bodies check and approve these tests.

There are four types of tests on the market:

"1. Neutralization tests can indicate whether the patient has active, functional antibodies to the pathogen in question by measuring how much the antibodies can inhibit viral growth in the lab (Figure 1). This can be used with SARS-CoV-2 virus in a biosafety level 3 setting or with pseudoviruses that express certain SARS-CoV-2 proteins in a lower biosafety level setting.2 Surrogate neutralization assays may use a modified ELISA technique (see below) to establish levels of neutralizing antibodies.

2. Chemiluminescent immunoassays (CLIAs) shows whether a patient has antibodies to a pathogen by displaying a fluorescent signal when patient antibodies interact with virus proteins.

3. Enzyme-linked immunosorbent assays (ELISAs) are more rapid serology tests performed in a lab that provide a readout of antigen–antibody interactions. Essentially, patient antibodies are 'sandwiched' between the viral protein of interest and reporter antibodies, so that any active patient antibodies are detected.

4. Lateral flow assays (LFAs), also called rapid serology tests, display a colorimetric, qualitative readout of the presence of antibodies. These are often used in point-of-care settings. The patient sample is flowed over a membrane that has the target antigen anchored. If the sample contains antibodies specific to that antigen, they form a complex that results in a coloured band on the strip. These are functionally similar to pregnancy tests." [55]

Although the spike protein is the only protein used in current vaccine designs, there are several serology tests with a target antigen other than the spike. Many companies produce tests that detect immunity from infection as well as vaccinated immunity. These companies operate through point of care. (See **Table 4**) The price for these tests varies widely by company, countries and so on.

As SARS-CoV-2 mutates, current serology tests will decline in accuracy, so it is critical to develop tests that can account for emerging variants. A recent breakthrough serodiagnostic technology has emerged with the capacity to overcome the inherent technological limitations of existing serology platforms. It is a testing technology that will shed light on whether someone has been exposed to Covid-19 variants. Researchers at the University of Aberdeen, in collaboration with biotech company Vertebrate

Antibodies and NHS Grampian, have developed a serology test that can detect antibody responses to the virus with 100 per cent specificity and more than 98 per cent accuracy. [56] The technology employed is a game-changer in the diagnostic sector and is likely to soon be adopted by many in vitro diagnostic companies and pharma companies to develop more accurate serology tests for other pathogens, and for vaccine development and efficacy studies. Key to the development of the new test is EpitopePredikt, an artificial intelligence (AI) software that identifies the virus's specific elements "hot-spots", known as immunodominant epitopes, that activate the body's immune system. The selected viral elements were assembled and displayed as they would naturally appear in the virus, using a bioengineered structure. Focusing on immunodominant epitopes enriches for the positive signal, as subdominant and cross-reactive regions that mask and interfere with the signal are eliminated. Multiple viral elements corresponding to different SARS-CoV-2 proteins can be assembled into one complex that will overcome the population's humoral response heterogeneity. As a result, test detection rates are improved. For instance, the test developed utilises five SARS-CoV-2 proteins in one test, rather than one antigen (either the spike or nucleocapsid).

Accumulating mutations are one reason for the decline in performance of current serology tests. Mutations abolish antibody binding sites and often create new antibody responses that the novel technology can capture, simply by incorporating prevalent mutations into the test. The same group has developed a differential Covid-19 test that can distinguish between vaccine-induced and infection-induced antibody response. The researchers are also developing a test that accurately identifies threshold levels of antibodies necessary for protection. This is a significant advance given that we currently have only biostatistical models that predict correlates of immunity. The technology can also be utilised for assessing the impact of a single/multiple mutation on antibody response, evaluating vaccine performance on emerging variants and monitoring variants. Importantly, the technology is compatible with established platforms with no requirement for specialised laboratories, equipment and training. It is therefore designed to support national health services and LMICs.

