

COVID-19 immunology research

What do we know and what are the research
priorities?

1 May 2020

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As this has been a rapid review, it is a summary of the current research available at the time of writing; it is not an exhaustive literature review. It is the considered input of the advisory group and does not necessarily represent the position of either the Academy of Medical Sciences, its Fellows, the British Society for Immunology and its members or the individual members of the advisory group.

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Foreword

An event in December 2019 changed the world. A new type of viral pneumonia appeared in Hubei Province, China, that appeared to be highly infectious and resistant to therapy, quickly infecting medical staff and other patients. Initially, it was unclear how serious this would become, but there were similarities between this outbreak and the SARS1* coronavirus outbreak in 2002–04. The SARS1* outbreak caused over 8,000 infections with a high mortality rate of 10% and led to the deaths of over 770 people. This new disease, now called COVID-19* and caused by a virus termed SARS-CoV-2*, appeared milder, but still caused death in about 1 in 100 people.

By February 2020, outbreaks started to appear outside China, most notably in Italy and Iran. It became clear that COVID-19* could spread globally and in March 2020, the World Health Organization (WHO) declared a pandemic. As this pandemic is caused by a novel virus, so there are many scientific unknowns. It is important now more than ever to initiate a coordinated research response to identify and address the important questions to help inform our response to the disease outbreak.

I was pleased to be approached in early April 2020, to be the Chair of an expert advisory group being established by the British Society for Immunology (BSI) and Academy of Medical Sciences (AMS). We brought together experts across the field of immunology to focus on the immunology of COVID-19* (composition of the advisory group in Annex 5). In this document we share our rapid review of the relevant immunology research to help us understand how it can inform our response to the COVID-19* pandemic and the key research priorities we have identified for COVID-19* immunology research.

We have moved rapidly to keep up with the fast-moving situation, however our work is limited by the scant research that was currently available and the timeframes involved. The purpose of this report is to highlight the many additional aspects of COVID-19* immunology that still need to be addressed through research. This has been a great partnership between the AMS and the BSI and we look forward to supporting the research and clinical communities to help bring the COVID-19* pandemic under control.



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Executive Summary

SARS-CoV-2* is a novel coronavirus that causes the disease COVID-19*. Scientific investigation of the disease is unprecedented and based on a remarkable mobilisation of international expertise and data sharing. The UK is at the forefront of immunological research globally and is contributing at the highest level to tackling the pandemic. Much has been learnt about who the disease affects and its mechanisms, leading to new therapeutics and prevention prospects.

This report aims to summarise what we know, and what we do not, about the immunology of COVID-19*, and set immunology research priorities. An asterisk (*) denotes words that appear in the glossary (Annex 4).

SARS-CoV-2* is more highly infectious than the SARS1* virus, and COVID-19* has become a deadly pandemic. Until we have a protective vaccine or effective therapeutics, social (physical) distancing is the most effective measure available to control the virus.

Studies are underway to discover the number of us that have been infected with and so have specific antibody to SARS-CoV-2* ('sero-prevalence*'). However, scaling lab-based antibody tests to commercial equivalents is challenging; some high-throughput tests may produce false-positives to antibodies against other coronaviruses, like the common cold. Questions also remain around to what extent the antibody response mounted by those exposed to SARS-CoV-2* can protect against future infection, and what role immune cells including T lymphocytes* may play in protective immunity. This means 'antibody-positive passports' cannot be relied upon at this stage.

Exposure to higher doses of the virus may lead to more severe disease, so the use of personal protective equipment by healthcare workers is particularly important. Although we do not yet have good tests for infectiousness, studies suggest that people with severe disease may remain infectious for longer than those who experience mild symptoms. Physical distancing therefore remains crucial while we learn more about the spread of this disease and what types of immunity are most protective, and for how long.

Elucidating biomarkers to identify which people may develop more severe disease will be extremely valuable to predict and prevent intensive care admissions, and some candidates are being explored. The ability to precisely manipulate the immune response to encourage protective responses and decrease immune-mediated organ damage will be vital to manage the disease outbreak and limit deaths from COVID-19*. This can be achieved through immune modulators*, anti-inflammatory drugs and antiviral therapies.

Vaccines or effective therapeutics are the only realistic prospect of long-term outbreak control and the ultimate lifting of social restrictions. It is absolutely vital that efforts to develop these are supported. There are promising vaccines at various stages of development, but these must be verified as safe and able to induce protective immunity, and their effectiveness carefully assessed by different groups of researchers.

This expert advisory group has identified 13 immunology research priorities, many of which have the potential to deliver results within the next 12 – 18 months and lead to rapid public health impacts. However, there are many more research questions that can help to optimise our response to COVID-19*, which are explored in this rapid review and continue to develop in the growing evidence base. Key assumptions relied upon by the scientific community and this group include:

- Prior infection will confer some protection against future infections
- The disease is highly variable, ranging from asymptomatic to lethal
- Dysregulated immune responses may contribute to severe disease
- Immunity will differ across the population (for example, by age, sex, ethnicity, occupation and location)
- Immune protection will provide greatest benefit to those most vulnerable

The research priorities

Understanding our immunological response to the SARS-CoV-2* virus will help us to develop successful treatments and vaccines, identify vulnerable groups and inform public health measures to control the COVID-19* outbreak. Research to answer questions about this virus and the disease it causes is therefore fundamental to an effective pandemic response. This is known scientifically as ‘understanding the host-pathogen relationship’, and is key to all investigations of infectious disease.

