Immunity & COVID-19

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Executive summary

Understanding immunity to COVID-19, induced by both natural infection and through vaccination, is key to our ability to exit the current pandemic.

In this report, you will find the answers to key questions around what we know and don't know about immunity to the virus SARS-CoV-2, which causes the disease, COVID-19. This includes the effectiveness of the immune response, how to measure and track immunity, the benefits of vaccine-mediated immunity, and the longevity of any immunity conferred. We have sought to make the subject matter relevant to both the public policy discussions that are ongoing and those that will arise as the pandemic situation begins to change over the next few months.

It is important to say that there are differing degrees of immunity. Different individuals will create different immune responses to invasive pathogens, and the case of the SARS-CoV-2 virus is no exception. Some people create a very effective immune response, so they will not get sick again from SARS-CoV-2 and will not pass the virus to anyone else (so-called 'sterilising' immunity), while others will make antibodies* and be protected from the disease COVID-19, but may still be infected with the SARS-CoV-2 virus and transmit it to others ('protective' immunity).

Immunity can be difficult to measure. The best marker currently is neutralising antibodies*, which have been shown to persist in some individuals up to 8 months after original infection. While immunity can also be measured by looking at memory immune cells, methods for doing this at scale are not currently available. Immunity can wane over time and this can lead to the small chance of reinfection. Exactly how long immunity following COVID-19 lasts will need a longer time to determine.

Vaccine-mediated immunity is preferable and safer than naturally acquired immunity. While clinical trials recorded the ability of the vaccines to protect from COVID-19 disease, questions remain around whether the vaccines being administered currently will prevent people from being able to carry and transmit the SARS-CoV-2 virus. Currently not enough time has elapsed between the vaccines first being administered in humans and the present time for durability of vaccine-induced immunity to be determined, but this is the subject of ongoing phase 3 vaccine studies.

The answers to all these questions will have a profound impact on the policy decisions that the Government makes. Questions over how immunity can be measured, how long immunity lasts and the reliability of such tests can undermine the usefulness of 'vaccine passports', and whether the vaccine stops the spread of the SARS-CoV-2 virus to others or simply stops the person who has been vaccinated from contracting the disease, COVID-19, will be vital to finding our way out of this pandemic. The longevity of immunity conferred by a vaccine will determine whether there will be need for an annual COVID-19 vaccination programme, like that currently carried out for flu.

With so many key policy issues resting on issues of COVID-19 immunity, it is integral to the country's future that we immediately implement a robust and widespread immune monitoring programme to understand in detail the immunity conferred through vaccination in different individuals. It is also crucial that we ensure proper surveillance of viral variance at a global scale and through this the ability of any variants to escape vaccine-mediated immunity. With the UK being an international leader in the rollout of COVID-19 vaccines, we can lead the world in immune monitoring protocols that will allow us to emerge from this pandemic more safely and quickly. This is an opportunity that we should seize with both hands.

This report aims to summarise what we know, what we do not, about immunity to COVID-19, and to provide research recommendations. An asterisk (*) denotes words that appear in the glossary (Annexe 7).

What do we know about immunity to SARS-CoV-2 following natural infection?

Does everyone make the same immune response to SARS-CoV-2?

No. Immune responses can vary hugely between different individuals. Some people seem to make a very effective immune response such that they cannot be infected again and therefore will not get sick again from SARS-CoV-2 and will not pass the virus to anyone else (so called 'sterilising' immunity*). Other people make antibodies* and are protected from disease, but not from future infection by the virus.[1] In theory these people could still pass the virus to other people.

People vary in the number of antibodies* they make after infection, in the quality of those antibodies* (how good they are at preventing infection) and in the number and quality of the T cell* response they make. We don't yet know exactly how important these variations in antibodies* and T cells* are in terms of levels of protective immunity* but ongoing research (by the UK Coronavirus Immunology Consortium) is designed to answer this question.

How can we tell whether a person has encountered the virus and mounted an immune response?

Currently the easiest indication is whether they have antibodies* in their blood which recognise unique components of SARS-CoV-2. Memory T cells* and memory B cells* able to recognise these unique components also indicate prior infection but are harder to measure. The presence of antibodies* does not always predict the presence of specific T cells* or memory B cells*.[2, 3]

What does effective immunity to SARS-CoV-2 look like?