Conclusion

Understanding how antibodies interact with the SARS-CoV-2 virus is critical for effectively responding to the pandemic, particularly in the context of the proliferation of variants. Serological testing has evolved since its inception and is a useful tool in several ways. It can help doctors understand immunity (and vaccine failure) on an individual level, determine seroprevalence in different demographic groups and at the population level, and provide answers about vaccine durability. Moreover, serological testing can complement antigen testing as the latter may not always be fully accurate in terms of understanding infection levels. Political leaders need this information to guide decision-making about vaccination strategy, especially in settings where vaccine supply is limited and within the context of proliferating variants.

There are, however, limitations. Conventional serological tests' accuracy will continue to decline as SARS-CoV-2 mutates unless companies that make the tests implement novel technologies designed to overcome such challenges. Serological testing is unable to determine correlates of immunity, with few exceptions. Further investments in research to both develop better serological tests and adopt novel platforms will be necessary to improve our understanding of how antibodies work, so that vaccine development and vaccination strategies can be refined and made more effective.

The threat posed by newly emerging viral infections is one of the top global challenges for humanity. The ongoing Covid-19 pandemic shows the urgent need for future preparedness in order to fight infectious diseases that can evolve into pandemics. Antibody testing is an important part of coping with not only Covid-19 but also future outbreaks.

Table 1 – Covid-19 vaccines

Vaccine (type)	Approval Status	Efficacy	Efficacy against VOCs	Number of Doses	Cold Storage Requirements
Pfizer/ BioNTech (mRNA)	WHO EUL; US FDA; UK MHRA	95% (clinical)	Alpha: 87–95%	2 (3 weeks apart)	-20°C transport (5-day lifespan at 2°C to 8°C)

		90–91.3% (real world)	Beta: 72–75% Gamma: Works, minimal loss of neutralisation Delta: 88%, some loss of neutralisation		
Moderna (mRNA)	WHO EUL; US FDA; UK MHRA	94.1% (clinical) 90% (real world)	Alpha: Works Beta: Works, some loss of neutralisation Gamma: Works, minimal loss of neutralisation Delta: Works, some loss of neutralisation	2 (4 weeks apart)	-20°C transport (30-day lifespan at 2°C to 8°C)
Oxford/ AstraZeneca (Viral Vector)	WHO EUL; UK MHRA	76% (clinical US) 67–90% (real world)	Alpha: 66–74% Beta: 10–22%	2 (4 to 12 weeks apart)	2°C to 8°C (at least 6-month lifespan)

			Gamma: Works, minimal loss of neutralisation Delta: 60-67% (UK)		
Janssen/ Johnson & Johnson (Viral Vector)	WHO EUL; US FDA; endorsed by Africa Regulatory Taskforce	66% (clinical) 72% (real world US) 68% (real world Brazil) 64% (real world South Africa)	Alpha: Works Beta: 64% (82% against severe illness) Gamma: 51% Delta: Works	1 (two-dose trial in process)	2°C to 8°C (3-month lifespan; 2-year lifespan if stored at -20°C)
Sinopharm (Inactivated)	WHO EUL	78.1% (clinical); real world data may point to lower efficacy	Alpha: Works Beta: Works, minimal loss of neutralisation Gamma: Unknown Delta: Unknown	2 (3 weeks apart)	2°C to 8°C

Sinovac/ CoronaVac (Inactivated)	WHO EUL	50–83.5% (depending on clinical trial)	Alpha: Works Beta: Works, minimal loss Gamma: 50% Delta: Unknown	2 (2 weeks apart)	2°C to 8°C	

Table 2 – Notable Covid-19 strains so far

WHO Name	Strain Name	First Detected	Class of Variant	Mutations	Attributes*
Alpha	B.1.1.7	Kent, UK	Concern	N501Y (increases transmissibility) P681H 69/70 deletion	~50% increased transmission Potentially increased severity based on hospitalisations and case fatality rates No impact on susceptibility to EUA monoclonal antibody treatments Minimal impact on neutralisation by convalescent and post-vaccination sera