Scientific research often takes years to conduct, but the outbreak of a novel virus demands rapid evidence generation and a pragmatic approach. As well as investing in long-term learning, it is relevant to identify and prioritise research that can deliver public health benefits for the current outbreak, and help to save lives now.

The expert advisory group have rapidly identified 13 priority areas where immunology research could deliver significant public health impacts either quickly, meaning within 12 – 18 months, or in the future. It is hoped that these priorities may serve as a tool to support the coordination and mobilisation of the immunology research community, and catalyse progress on these key issues.

These priorities focus on immunology, but are not an exhaustive list of the immunological or wider research questions that are important to tackling SARS-CoV-2*. Other key unknowns that are also highly worthy of research investment are explored throughout this paper, listed at Annex 1, and may be found in the literature beyond this rapid review.

Group 1: Rapid learning about immunity for public health impact

Research about immunity that could be delivered in 12 – 18 months

- What, if any, antibody properties confer protection against the virus, and what proportion of antibody responses are protective?
- What are the roles of immune cells from the adaptive (T-cells*) and innate systems, such as Natural Killer cells and T-cells, in protective immunity?
- What is the sero-prevalence* of SARS-Cov-2* antibodies? What proportion of individuals mount either an antibody, or a cellular response or both after infection?
- How can laboratory-based antibody tests be safely scaled to reliable commercial equivalents that are not confounded by cross-reactivity to other coronaviruses?

The answers to research questions in **group 1** would have high utility in public health decision-making, and it is likely that with funding and support for relevant research, these answers could be delivered within 12 – 18 months.

These priorities can help us to understand what herd immunity to this virus may currently exist, or develop within the population. Reliable, commercial antibody testing has clear importance in sero-prevalence* studies and should be prioritised. However, it is limited in what it can tell us about protective immunity until we have clarified the ‘correlates of protection’ (CoP)* to SARS-CoV-2*.

We need to better understand the CoP* to SARS-CoV-2* – essentially, the elements of our immune response (including antibodies and T-cells*) that can prevent future infection. Although antibodies to the virus can indicate who has been exposed to SARS-CoV-2*, not every person who is exposed to the virus will produce antibodies, and not all antibodies will be protective against reinfection i.e. are able to prevent the virus from entering human cells. Also key is understanding

whether T-cells* are involved in generating immunity against COVID-19* is also key. Elucidating how these two parts of the immune system may interact to generate protective immunity against SARS-CoV-2* will help inform the development of safe and effective treatments and vaccines.

Group 2: Rapid impacts for COVID-19 treatment

Research that could be delivered in 12 – 18 months and tell us more about how to treat COVID-19*

- What is the full immunopathology* of COVID-19* in the lung and other organs?
- What are the biomarkers predictive of severe disease?
- What is the potential role for antiviral and immunomodulation therapies* in COVID-19* treatment?
- How can we reliably test whether COVID-19* patients remain infectious?

Learning about the disease process of COVID-19* is extremely important to optimise the treatment of individual patients, and plays an important role in managing the burden on health systems. The priorities in **group 2** address this area, and could also be delivered within 12 – 18 months.

Better understanding of the underlying physiology of infection, including both peripheral blood markers and what is happening to cells in the lung, is important to allow us insight into how the body responds to SARS-CoV-2* infection. Similarly, biomarkers that help us to identify which people with COVID-19* are at risk of their disease becoming severe can help us to treat them more effectively. Understanding how the virus acts at the site of infection may deliver powerful learnings for how best to treat it – as well as informing important questions about immunity and spread.

The investigation of drug therapies for COVID-19* is also essential. Vaccine development is a long and complex process. In addition to exploring drugs that directly inhibit the virus, the ability to manipulate the immune response, such as with immune modulators* and anti-inflammatories, may be vital to prevent death from COVID-19*.

There are many other questions about the disease that are equally important, but it is more difficult to say when research will be able to deliver useful answers. For example, whether, and how, the immune response may enhance disease? Why the disease is often severe in older people, and rarely in children? And why do we see differences in disease severity between males and females, and different ethnic groups? A better understanding of the immunopathology* of COVID-19* may have important contributions in these areas, and such further research should also be progressed.

Group 3 sets out research questions that are essential for our effective control of COVID-19* over the long term, and will inform how we tackle outbreaks of other novel viruses in the future. Broadly, these aim to understand who has developed protective immunity to the virus; how and to what extent we can protect people with safe and effective vaccines; and how long immune protection will last. Although many vaccine candidates have already been identified, they will have very different features and durability of response. Notwithstanding the urgency to develop a vaccine, we must invest carefully in the most promising options.

This group also highlights the importance of research into the immunogenetics* of SARS-CoV-2*. Such long-term studies could help identify genetic factors in our immune response that predispose us to or lead to more severe disease. Understanding the role this plays in COVID-19* and in immunity to SARS-CoV-2* could help identify new therapeutic targets.