The immunological measurements that have been made so far have mostly been of total IgG* antibody levels*, with some papers also reporting IgA*, IgM* and neutralising antibody* levels. A few papers have reported memory B* and T cell* levels. Follow-up of these cohorts is needed to determine which metrics correlate with protection. In addition, there are more detailed immunological metrics that are candidates for correlate of protection* which have not yet been fully investigated.

The initial immune response appears to correlate with severity of disease (i.e. the more severe the illness you experience, the stronger your subsequent immune response). However, in some cases the immune response itself is pathogenic, for example producing antibodies*, [4] that damage your tissues,[5, 6] or inducing excessive inflammation,[7] so we need to be able to distinguish between a protective immune response and a damaging immune response.

What proportion of infected individuals mount an effective immune response?

The majority of people who have a confirmed infection make some form of immune response but whether this is effective at preventing reinfection is not easy to determine. Around 90% of recovered patients have detectable anti-SARS-CoV-2 antibodies* for several weeks or months after their infection.[2, 8, 9] Studies to determine the frequency of reinfection in healthcare workers indicate that presence of SARS-CoV-2-specific antibodies* offers approximately 95% protection against COVID-19 symptoms and about 75% protection against being infected.[1, 10] Presence of T cells* that can respond to SARS-CoV-2 has also been shown to be a protective factor.[11]

Can immunity be lost over time? If so, how?

Yes, immunity can be lost. Antibody* concentrations can decline over time. The rate of decline varies from virus to virus. For example, Respiratory Syncytial Virus (RSV) elicits a very short-lived immunity and wanes over time, whereas immunity to measles can last a lifetime.[12] In some cases, another disease can damage your immune system and cause you to lose immunity that you already had, for example, HIV infection.

Even if antibodies* are lost, immunity can be reactivated. Antibody-secreting cells can be renewed from the memory B cell* population, with help from memory T cells*, if the person encounters the virus again (either naturally or by vaccination, or booster vaccination). So, while measuring antibodies* is one good indicator of immunity, it may be that measurements of memory lymphocytes* of different types would provide a better correlate of protection*.

How long does this immunity last?

Currently, the best marker that we have of protection from future disease is the level of neutralising antibody* in the blood. This is the component of the antibody* repertoire that can stop viral entry into cells. While a decline in neutralising antibody* is seen,[13] it can persist in individuals for at least 8 months, and possibly longer, after infection.[3] B* and T* lymphocytes* recognising SARS-CoV-2 can also be seen after 8 months, and T cells* capable of mounting robust responses have been detected after 6 months.[3, 14] As SARS-CoV-2 has only been around for a year, ongoing research is required over the coming months and years to fully understand how long immunity lasts after infection.

Is viral load connected to levels of immunity?

Severely ill patients generally have higher viral loads[15] than those with mild illness. In one study, in severe patients in the acute phase of illness (2–3 weeks), higher viral loads coincided with higher IgM* antibody* levels. IgM* antibodies* are the rapid responders to the infection emergency but are not that good at fighting the virus and do not last very long. In contrast, highly effective IgG* antibody* levels did not reflect the viral loads or were negatively correlated with them[16] in the acute phase of illness. People with a high viral load during the acute phase of their infection seem, several weeks later, to have higher levels of antibodies*.

Could people with evidence of an immune response have 'immunity passports' and fully return to life pre-COVID activities and mixing?

Because each person has a different immune response, and immunity may wane over time, we could only issue an 'immunity passport' if we had accurate ways of measuring a person's immunity to infection and knowing how long it will last. While we do know that neutralising antibodies* are associated with disease protection,[17] and memory B* and T cell* responses are also important,[3] we do not have good enough data to be able to accurately predict an individual's level and duration of protection from SARS-CoV-2 for an 'immunity passport'. A dated vaccination certificate (as already exists for diseases such as yellow fever) would indicate that immunity is likely but would not guarantee that the person is immune. Furthermore, the presence of antibodies*, or other measures of an immune response, may not guarantee that an individual cannot spread the SARS-CoV-2 virus to others, even if they are protected from resultant COVID-19 disease themselves.

Is reinfection with SARS-CoV-2 possible?

Yes, it is possible, although not frequent. Reinfection depends upon both the level of immunity a person gains from the first infection and the level of likely exposure due to social and working environments. The absolute proof of reinfection, to rule out persistence of viral RNA*, is taken to be when both the first and the second infections have been sequenced and shown to be different variants of the virus. This evidence is difficult to acquire but at the time of writing there are 47 such documented cases worldwide,[18] which prove that reinfection is possible and in a relatively short period of time (months) between the infections.