Beta	501Y.V2 or B.1.351	South Africa	Concern	N501Y (increases transmissibility) E484K (reduces antibody recognition) K417N (reduces antibody recognition)	~50% increased transmission Significantly reduced susceptibility to the combination of bamlanivimab and etesevimab monoclonal antibody treatment, but other EUA monoclonal antibody treatments are available Reduced neutralisation by convalescent and post-vaccination sera
Gamma	P1	Brazil	Concern	L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G, H655Y, T1027I	Significantly reduced susceptibility to the combination of bamlanivimab and etesevimab monoclonal antibody treatment, but other EUA monoclonal antibody treatments are available Reduced neutralisation by convalescent and post-vaccination sera
Delta	B.1.617 (February 2021)	India	Concern	Carries the L452R spike mutation, among others	Potential reduction in neutralisation by some EUA monoclonal antibody treatments Reduced neutralisation by post-vaccination sera

***** *Entries in this column are taken directly from CDC, "SARS-CoV-2 Variant Classifications and Definitions," CDC website, 4 June 2021, available online at https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-info.html#Concern*

Note: Table is an updated version of one that appears in Hermione Dace, Brianna Miller, Rania Ramli, Daniel Sleat, Eva Thorne, and Ryan Wain, "The New Necessary: How We Future-Proof for the Next Pandemic," Tony Blair Institute for Global Change, 26 February 2021, available online at https://institute.global/policy/new-necessary-how-we-future-proof-next-pandemic

Table 3 – Vaccine durability

Drug Maker and Date of EUA	Available data on durability	Are boosters under development?
CanSino 20 June 2020	Immunity against Covid-19 found to wane "significantly" after six months.[57] Company claims that a booster shot six months later led to a seven-to-ten-times increase in neutralising antibody levels, with expected efficacy over 90%.[58]	Yes
Sputnik V Authorised for limited use in August 2020, without either safety or efficacy data from Phase III clinical trials[59]	There are conflicting claims and concerns about lack of access to full data. Russia's Health Ministry scientist stated that revaccination with Sputnik V is possible after six months since immunity weakens.[60] However, the head of the Gamaleya Research Institute asserts that the vaccine will confer protection for up to two years.[61]	Yes
Sinovac	CEO claims an 80–90% efficacy rate within two months after two shots, but this has yet to be independently verified. The company is now analysing data on protection rates after six months as well as	Yes

31 August 2020	conducting experiments on administering a third injection to recipients to see if there is a higher protection level.[62]	
Sinopharm 9 December 2020	"Bahrain and the United Arab Emirates have also achieved high vaccination coverage, predominantly with Sinopharm. They also experienced recent COVID-19 surges, and are offering a booster dose of Pfizer six months after two Sinopharm doses, because of concerns two doses of Sinopharm may not provide sufficient protection."[63]	N/A
Pfizer 11 December 2020	Efficacy for its vaccine remains at 91.3%, measured seven days through up to six months following the second dose.	Yes
Moderna 18 December 2020	It remains effective at six months, but antibody levels did seem to fall according to the increasing age of the study participants (ages 18–71)	Yes
AstraZeneca 30 December 2020	"While it is too soon to gauge the optimal immune response to, or the duration of effect of a COVID-19 vaccine, we can refer to results from a previous clinical trial of a vaccine in development against another coronavirus (responsible for causing Middle East Respiratory Syndrome [MERS]) in which an adenoviral vector platform was used. These results demonstrated that the vaccine-induced immune response was maintained for over a year."[64]	Yes

Johnson & Johnson 27 February 2021	"The data showed that the durability of the immune response lasted through at least eight months, the length of time evaluated to date. The two preprint study summaries have been submitted today to *bioRxiv*."[65]

Table 4 – Selected antibody test manufacturers

Developer	Test	Technology	Target	Sensitivity	Specificity
Abbott Laboratories Inc.	AdviseDx SARS-CoV-2 IgG II (Alinity)	Semi-Quantitative High Throughput CMIA	Spike	98.1%	99.6%
Abbott Laboratories Inc.	Alinity i SARS-CoV-2 IgG	High Throughput CMIA	Nucleocapsid	100%	99%
Abington Health Inc.	AbC-19 – SARS-CoV-2 Rapid IgG Neutralising Antibody Test	Lateral Flow	Spike	98.3%	99.56%
Assure Tech (Hangzhou Co. Ltd)	COVID-19 IgG/IgM Rapid Test Device	Lateral Flow	Spike and Nucleocapsid	100% (IgM)	98.8% (IgM)