Group 3: Key long-term research investments

Important research questions that will take time to answer

- What is the rate of asymptomatic spread, and how does this contribute to transmission?
- What proportion of infected individuals mount a protective immune response?
- How long is natural and vaccine immune protection likely to last?
- What immunological factors correlate with protection to SARS-CoV-2* by vaccines, and how effective are vaccines at protecting older people?
- What is the role of immunogenetics in SARS-CoV-2* infection, and what can this tell us about potential therapeutic targets?

These answers may take more than a year to determine, and establishing duration of immune protection, for example, will involve many years of longitudinal follow-up. They are no less important, however. Currently, our response to SARS-Cov-2* is guided by what we know about vaccines and long-term immunity to SARS1*. Gathering specific data for this virus will not only help to hone our response, should we see further waves of COVID-19*, it will also guide our response to future emergent infections.

COVID-19 immunology research summary

What happens when a person is exposed to SARS-CoV-2*, and during early infection?

How does our immune system respond to a new viral infection?

- Defence against a viral infection is determined by the immune system's ability to specifically recognise and 'neutralise' the new virus. The immune response is in two parts: firstly, the early 'innate' response, which is not specific to the new virus. Later, the 'adaptive' response creates a tailored or 'specific' response to the virus, and an immune memory to help fight future infection.
- Innate immune responses* occur in many cells, but there are special cells (such as Natural Killer cells, an unique non-conventional T-cells* that are found within mucosal surfaces) that potently enhance these responses. As part of the innate immune system*, inflammatory proteins called 'interferons*' are released. These have broad antiviral functions, fighting the virus until adaptive responses take over.
- The adaptive response involves cells called B-cells*, which produce antibodies. Antibodies are important in defence against many viral infections such as flu, and are produced in response to vaccines. T-cells* are also part of the adaptive response; they help B-cells* make antibodies that can directly destroy virus-infected cells. Adaptive responses are tailored to the exact virus involved, take at least a week to develop and must be activated by cells of the innate immune system*.
- How the innate and adaptive responses work in sequence and together to protect against viruses varies depending on the infection. Sometimes T-cells* may be more important than antibodies. In other cases, innate defence or antibodies can be the key to success. This means it is important to identify precise CoP* against a particular virus, to help identify the most

If I am exposed to SARS-CoV-2* (the virus), how likely am I to become infected?

There is little direct data, but we can make some reasoned assumptions. Firstly, the basic reproduction number (R0)* is estimated at between 2.5 and 3.51 – higher than SARS1* or MERS*. Similarly, ‘super spreading events’, where one case infects many people, indicate that SARS-CoV-2* is infectious to most people.

One likely reason it is so infectious is the virus’ apparent ability to infect the upper respiratory tract, whereas SARS1* and MERS* predominantly infected the lower tract. This means viral particles have to travel less distance in the airway to reach a target cell, increasing the ease of transmission. This also offers infected individuals an opportunity to clear the virus from the upper airways, before it descends to potentially cause pneumonia. This may partly explain why SARS-CoV-2* induces serious disease in fewer people than SARS1* or MERS*.

Why is the early (innate) immune response important?

The first line of immunological defence is the innate immune system*, which can limit or prevent infection. Though no direct evidence is available, a robust early innate immune response* likely prevents infection or decreases disease severity. This early response is influenced by characteristics such as age.

A person’s immune response to infection and their disease severity likely determines how long they are infectious. Some studies suggest individuals with mild to moderate symptoms may be infectious 8 days post-symptom onset^{2,3} while severe cases may spread greater quantities of virus and be infectious for weeks. This suggests that people with mild or moderate symptoms should self-isolate for more than 8 days, while those with persistent symptoms may need to self-isolate for considerably longer. Longitudinal studies are needed to learn more about the duration of infectivity, and guidance for self-isolation should be led by these findings.

Are asymptomatic or pre-symptomatic individuals infectious?

There is good evidence that asymptomatic individuals can spread SARS-CoV-2*.⁴ These individuals may go on to develop symptoms later (generally about 5 days post-exposure),⁵ or develop negligible symptoms and not believe they have been infected.⁶ Those that develop symptoms are believed to become infectious around 2.5 days prior, and peak around 0.6 days prior, to symptom onset.⁷ **Modelling studies based on Chinese data estimate about 44%, and potentially up to around 60% of infections arise from asymptomatic spread.**⁸ This is likely to play a more significant role in transmission of COVID-19* than symptomatic ‘super-spreaders’, and increases the difficulty of eliminating the disease.

Does high exposure to the virus influence disease severity?

The dose of virus an individual is exposed to may influence their disease severity. This is particularly evident in healthcare workers (HCWs) in hospital settings who are likely exposed to high virus concentrations, especially from severely ill patients.⁹ In China, HCWs accounted for 3.8% of cases, with 14.8% of these having severe/critical disease despite their younger age and fewer comorbidities relative to other severe COVID-19* cases.¹⁰ High incidence of nosocomial* infections has been reported and studies to collect further data in this area are important. The concentration of virus that HCWs are exposed to in community settings (e.g. long term care facilities and home visitors), is yet to be determined, although it is likely severely ill patients in the community also shed high virus concentrations. Physical distancing, in addition to limiting HCW exposure through effective personal protective equipment (PPE), is paramount to limiting transmission.