A less rigorous way of looking for reinfection is to document a positive PCR test at a set time interval after the last known PCR or antibody* test. A study in Mexico, using a minimum interval of 30 days found 258 instances of reinfection in a cohort of 100,432 (2.6 per 1,000). Rates of reinfection have been associated with levels of anti-SARS-CoV-2 antibodies*.[9] In a UK study of 1,177 healthcare workers with detectable anti-SARS-CoV-2 IgG* antibodies*, two had a positive PCR test (but no symptoms) in follow-up with 60 days minimum interval (1.7 per 1,000).[1] Reports from Public Health England, in assessing the 202012/01 variant* and using a minimum interval of 90 days between PCR tests, showed figures of between 0.6 and 1.4 reinfections per 1,000 people.[19]

Could there be any cross-immunity with the cellular response from other coronaviruses?

Studies have now reported the presence of T cells*,[20] that can recognise both SARS-CoV-2 and other coronaviruses, such as those that cause common colds. One such study indicated that over 80% of uninfected individuals studied had T cells* capable of recognising SARS-CoV-2.[21] We don't yet know if these cross-reactive responses are protective, but a recent study found that NHS workers who had such T cells* were less likely to catch COVID-19 than their colleagues who did not have such cells[11] but the protection afforded is likely to be small.

Similarly, antibodies* that can neutralise SARS-CoV-2 have been found in a small proportion of blood samples taken from people prior to the SARS-CoV-2 pandemic.[22] These are thought to be cross-reactive with common cold coronaviruses and were found to be more prevalent in children.

Will other factors (e.g. age) have an impact on the level of immunity generated?

Yes. Previous evidence shows that older people are less likely to make effective immune responses to infection and vaccination.[23] Nonetheless, a number of studies showed that antibody* responses to infection either did not vary with age in adults[24] or were higher in older patients.[25–27] There is also evidence of a reduced breadth of antibody* responses to SARS-CoV-2 proteins in children compared with adults.[25] Others whose immune systems are compromised by immunodeficiency diseases, autoimmune diseases, or by taking certain types of medication will not be able to make as good an immune response as young healthy people.[28]

What do we know about immunity to SARS-CoV-2 following vaccination?

What sort of protection does COVID-19 vaccination give me?

What we know so far is that at least five vaccines (BioNTech/Pfizer, Moderna, Oxford/AstraZeneca, Novovax, Johnson & Johnson) reduce the number of people becoming sick from COVID-19; the vaccines seem to prevent both mild/moderate and severe COVID-19 symptoms.[29–31,41–42] Three of these vaccines (BioNTech/Pfizer, Moderna, Oxford/AstraZeneca) are currently approved for use in the UK. We don't yet know if any of the vaccines stop people becoming infected or whether they can still go on to shed virus, i.e. become infectious. The AstraZeneca and Moderna teams are assessing the incidence of asymptomatic infection and viral shedding after vaccination, to work out whether vaccination affects infectiousness.[31] Once the vaccines are widely rolled out, epidemiologists will be able to estimate the overall level of transmission reduction.

Can vaccines tell us what aspect of the immune system confers immunity to SARS-CoV-2?

Given that all published efficacy data to date has been early interim analyses, on vaccines with high efficacies, there are no data available yet on correlates of protection* following vaccination. All vaccine trial groups will look for these in due course, when more data are available.

Observational studies of SARS-CoV-2 infection as well as data from vaccine trials[32,33] are starting to provide evidence that robust neutralising antibody* titres and virus-specific T cell* responses provide protection against disease.

Are there any individuals who might not be able to generate an effective immune response following vaccination?

Yes, in the same way as we predict that older people and immunocompromised people might not make as good an immune response to SARS-CoV-2 infection, they may similarly be less likely to make as strong an immune response to a vaccine compared with a young healthy person. However, the Pfizer/BioNTech, Moderna and Oxford/AstraZeneca teams have specifically looked at the issue of ageing and found that the vaccines generate similar immune responses in older people and younger people.[29, 34, 35] There are limited efficacy data specifically for older individuals at present, but this will continue to be evaluated. None of the Phase III trials enrolled immunocompromised individuals, so there are no data evaluating the immune responses or efficacy in these groups, but vaccination is still recommended as immunocompromised individuals may be at higher risk of severe SARS-CoV-2 infection.[36, 37]

How long will immunity provided by vaccination last? What are the implications if it is not long?