				90% (IgG) 100% (combined)	100% (IgG) 98.8% (combined)
bioMérieux SA	VIDAS SARS-CoV-2 IgM	ELFA	Spike	100%	99.4%
BioPanda Regents	COVID-19 IgM/IgG Rapid Test Kit	Lateral Flow	Spike	100%	99.2%
Roche Diagnostics, Inc.	Elecsys Anti-SARS-CoV-2 S	High Throughput ECLIA	Nucleocapsid	100%	99.8%
Siemens Healthcare Diagnostics, Inc.	ADVIA Centaur SARS-CoV-2 IgG (COV2G)	Semi-Quantitative High Throughput CLIA	Spike	100%	99.9%

Annex A: Antibodies and Serological Testing

Serological tests vary depending on which viral antigens are measured; receptor-binding domain, nucleocapsid (N) protein, and spike (S) protein are the ones most widely used to detect antibodies for the virus. Tests that focus on the N or S proteins might predict immune status better. Some antibody tests measure IgA, which is the main antibody isotype associated in the mucosal immune system. It is found in the respiratory tract, saliva, tears, the gastrointestinal tract and colostrum. The clinical impact of IgA antibody following infection or vaccination have been fully studied. This is noteworthy given that the SARS-CoV-2 virus initially infects the upper respiratory tract. [66]

Serological test results provide just a partial understanding of the immune system responses against SARS-CoV-2 because T-cell mediated responses are not considered. "The induction of SARS-CoV-2-specific memory T-cells is also important for long-term protection and play a vital role in virus clearance. T-cells may be maintained even if there are not measurable levels of serum antibodies. This further complicates the assessment of the existence and duration of immunity based on antibodies only. Individuals may also have varying immune responses to infection." [67]

IgM, IgG and IgA antibodies against S and its subunits are detectable within one to three weeks post-infection. IgM and IgA antibodies decay faster than IgG, while IgG and IgM antibodies can arise at about the same time; the importance of IgA in the virus is unknown. [68] It is not clear how long anti-SARS-CoV-2 antibodies last post-infection; what is clear is that IgG antibodies – including IgG against the S and N proteins – remain for at least several months in most people. [69] While mild disease generates an antibody response, more severe disease is associated with an even stronger antibody response, characterised by IgA, IgG and IgM all showing higher titer levels (the higher the titer, the better the body is likely to protect against infection) and remaining longer. There is variation in the amount of time that antibodies remain present, depending on which test is taken, with some studies finding that between 5 per cent and 10 per cent of participants do not develop detectable IgG antibodies post-infection. [70] While the main determinants of protection from infection are neutralising antibodies, serological tests – with one notable exception – do not indicate the exact levels of SARS-CoV-2-neutralising antibody that are protective against reinfection post-vaccination. Biostatisticians are developing models to determine correlates of protection, but these remain hypothetical predictive models and cannot replace experimental data.

Two characteristics are central to antibody tests. Their *sensitivity* is their ability to identify people with antibodies to the virus (true positive rate), while their *specificity* relates to identifying people without the antibodies (true negative rate). The former is estimated by whether the test can pick up antibodies in blood samples from people who have confirmed cases of Covid-19 with a nucleic acid amplification test

(NAAT). Specificity is estimated by testing large numbers of samples that were collected and frozen prior to the virus circulating to show that it does not produce positive results generated by the presence of other causes of respiration infections, such as other types of coronaviruses. [71] The estimates for both sensitivity and specificity include 95 per cent confidence intervals. These are "...the range of estimates we are about 95 per cent sure a test's sensitivity and specificity will fall within given how many samples were used in the performance validation. The more samples used to validate a test, the smaller the confidence interval becomes, meaning that we can be more confident in the estimates of sensitivity and specificity provided." [72]