1 Park M, Thwaites RS & Openshaw PJM (2020). *COVID-19: Lessons from SARS and MERS*. *European Journal of Immunology* **50**, 308–316.

2 Woelfel R, et al. (2020). *Clinical presentation and virological assessment of hospitalized cases of coronavirus disease 2019 in a travel-associated transmission cluster*. medRxiv preprint.

3 Hoehl S, et al. (2020). *Evidence of SARS-CoV-2 Infection in Returning Travelers from Wuhan, China*. *New England Journal of Medicine*. **382(13)**, 1278–1280.

4 Rothe C, et al. (2020). *Transmission of 2019-nCoV Infection from an Asymptomatic Contact in Germany*. *The New England Journal of Medicine*.

5 He X, et al. (2020). *Temporal dynamics in viral shedding and transmissibility of COVID-19*. *Nature Medicine*.

6 Li Q, et al. (2020). *Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia*. *The New England Journal of Medicine* **382**, 1199–1207.

7 Ibid., He X, et al. (2020).

8 Ibid., He X, et al. (2020).

9 Yang L, et al. (2020). *Viral dynamics in mild and severe cases of COVID-19*. *The Lancet Infectious Diseases* Epub ahead of print.

10 Wu Z & McGoogan JM (2020). *Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention*. *JAMA* Epub ahead of print.

Does previous exposure to other coronaviruses confer cross-protection?

There is little data on whether immunity induced by previous exposure to other strains of coronavirus confers cross-protection. Generally, there are two possibilities; existing immunity may offer cross-protection or it can make the second infection worse. This latter scenario is observed for Dengue virus and some animal coronavirus infections.

What is known about the immune response during disease, and does it vary from person to person?

A strong T-cell* mediated adaptive immune response has been observed in COVID-19* patients which may support development of protective immunity.¹¹ However, this response varies between individuals and may be reduced in older people.

There is also evidence of an over-exuberant response in some patients, causing inflammation that blocks airways and high levels of cytokine* release (potentially leading to a 'cytokine storm*'). Post-mortem lung examination demonstrates a high number of immune cells and mucus in the airways;¹² haemorrhage and activation of blood clotting proteins also obstruct small blood vessels. Such extreme responses may provoke inflammation outside the lungs, overwhelming other organs, such as the kidneys and liver and potentially leading to multi-organ failure.

The ability to manipulate the immune response may be extremely important to prevent death from COVID-19*.

Manipulating the immune system in this way involves drugs that modulate the immune response, known as 'immune modulators*'. Many NIHR national priority trials include immune modulators*.

As well as developing new drugs, for rapid solutions it is important to re-examine how existing therapies could be used to treat COVID-19*. A group of anti-inflammatories, known as glucocorticoids, were somewhat successful in treating SARS1*. However, a better understanding of disease progression is key to choosing the correct immunological pathway to modulate and when to do so.

Why are older people, men and people from BAME backgrounds more severely affected?

Ageing has a negative impact on the immune system, airways and lungs (see Annex 3 for more information). This helps to explain why approximately 50% of excess deaths from COVID-19* occur in people over 80 years old, and 40% in those aged 60–79 years.

Older people are more prone towards inflammation and show reduced lymphocyte* responses. A study suggests some older patients do not progress to the second, lymphocyte*-driven stage of immune response that is important to clearing viral infection and get stuck in the early stage, which is highly inflammatory and tissue damaging. Anti-inflammatory treatments therefore have an important role in treatment, but must not suppress important, protective lymphocyte* driven responses.

The impact of ageing on the immune system also has implications for the efficacy of SARS-CoV-2* vaccines for older individuals, as they may respond differently to vaccines than younger people. **This highlights the importance of developing effective anti-inflammatory and antiviral drug treatments for COVID-19*, in addition to vaccines.**

Emerging data suggests a higher rate of COVID-19* incidence among men compared with women, however, published studies are still awaited and the reasons behind this are not yet understood. Similarly, individuals from a BAME background appear to be at higher risk of severe disease and death, with 17% of deaths reported in England up to the 21 April 2020

11 Liao M, et al. (2020). *The landscape of lung bronchoalveolar immune cells in COVID-19 revealed by single-cell RNA sequencing*. medRxiv preprint

12 Wang C, et al. (2020). *Alveolar Macrophage Activation and Cytokine Storm in the Pathogenesis of Severe COVID-19*. Research Square preprint

occurring in these individuals.¹³ It will be important to explore whether this has an immunological basis, is due to a higher rate of comorbidities in these individuals, reflects additional risk factors or is a combination of these issues.

What do we know about patients who have comorbidities?