We don't yet know, but the published immunity data from the disease suggests that immunity will last for at least a year.[3] Thus, the worst-case scenario would be that we need to revaccinate people at high risk of severe disease every year. Since we already have an annual winter vaccination programme for flu, this would be a feasible proposition. The emergence of novel strains of SARS-CoV-2 also highlights the possibility that the current vaccines may become less effective over time (though current mutant strains are considered to still be susceptible to existing vaccines). Future vaccines may therefore require periodic modification to most effectively combat the circulating strain(s). Again, this is not necessarily a major problem as we already update the flu vaccine every year to combat the currently circulating variants of flu.

What do we need to achieve herd immunity?

Herd immunity is when transmission of the virus within a population is markedly reduced due to the high proportion of people who are already immune. If sufficient people in the population are immune, the virus remains at low or undetectable levels, thus protecting anyone who is not yet vaccinated (e.g. infants), those unable to make a good immune response themselves (e.g. people who are frail, very elderly or immunocompromised), or those who are allergic to components of the vaccine.

Importantly, for a vaccine to confer herd immunity, it has to either stop or substantially reduce transmission. If the vaccine prevents symptoms but has little effect on infections, it cannot confer herd immunity (as vaccinated people will continue to get infected and continue to transmit the virus, but without getting the COVID-19 disease themselves).

The proportion of the population who have to be immune, or otherwise not susceptible, in order to stop transmission depends on how infectious that pathogen is (does it spread easily or not?), how long someone remains infectious (is it just a few days or many months or years?) and whether people know they are infected/infectious (do they always have symptoms or not?).

In essence, the number of people required to have immunity is deduced from a mathematical formula dependent on the R_0 value for the virus. In the case of SARS-CoV-2 and vaccine efficacies of ~95% it is estimated that 63–75% of people need to be immune to provide herd immunity[38] so we will need a high uptake of vaccines, or widespread natural immunity following infection, to achieve this.

Can the vaccine stop me getting long COVID?

The vaccines that are currently approved have been shown to effectively reduce the chance of getting COVID-19, therefore they will also reduce the risk of any long-term effects of COVID-19.

Some patients with long COVID are nervous about being vaccinated, either because they feel they made an inadequate immune response to the natural infection so would not benefit, or because they suspect they may have made an excessive or dysregulated response to natural infection that may be exacerbated by further immune stimulation. We don't yet have any data to confirm or refute these suspicions, but these data should emerge over the next few months as more and more people with long COVID are vaccinated. In the meantime, the assumption is that, like others, people with long COVID would benefit from vaccination to reduce their risk of further infection.

Does changing the interval between first and second dose affect immunity?

There is evidence from the AstraZeneca/Oxford vaccine that a longer interval between vaccine doses improves immunity.[30] There is no such evidence from the Pfizer/BioNTech vaccine, but we would not expect it to be reduced. For all currently available COVID vaccines, it is critical that everyone receives two doses of the vaccine to maximise the immunity conferred.

Will the vaccines still work against the new variants of virus?

Our knowledge of the immune system leads us to assume that vaccines will still be effective against minor variations of the virus. The antibody*, B cell* and T cell* responses that are made after vaccination are extremely diverse and recognise different parts of the virus spike protein. So, a change in one part of the protein might mean that a few types of antibodies* and T cells* will no longer recognise it but there will be a part of the immune response that will still be effective. How big a part of the immune system, i.e. how much reduction in protection the variants will cause, is still unknown.

At time of writing, there are three variants of concern. B.1.351 (discovered first in South Africa), B.1.117 (discovered first in the UK) and P.1, prevalent in Brazil. All three appear to show increased transmission, due to increased infectivity and/or escape from the immune system.

The approved vaccines were tested before the new variants were widespread, so we do not have a lot of information yet on their real-world efficacy against variants. This is being addressed over the next few weeks and months as the new variants spread.