Tests are also described by their positive and negative predictive values (PPV and NPV). These measures are calculated using a test's sensitivity and its specificity, and using an assumption about the percentage of individuals in the population who have antibodies to SARS-CoV-2 (which is called "prevalence" in these calculations). Every test returns some false positive and false negative results. The PPV and NPV help those who are interpreting these tests understand – given how prevalent individuals with antibodies are in a population – how likely it is that a person who receives a positive result from a test truly does have antibodies to SARS-CoV-2 and how likely it is that a person who receives a negative result from a test truly does not have antibodies to SARS-CoV-2. The PPV and NPV of a test depend heavily on the prevalence of what that test is intended to detect. Because all tests will return some false positive and some false negative results, including tests that detect antibodies to SARS-CoV-2, broad use of the tests – when not appropriately informed by other relevant information, such as clinical history or diagnostic test results – could identify too many false-positive individuals." [73]

Annex B: Covid-19 Vaccines, Immune Response and Variants of Concern

The Lancet recently published a research letter by scientists at the Francis Crick Institute and the National Institute for Health Research (NIHR) UCLH Biomedical Research Centre reporting results from a study that show that two AstraZeneca doses induce lower levels of antibodies with the ability to detect and fight the Delta variant than against other variants; the Pfizer vaccine performs better. [74] While both vaccines showed a decline in protection their effectiveness remains high. Public Health England (PHE) published results on Pfizer and AstraZeneca showing that both are as effective at preventing hospitalisation in the case of the Delta variant as they are against the Alpha variant. Despite declines in antibodies against the Delta variant, Pfizer is 88 per cent effective against symptomatic Covid while AstraZeneca is 60 per cent effective. The results mean that full courses of both vaccines are necessary to maximise protection against the Delta variant. BioNTech, Pfizer's partner, is trialling a third dose to determine whether it would increase protection against variants; it is also weighing the development of a variant-specific vaccine that could replace the existing one, or be used alongside the existing one, which may be more effective. [75] AstraZeneca is also working on a booster. Recent data from Israel and a study about to be published in the United Kingdom suggest that antibodies from vaccines appear sufficient for non-Delta variants for at least nine months – but only for six for the Delta variant. The Delta variant affects both the unvaccinated and the vaccinated. In the case of the latter, the Delta variant becomes an issue with declining immunity.

On 29 June 2021, Moderna announced that its mRNA vaccine produced multiple antibodies against several variants, with only a "modest reduction in neutralising titers" against the Delta variant. Moreover, "vaccination with the Moderna COVID-19 Vaccine produced neutralizing titers against all variants tested, including additional versions of the Beta variant (B.1.351, first identified in South Africa), three lineage variants of B.1.617 (first identified in India), including the Kappa (B.1.617.1) and the Delta variants (B.1.617.2); the Eta variant (B.1.525, first identified in Nigeria); and the A.23.1 and A.VOI.V2 variants first identified in Uganda and Angola, respectively." [76] What is not clear from the company's announcement is the impact on the vaccine's effectiveness, as percentages were not provided. Data from the study were submitted to the preprint service, bioRxiv, ahead of publication in a peer-reviewed journal. [77] Moderna is exploring the possibility of including protection against the various variants directly in its main candidate. These potential doses could not be sold – at least early on – to those who are already vaccinated, and they would be slightly more expensive for Moderna to make. [78] The makers of the Russian viral-vector Covid-19 vaccine, Sputnik V, declared that the two-shot vaccine provides a high level of effectiveness (around 90 per cent) against the Delta variant, although at a lower level (2.6 times lower) than against other strains. [79] Data have not been made available publicly. Johnson & Johnson