Studies are underway to develop consensus around comorbidities that enhance risk of severe disease; these include hypertension and obesity. At present, less is known about comorbidities that increase baseline lung inflammation, such as asthma and its subtypes. Furthermore, pregnancy is associated with suppressed immunity, but there is currently no clear data indicating any impact on COVID-19* susceptibility. The European Centre for Disease Prevention and Control (ECDC) reports that symptoms in pregnancy range from asymptomatic to mild, with some unusual findings such as high white blood cell counts.¹⁴

In recent studies from Wuhan and Hong Kong, a large proportion of patients displayed indicators of possible bacterial infection, although this was not confirmed by culture.^{15,16} However, secondary bacterial infections have so far not been highlighted as a major feature in UK COVID-19* patients. Notwithstanding, it should be noted that the elderly are generally more vulnerable to secondary bacterial infections due to their poorer immune cell function.

What role does the genetics of our immune system play?

It is likely that our 'immunogenetics*', the genetics of our immune system function, contributes to how susceptible we are to severe disease with COVID-19*. Better understanding the role of our immunogenetics* in SARS-CoV-2* infection could identify what pathways are driving this risk, and help identify targets for therapies including drug treatments. Monogenic causes of disease, meaning those controlled by a single gene, are most easily found in children. However, sequencing the whole genetic code or 'genome' of large groups of adults has been recently shown to be effective in helping us understand complex genetics in adult-onset disease,¹⁷ which is of more clinical relevance in COVID-19*. Well-powered genetic and immune follow-up studies are therefore a longer term priority in COVID-19* research.

What can immunological markers tell us about clinical prognosis, and how to treat hospitalised patients?

What can biomarkers tell us about the disease and how to treat it?

Accessible, validated biomarkers would be extremely valuable to help earlier identification of patients who may fare poorly, who could then be managed to prevent admission to intensive care.

Several studies are examining possible serum biomarkers of severe disease. A promising one appears to be the cytokine* known as interleukin-6 (IL6), an indicator of over-exuberant immunity. Trials are investigating several therapeutics that block its activity.

Active infection outside of the respiratory system

It has been argued that SARS-CoV-2* infection is not limited to airway cells but might target cardiac, gut and some immune cells. Although viral genetic material (viral-RNA*) can be found in different sites, **there is no substantial evidence that the virus replicates in tissues besides the airways.**¹⁸ Viral-RNA* in non-respiratory tissues may reflect killed or inactivated virus that has been cleared from the airway and is no longer infectious.¹⁹ Pathologies in other sites are likely the secondary results of inflammation and blood clotting.

13 NHS England (2020). *COVID-19 Daily Deaths*. Available at: <https://www.england.nhs.uk/statistics/statistical-work-areas/covid-19-daily-deaths/>

14 The European Centre for Disease Prevention and Control (2020). *Coronavirus disease 2019 (COVID-19) in the EU/EEA and the UK – eighth update*

15 Li X, et al. (2020). *Clinical characteristics of 25 death cases with COVID-19: a retrospective review of medical records in a single medical center, Wuhan, China*. *International Journal of Infectious Disease*, Epub ahead of print.

16 Wang L, et al. (2020). *Coronavirus Disease 2019 in elderly patients: characteristics and prognostic factors based on 4-week follow-up*. *The Journal of Infection*, Epub ahead of print.

17 Thaventhiran et al. (2020). *Whole genome sequencing of a sporadic primary immunodeficiency cohort*. *Nature* 2020 in press.

18 Ibid., 10. Woelfel R, et al. (2020).

19 Ibid., 10. Woelfel R, et al. (2020).

How can we know whether hospitalised patients are still infectious?

Detection of viral genetic material (viral-RNA*) indicates ongoing infection, but not whether the individual remains infectious. A patient may continue to produce viral-RNA* from the airway (and be symptomatic) after they stop being infectious.

Individuals are likely to stop being infectious a few days before viral-RNA* tests become negative and their symptoms resolve. However, current high-throughput tests cannot determine infectiousness. Existing tests for infectiousness require specialised personnel and facilities, take several days and are not scalable.

Testing for viral subgenomic-RNA* (sgRNA) rather than just genomic RNA (gRNA) might indicate active ongoing infection,²⁰ and so help discern infectious patients from resolved cases that continue to shed viral-RNA*. ^{21,22} However, it is also possible that once a person has developed SARS-CoV-2* specific antibodies that can stick to and 'neutralise' the virus, preventing it from entering human cells, that any new virus produced in the body will be inactivated as soon as it is released from an infected cell. If this is the case, the presence of sgRNA will not be a definitive indicator of infectiousness.

What do we know about post-infection immunity, and what can this tell us about herd immunity and vaccine development?

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

Assessing an individual's specific antibodies to the virus can provide some answers. The initial antibody response (IgM*) is seen from around day 7 after symptom onset. A more refined, IgG* antibody response is seen from around day 10.

Antibody data can be used in 'sero-prevalence'* studies, where a population is tested for antibodies to estimate what proportion of people have encountered the virus. Modelling predicts that 10% of the Italian population have been infected.²³ This information is not yet known for the UK and has been shown to vary in other countries depending on type of test is used to identify those that have 'seen' the virus. This knowledge can help contribute to calculations of when we have attained protective 'herd immunity'. **On the basis of an R0* of about 3.5, immunity would be needed in approaching 80% of the population to stop transmission.**

To what extent do antibodies, or other elements of the immune response, provide future protection?