Novavax have reported that their vaccine was 89.3% effective, in a UK population where there was a high prevalence of the 'UK variant'.[41] In Israel, where the 'UK variant' is widespread, the Maccabi Health Fund reported 92% efficacy of the Pfizer vaccine. This is in spite of laboratory tests showing slightly lower antibody neutralisation activity in the serum from patients or vaccinees against this variant.[43] The 'South African' and 'Brazilian' variants carrying the mutation E484K are more concerning, as this mutation has been associated with antibody escape in laboratory tests, and lower antibody neutralisation activity in the serum from patients or vaccinees has been shown against the 'South African' variant.

We will need to monitor emerging virus variants and check whether both laboratory and real-world immunity against them is altered. Already the vaccine companies indicate that they are working on next generation vaccines, to include the new variants.

What is the difference between naturally acquired immunity and vaccine-mediated immunity?

The obvious advantage of a vaccine is that any side effects (e.g. fever, headache, muscle aches, arm pain), if present at all, are relatively mild and short-lived (usually resolved within 72 hours). With very rare exceptions, these are insignificant in comparison to the much more serious consequences for individuals of any age who develop COVID-19 disease following natural infection. Vaccines pose no risks to your friends, family and society whereas with natural infection you may unwittingly pass the virus to someone who is unable to make a good immune response. One difference between vaccination and infection is that the dose of vaccine you will receive has been tested to ensure you develop good immunity; the amount of virus you are exposed to during a natural infection, however, is not controlled and may be too little to induce an optimal immune response or so much that it causes substantial disease.

The currently available SARS-CoV-2 vaccines focus the immune response onto one, or a small number, of virus components in a stabilised conformation that likely maximises immune responses, rather than the whole virus. So, the immune response induced by the vaccine will be highly targeted to crucial components of the virus whereas the response to natural infection will be broader, including responses to less critical or unimportant components of the virus. Natural infection has also resulted in 'off-target' autoantibodies in some cases, which could be detrimental to health. There is a fine balance here, however, as while a highly focused response to the vaccine may be more effective at blocking the original virus, it is possible that a broader response provides better protection against an expanding range of virus variants.

When the immune system responds to a virus it does so in an environment that is perturbed by the inflammation and tissue damage caused by the virus. Some common coronaviruses have the ability to subvert an effective immune response. So, in more severe cases of COVID-19 disease the immune response may not be able to work optimally. In this instance we would predict that the immune response to a COVID-19 vaccine will be better than that to the natural infection.

Vaccination is a much safer way to gain protection than through natural infection. The caveat is that immunity to any emerging virus variants of concern should be monitored closely to ensure the current vaccines are still protective.

Is there a difference in the herd immunity acquired from natural- versus vaccine-induced immunity?

We don't yet know although, as described above, the prediction is that vaccine-induced immunity will be much more durable. The most important things for herd immunity are that the immune response reduces infectivity/transmission and that it is long-lasting.

How does immunity acquired following infection interact with vaccination?

On the whole, infection-induced immunity and vaccine-induced immunity should be complementary with vaccination boosting infection-acquired immunity and natural exposure to the virus boosting vaccine-induced immunity.[44] Since we cannot be certain what levels of immunity are gained from natural infection, it is recommended that everybody is vaccinated.

What are the options if the immune system doesn't respond to vaccine?

As detailed above, herd immunity will help to protect people who haven't yet been vaccinated, can't be vaccinated for various reasons, or can't make an effective immune response. We may eventually see that some vaccines will be more effective for some people than others and so we could modify our vaccination strategies accordingly, for example, for people of different age groups, with immunodeficiencies, autoimmune disease, cancers, and so on. There are however other options for the very small proportion of people whose immune systems are so damaged that they cannot make an effective response to a vaccine, for example, patients with Common Variable Immune Deficiency (CVID). One is so-called 'passive immunisation' where these individuals are periodically given an injection of immune plasma or engineered ('monoclonal') antibodies*. Other anti-viral therapies are also being investigated. The Academy of Medical Sciences has a database[39] of preclinical therapeutic candidates under investigation. Until herd immunity is achieved, we will continue to need effective treatment options for those patients who develop COVID-19. The RECOVERY trial is continually evaluating potential treatments as they become available; an early success was to demonstrate the benefit of the steroid dexamethasone[40] for those with severe lung disease. Ongoing research to better understand the underlying drivers of disease severity, for example, ISARIC-4C and GenoMICC, will identify more potential drug targets, allowing new therapies to be developed and tested.