recently released information indicating that its single-shot vaccine protects against the Delta variant. A researcher and former deputy director at the Chinese Center for Disease Control and Prevention said on China Central Television that antibodies triggered by two Chinese inactivated vaccines (Sinopharm and Sinovac) are less effective against the Delta variant compared with other strains but that the shots still offer protection. [80] Data on the single-shot CanSino vaccine are not available. In positive – yet somewhat unexpected – news, Johnson & Johnson announced on 1 July that it had submitted preprint study summaries to bioRxiv containing "…data that demonstrated its single-shot COVID-19 vaccine generated strong, persistent activity against the rapidly spreading Delta variant and other highly prevalent SARS-CoV-2 viral variants. In addition, the data showed that the durability of the immune response lasted through at least eight months, the length of time evaluated to date … These data showed that the Johnson & Johnson single-shot COVID-19 vaccine elicited neutralizing antibody activity against the Delta variant at an even higher level than what was recently observed for the Beta (B.1.351) variant in South Africa where high efficacy against severe/critical disease was demonstrated." [81] The after-effects of the announcement were short-lived. A new study based on lab experiments conducted on blood samples has found that the Johnson & Johnson vaccine is much less effective against the Delta variant. The study, posted online on 20 July, contradicts results from smaller studies the company has previously published indicating the single-shot vaccine is effective against the Delta variant. The study has not yet been peer-reviewed. [82] This announcement has revived discussions among virologists as to whether people vaccinated with the Johnson & Johnson vaccine should receive a booster shot with either Pfizer or Moderna.

The current direction of travel in discussions among immunologists and public-health officials in rich countries is to explore the feasibility of combining different vaccines to generate a better immune response to VOCs. This is a direct response to the rise in breakthrough infections among vaccinated people. Third doses to strengthen immunity are being explored in clinical trials in the UK, for example. Some countries are going ahead with such a programme in the absence of clear data justifying the need for boosters. United Arab Emirates, Thailand and Bahrain are already providing third doses to some who are vaccinated with vaccines made by AstraZeneca, Sinopharm and Sinovac. Both previously administered shots and mRNA vaccines are being used.

Annex C: Covid-19 Vaccines and Durability

Knowledge of durability is currently imprecise and will require the passage of time to make more informed assessments. We know that Pfizer and Moderna last for six months, with the possibility that annual shots will be necessary. Data for Johnson & Johnson's vaccine are accurate for 71 days only. There are conflicting reports about the length of immunity for the Sputnik V vaccine. Serology tests administered to some Russians showed a drop in antibodies, leading to revaccination with third and fourth shots of the vaccines. [83] However, Russian researchers counter that the revaccinations are not required because the immediate increase in antibodies post-revaccination indicated as much. A fall in antibodies does not necessarily indicate that immunity levels have fallen below protective levels; moreover, memory cells are involved in conferring protection against Covid-19. [84] The number of people revaccinated is believed to be small, and the head of the Gamaleya Research Institute that made the vaccine asserts that the vaccine will provide protection for two years. In a similar vein, AstraZeneca has expressed optimism that its vaccine may be effective for at least a year, based on other studies. University of Oxford (AstraZeneca's partner) has an unpublished study, reviewed by the *Financial Times*, that shows that a third dose of the two-shot vaccine increased antibodies. [85] More time is needed for trials in order to be confident about durability, especially in the context of variants. [86]

Sinopharm has been in use in Bahrain and UAE since December. Both countries are experiencing a surge in Covid-19 infections and are already offering Pfizer as a booster to people, which indicates a concern that Sinopharm has not provided sufficient protection. [87] The focus of the boosters in Bahrain is those with weakened immune systems, the elderly, people over 50 and those who are obese. Sinovac is studying (having reached Phase II clinical trials) a third dose of its inactivated vaccine, administered three to six months after the second shot, with the company claiming that the additional dose would increase antibody response by tenfold in just one week; Phase III trials are next. [88] The company is also studying immunogenicity of the variant strains. CanSino is studying a booster shot to go with its vaccine, as well as one to be given to people inoculated with other vaccines. [89] The booster for the CanSino single-shot vaccine would be administered roughly six months after the first dose; in studies the booster generated a seven- to ten-fold increase in neutralising antibody levels, leading to efficacy of over 90 per cent. [90]

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