A key immunological concept is 'correlates of protection' or CoP*. There are many facets to successful immunity in humans; the weaponry needed to defend against a given virus can be specific. **There is an urgent need to better characterise the CoP* of COVID-19*.**

While antibodies are markers of who has 'seen' the virus, we cannot yet know if these antibodies offer protection against infection. Protection may also depend upon T-cell* responses, which are not measured by serological tests.

We will not reliably know if there is 'herd immunity' unless we have a true sense of what effective immunity comprises. This means the idea that an 'antibody-positive' passport would allow safe re-entry to the workplace should be considered with caution.

20 Ibid., 10. Woelfel R, et al. (2020)

21 Thevarajan I, et al. (2020). *Breadth of concomitant immune responses prior to patient recovery: a case report of non-severe COVID-19*. Nature Medicine 26, 453-455.

22 Ibid., 10. Woelfel R, et al. (2020)

23 Imperial College COVID-19 Response Team. Flaxman S, et al. (2020). *Estimating the number of infections and the impact of nonpharmaceutical interventions on COVID-19 in 11 European countries*. Imperial College London report

Furthermore, **total measurable antibody is not the same as protective, virus-neutralising antibody***. The amount of antibody to the viral spike antigen* (the spike protein, particularly its receptor binding domain (RBD)*, is a target for neutralising antibodies* and is being used as a target or 'antigen'* during vaccine design) may be important to confer immunity, as it can stop viral entry into human cells. However, not all antibodies have this property.

In addition, 10–20% of people with COVID-19* show little or no detectable antibody.²⁴ Low antibody levels may correlate with very different states or factors, such as lethal or near-lethal infection, old age, or having only had a mild infection. However, for MERS*²⁵ and flu, some people who failed to show specific antibody still had specific immunity through anti-viral T-cells*.

Understanding whether T-cells* are protective is key. Severely infected people show a transient depletion of T-cells*, so we also need to understand if this impairs the establishment of long-term, protective immunity in recovered patients.

What are the important issues for developing useful antibody tests?

Reliable, lab-based, quantitative, antibody tests ('ELISA'*) are being used to collect extensive COVID-19* data in New York, the UK^{26,27} and elsewhere. However, the translation and scale-up of these tests into high-throughput, point-of-care, commercial units requires development and validation that takes much longer to optimise. **To be reliable, tests must not give false-positives to antibodies that many people will have generated to related coronaviruses that cause common colds.**

How long might immunity last and what do we know about re-infection?

Understanding the longevity of immune protection is important to help prevent or manage future 'waves' of SARS-CoV-2*. Only preliminary data for acquired protective immunity in COVID-19* patients are available. SARS1* patients produced neutralizing antibodies which persisted with declining potency for at least 2 years post-infection, and up to 12 years in some cases.^{28,29,30,31} Plasma from recovered SARS1* patients was effective in treating new cases, indicating it contained durable protective antibodies*.³² However, the antibody levels seen in SARS1* and MERS* patients were not always stable over the long-term.

There are anecdotal reports from China and South Korea of people testing positive for viral-RNA* following apparent recovery from COVID-19*. It is unclear whether the virus may persist in these individuals at undetectable levels before 're-emerging', causing a relapse with the original infection, or if it is possible to become newly infected because a person has not developed protective immunity. **Whether people can be reinfected with SARS-CoV-2* requires further data and research.**

Determining the gene sequence of viral-RNA* can tell us whether people who retest as positive for COVID-19* have contracted a new strain of the virus, or have relapsed with their original infection.

What are the opportunities and challenges for new vaccines?

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What makes a successful vaccine?

The ideal vaccine candidate will be very safe, produce a strong, long lasting, protective immune response, require few doses, and be scalable to an equitable, affordable and accessible vaccine for global access. Vaccine selection must also involve rigorous, uncompromised efficacy and safety testing

It will take time to establish that a vaccine candidate meets these criteria and is safe. Notwithstanding the urgent timeline, it is important that we evaluate as many vaccine candidates as possible, to find one that reaches the highest possible safety and efficacy standards.

As we await a vaccine while this important process is followed, it is also imperative that we invest in finding drug therapies that could ameliorate the disease and support COVID-19* patients. As vaccines are not always equally effective in all groups, drug therapies will be key to preventing and treating disease in some populations, such as older people.

What vaccine strategies are being explored?

More than 90 vaccines against SARS-CoV-2* are in different stages of development by groups across the globe. These vaccine candidates are each taking a different approach to attempt to induce robust, long-lived immunity to SARS-CoV-2* in a safe manner.^{33,34}

Effective vaccine protection might be mediated by either antibodies or cellular immunity, or a combination of both, and defining these CoP* in naturally-acquired and vaccine-mediated immunity will be vital. Although fully characterising the CoP* is not a prerequisite to finding a successful vaccine, it will support rapid development of effective new vaccine candidates. This will be particularly important if, like is seen with seasonal flu, mutations in SARS-CoV-2* mean that initially successful vaccines are less effective against new strains of the virus in the future.