Research recommendations

1   **Correlates of protection and disease:** we need to identify which immune markers (antibodies*, memory B* and memory T cells* etc.) predict who is immune to COVID-19 and who is susceptible to either mild or severe disease. These markers will allow us to identify people who are at particular risk, figure out how often booster vaccinations might be needed, and to speed up the development of even better vaccines and immunotherapies. This will require long-term, detailed studies of immune response generated in vaccinated individuals and those who were naturally infected with severe, mild or asymptomatic disease.

2   **Monitoring for, and response to, new SARS-CoV-2 variants:** we need ongoing, detailed monitoring to keep track of new SARS-CoV-2 virus variants that might emerge on a global scale. This should include thorough evaluation to assess if current vaccines will continue to provide protection against these new variants. Updates to vaccine design to ensure they induce maximum protection should be implemented if necessary.

3   **Understanding viral mutations:** we need to understand which mutations are compatible with the virus remaining infectious but evading antibodies*. Some mutations will immediately cripple the virus, and we don't need to worry about these. Other mutations will not damage the virus but allow it to escape the vaccine-induced immunity. If we can predict these mutations (using structural biology modelling), we can proactively develop vaccines to combat them before they arise.

4   **Monitoring vaccine efficacy across different populations:** we need to understand how well the vaccines work in different populations (e.g. age groups), so that guidance can be adapted to make sure that the right vaccines are directed to the right patients.

Annexe 1:
What is immunity?

Our immune system provides some immediate level of protection via a system of cells and signals that are very fast acting, called the **innate immune system**; for example, the interferon response. Although this is very rapid, it is not a flexible system and cannot adapt to all the different pathogens that we need protection from. There is a form of relatively short-lived 'memory' of innate cells which contributes to inflammation and antiviral interferon production and is antigen-dependent, but non-specific. Immune antibodies can enhance infection and inflammation through these myeloid cells under some circumstances.

This innate system works together with the **adaptive immune system**. A resting adaptive immune system contains cells that all have different receptors on the surface. When a new challenge, for example SARS-CoV-2, comes along, the cells that have receptors capable of binding to SARS-CoV-2 are activated and expand. Thus, our immune system is adapted towards SARS-CoV-2. These new cells are kept and form our immune memory, or immunity, to SARS-CoV-2. Adaptive immune cells are known as B and T cells* and the presence of SARS-CoV-2-specific memory B and T cells indicates that the immune system has seen the virus before and might indicate future immunity to COVID-19.

Innate immune cells include neutrophils, **dendritic cells*** and **monocytes/macrophages*** that are specially adapted to capture and kill pathogens.

T cells can include **killer T cells**, which kill any cells that are infected with virus, and helper T cells, which **help other T cells*** and B cells*.

B cells* can act to present antigen* to T cells* and help them, and they differentiate into a specialised form of B cell* known as a **plasma cell**. This cell is adapted to secrete large quantities of antibody* that will bind to the pathogen.

Cells of the innate immune system and adaptive immune system work together. Innate immune cells play an important role in processing and presenting antigens* to B and T cells* to induce antigen-specific immunity. In turn, these innate cells themselves respond to the activated B and T cells*, as part of their antiviral immune response. Antibodies* made by B cells* can help the innate immune cells to recognise antigen*. *The presence of antibodies* specific for SARS-CoV-2 indicates that the immune system has seen the virus before and might indicate future immunity to COVID-19.*

Annexe 2:
What is a vaccine?

As described in Annexe 1, our immune systems react to a virus such as SARS-CoV-2 by making immune memory, so that, having beaten the infection, we will be protected against it in future. A vaccine just uses a small part of the virus to stimulate our immune system, so that we can make immunity to the virus without having to be infected by it. The part of the virus that it uses to infect our cells is used in the COVID-19 vaccines. We may still feel some ill effects, because our immune system is being stimulated, but, because we aren't actually infected with the virus itself, these are short-lived and very mild.

For further information on how vaccines work, please see this explanatory graphic on the BSI website.

Annexe 3:
What is herd immunity?

Not all individuals in the population can make an effective immune response. Infants and older people have different immune systems. As do people with diseases that affect the immune system such as cancer, autoimmunity, immunodeficiency. However, if there are enough people who have made a good immune response that stop transmission of disease, they act as blockers to stop the virus reaching the vulnerable among us. This is known as herd immunity.

For further information on herd immunity, please see this explanatory graphic on the BSI website.