Some components of immunity to SARS-CoV-2* seem to be associated with poorer disease outcomes, so are avoided as vaccine candidates. Immune-mediated side effects were seen in some animal trials for SARS1* vaccine candidates, but it is not clear why this occurred.^{35,36,37,38,39,40} Vaccine candidates also need to be tested to ensure they do not cause antibody dependent enhancement (ADE*), whereby some antibodies actually facilitate rather than block carriage of virus into human cells.⁴¹ The extent to which ADE* plays a role in coronavirus infections is not understood, but SARS1* and MERS* animal studies indicate it may increase incidence of lung injury.

As SARS-CoV-2* has only recently emerged, the strategies currently being explored are mostly based on experimental findings from preclinical SARS1* vaccines. Most candidates target the spike protein RBD*.⁴² In animal studies on the SARS1* virus, this approach induced strong protection against infection.⁴³ However, similar vaccine candidates against coronaviruses in other species proved mostly ineffective and may have selected for new virus variants (i.e. led to new mutations).⁴⁴

More studies aimed at understanding the basis of natural human immune protection to COVID-19* are urgently needed to inform vaccine development.

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Annex 1: Key research questions

These immunology research questions are fundamental to improving our understanding of how to most effectively respond to the current outbreak of SARS-CoV-2*, potential future outbreaks, and how to best treat COVID-19*.

They complement and build upon the research priorities set out in the research priorities section. Those priorities were identified based on their scope for public health impact and how rapidly they could be delivered, and do not detract from the importance of timely, well co-ordinated research into these additional areas,

Immune response

- What is the role of innate mucosal defence in protection against infection?
- To what extent is SARS-CoV-2* able to modulate the human immune response and does this modulation have an effect on disease severity and/or the induction of long term protective immunity?
- Is there any immune cross-reactivity to related coronaviruses and what is the effect of this on disease progression?
- What is the role of immunogenetics in the immune response, disease susceptibility and severity?

Pathogenicity

- What tissues and cell types are infected (productively and non-productively) by SARS-CoV-2*?
- Is the cytopathogenicity of SARS-CoV-2* infected respiratory epithelial cells and the resultant inflammatory response predictive of disease severity?
- Does the type and extent of cell messaging and communication between SARS-CoV-2* infected respiratory epithelial cells and leukocytes vary between severe and mild disease, and therefore act as a predictor of disease severity?
- What is the prevalence and types of secondary bacterial, fungal and viral infections in COVID-19* patients and how do these correlate with disease outcome?
- What is the mechanism by which some co-morbidities, e.g. obesity, increase disease severity?
- Why are different age groups affected differently by COVID-19*?
- Why are different sexes and ethnic groups affected differently by COVID-19*?
- Why is severe asthma not a predictor of severe disease?
- What can viral gene sequencing tell us about the functional significance of different viral genotypes in the disease process and immune evasion?

Infectivity

- How does disease severity affect the duration of an individual's infectiousness?
- What are the rates and mechanisms of re-infection and/or relapse with SARS-CoV-2*?
- What is the likelihood of infection upon exposure?
- What is the role of antibody dependent enhancement* in SARS-CoV-2*?

Treatment

- Can we isolate SARS-CoV-2*-specific neutralising antibodies* from recovered volunteers with protective immunity, and use these to develop monoclonal antibodies for disease treatment, or prophylaxis (prevention) in groups who may not be able to produce protective immunity from vaccines?
- When in the disease process should anti-inflammatory treatment be started?

Annex 2: Virology

SARS-CoV-2 virus structure and genetics

SARS-CoV-2* is an enveloped positive sense single-stranded RNA virus with a genome that is around 29,000 nucleotides in length. SARS-CoV-2*, along with SARS1* cluster within the genus *Betacoronavirus* and subgenus *Sarbecovirus*. SARS-CoV-2* shows 79% nucleotide similarity with SARS1* virus⁴⁵ but is suggested to be most closely related to the horseshoe bat Sarbecovirus, RaTG13, having diverged from this around 40-70 years ago.

How SARS-CoV-2 infects humans

It is likely that SARS-CoV-2* has been circulating in bats and intermediate species (possibly the pangolin) before crossing into humans in Hubei province of China in late 2019. SARS-CoV-2* enters a human host cell by binding to the human angiotensin-converting enzyme 2 (ACE2*) receptor with the viral spike (S) protein*. The spike RBD*, which is the specific domain within the S protein that is responsible for binding to the human ACE2* receptor, is more divergent from RaTG13 (85% nucleotide similarity). Furthermore, compared to RaTG13, SARS-CoV-2* has also acquired a furin (human protease which enzymatic activity is exploited by numerous viral and bacteria pathogens) cleavage site insertion within the viral envelope (E) protein, which is speculated to increase its infectivity for humans.⁴⁶

Mutations and viral lineages of SARS-CoV-2

Since January 2020, SARS-CoV-2* has spread globally. Despite a relatively low mutation rate of around 2.5 mutations/genome/month which is similar to other coronaviruses, the huge numbers of infections has resulted in the accumulation of over 2000 known mutations within the viral genome.

Ongoing SARS-CoV-2* genome sequencing is critical to our understanding of the diversity of the virus and will inform vaccine development. Distinct viral lineages associated with geographical regions have emerged and been classified into viral genotypes. These genotypes will help us better describe how the virus is spreading both locally and globally.⁴⁷ To date, at least 16 of the 34 currently defined genotypes are circulating in the UK. This indicates the SARS-CoV-2* virus was introduced to the UK on multiple occasions.