Annexe 4:
How do we measure immunity?

Immunity to SARS-CoV2, whether as a result of infection or immunisation, can be assessed by measuring levels of anti-virus antibodies* in the blood plasma and the presence of virus-specific immune cells in the blood. Antibodies* are usually detectable in blood within a week or so of recovery; immune cells may take a little longer to appear. Virus-specific antibodies* and immune cells are considered to be 'correlates of protection'* – measurable signs that a person is immune to the disease – COVID-19 in this case.

Measuring anti-SARS-CoV-2 antibodies

Antibodies* are measured using manufactured versions of virus proteins such as the spike protein; the protein is stuck onto a surface – the wells of a plastic plate for the so-called ELISA assay or a thin membrane for the lateral flow assay. Patient serum is then added; specific antibodies* will stick to the virus protein and these can then be detected using a colour-labelled developer. ELISAs are sensitive, specific and measure how much antibody* is present – but are technically demanding and have to be done in the laboratory. Lateral flow tests are less sensitive, usually only give a yes/no answer – but are simple and can be done in the community.

Measuring anti-SARS-Cov2 immune cells

Immune cells come in various flavours. The most important are the T cells*. Compared with antibody tests, detection of antiviral T cells* is time-consuming, technically demanding and not easily automated or scaled-up for large numbers of samples. As a consequence, these tests are limited to specialist labs and in-depth studies of immunity. Later post-infection, 'memory' immune cells – either T-memory or B-memory cells (the latter able to re-activate antibody production) – persist and can be measured using even more complex tests.

How long does immunity last?

For most viruses, antibody* levels peak within a few months of infection and then gradually fall, usually over the course of a year or more and in some cases more quickly, eventually falling below assay detection limits. We don't yet know how long anti-SARS-CoV-2 antibodies* persist but even when antibodies* are no longer detected in the assays, absence of detectable antibody* does not equal absence of immunity. Immune cells, particularly the memory cells mentioned above, remain, ready to rapidly re-invigorate the immune response if the same virus is encountered a second time. Virus-specific antibody reappears within days to tackle the infection. For most viral infections this immune cell memory persists for years – of course, we don't yet know how long immune memory of SARS-CoV-2 will last.

Annexe 5: References

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Annexe 6: Advisory group membership

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Secretariat

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Dr Jennie Evans, Head of External Affairs, British Society for Immunology

Matthew Gibbard, Policy & Public Affairs Manager, British Society for Immunology

Annexe 7: Glossary

Adaptive immunity – a subsystem of the immune system, which comprises specialised cells and processes, that removes pathogens by preventing their proliferation in the body.

Antibodies – large Y-shaped proteins produced by B cells*. They act to neutralise invading pathogens such as the SARS-CoV-2 virus. They can also signal to other cells to help them recognise pathogens.

Antigen – a substance that triggers the body to produce antibodies* against it.

B cell – a type of white blood cell that produces antibodies* as part of the adaptive immune system*.

Correlate of protection – A specific immune marker, or measurable sign, that is associated with protection from becoming infected and/or developing a disease.

Dendritic cell – Cells that present antigens, or parts of antigens, on their cell surface for other cells to see.

IgA – immunoglobulin A is an antibody associated with mucosal surfaces such as you find in the nose and mouth. It can inhibit pathogen adhesion to epithelial cells.

IgG – immunoglobulin G is the commonest form of antibody found in the blood and extracellular fluid and binds many kinds of pathogens.

IgM – immunoglobulin M is the first antibody made in response to a new antigen.

Lymphocyte – a type of white blood cell; subtypes include T cells*, B cells* and natural killer cells.

Macrophage – a white blood cell that engulfs and digests matter foreign to the body including pathogens and cellular debris.

Monocyte – a white blood cell that is able to change into other cell types, including macrophages*.

Neutrophil – a white blood cell that is amongst the first cells to migrate to the site of inflammation.

Protective immunity - immunity conferred by an immune response which gives protection against an infectious disease. It will not prevent person to person transmission.

Sterilising immunity – immunity in which the immune system is able to prevent the replication of a pathogen within the body. It will prevent person to person transmission.

T cell – also known as T lymphocytes, T cells are a type of white blood cell that determines the specificity of immune response to antigens* in the body.

Viral RNA – in the same way that DNA is the blueprint for all the protein components of a cell in people, some viruses use RNA as their blueprint.

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