In addition to mutations, at least five different sequence deletions within mutational hotspots of the viral genome have been observed in circulating viruses. The functional significance, if any, of these remains unclear and neither deletions nor mutations have to date been associated with immune evasion.

Finally, studies following the viral evolution within the host (patient) over the course of infection and recovery will contribute towards our understanding of viral immune escape and the evolution of drug resistance.

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Annex 3: Infection and the life course

Infection in children

There have been a very small number of paediatric cases of COVID-19*.⁴⁸ Children are at reduced risk of disease and severe complications, but can be asymptomatic carriers. As in adults, underlying conditions increase susceptibility.⁴⁹ In one study, 11% of children admitted to hospital with respiratory infections had COVID-19*; all had good outcomes.⁵⁰

The effects of ageing on immune response

Physical changes

Parts of the airways and lungs that form a physical barrier to infections undergo changes with ageing. Poorer cough strength and reduced functioning of cilia (fine hairs) result in a reduced ability to expel mucus, which traps infections, and these build up in the lungs.

Inflamaging

Older people have more background inflammation in their bodies, even without any infection present. This process is called 'inflamaging', and is often linked to physical and medical frailty. A higher degree of frailty is linked to more background inflammation. This is important because increased inflammation is associated with decreased immune responses.^{51,52} Immune or vaccine responses to SARS-CoV-2* are therefore likely to be compromised in older and frailer people who have more age-associated inflammation.

Immune cells and response

Cells called macrophages* are key to the first phase of the immune response, and are less able to respond to infections in older people. Macrophages* also become less able to remove dead cells, leading to a build-up of debris in the lungs. In response, the body recruits more macrophages*, but this leads to more inflammation and lung damage.

The second phase of immune response, necessary to clear infection, and is dominated by lymphocytes*. Dendritic cells* (DC) are required to activate lymphocytes* and studies in older mice infected with respiratory viruses suggest DC activity may be reduced.⁵³ Output of young, precursor T-cells* from the thymus also decreases during ageing.

Data from recovering COVID-19* patients shows that older patients produced a high level of antibodies to the virus,⁵⁴ so this aspect of immunity does not appear to be an issue.

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Annex 4: Glossary

ACE-2 stands for angiotensin converting enzyme 2. The receptor for this has been identified as what SARS1 and SARS-CoV-2 use to enter human cells.

Antibody dependent enhancement (ADE) - occurs when non-neutralizing antibodies facilitate virus entry into host cells, leading to increased infectivity.

Antigen - a toxin or other foreign substance which induces an immune response in the body, especially the production of antibodies.

Basic reproduction number (R0) - the average number of secondary infections produced by a typical case of an infection, in a population where everyone is susceptible. This is used to measure the transmission potential.

Correlates of protection (CoP) - Correlates of protection to a virus or other infectious pathogen are measurable signs that a person is immune, i.e. protected against becoming infected and/or developing disease.

COVID-19 - the disease caused by the virus SARS-CoV-2.

Cytokines are signalling proteins that regulate a wide range of biological functions including innate and acquired immunity, haematopoiesis, inflammation and repair, and proliferation, mostly through extracellular signalling. They are secreted by many cell types and are involved in cell-to-cell interactions.

Cytokine storm is an overproduction of immune cells and their activating compounds, cytokines, which is often associated with a surge of activated immune cells into the lungs. The resulting lung inflammation and fluid build-up can lead to respiratory distress, and can be contaminated by a secondary bacterial pneumonia.

Dendritic cell (DCs), named for their probing, 'tree-like' or dendritic shapes, are responsible for the initiation of adaptive immune responses. They are the 'sentinels' of the immune system.

ELISA stands for Enzyme-Linked Immunosorbent Assay, and is a plate-based assay technique designed for detecting and quantifying substances such as peptides, proteins, antibodies and hormones.

IgG - representing approximately 75% of serum antibodies in humans, immunoglobulin G (IgG) is the most common type of antibody found in blood circulation. IgG molecules are created and released by plasma B-cells.

IgM - immunoglobulin M (IgM) another type of antibody produced by B-cells. IgM is the largest antibody, and it is the first antibody to appear in the response to initial exposure to an antigen.

Immune modulators are substances that modify immune responses. They can be both endogenous (produced naturally within the body) and exogenous (as pharmaceutical drugs), and they can either enhance an immune response or suppress it.

Immunogenetics is the study of the genetic basis of the immune response. It includes the study of normal immunological pathways and the identification of genetic variations that result in immune defects, which may result in the identification of new therapeutic targets for immune diseases.

Immunopathology is the study of undesirable reactions produced by immune mechanisms that primarily exist for protection against disease.

Innate immunity or Innate Immune system - Innate immune responses are not specific to a particular pathogen in the way that the adaptive immune responses are. They depend on a group of proteins and phagocytic cells that recognise conserved features of pathogens and become quickly activated to help destroy invaders.

Interferons - are a group of soluble, inflammatory proteins that are produced and released from cells in response to virus infection.

Lymphocytes - a type of immune cell that is made in the bone marrow and is found in the blood and lymph tissue. The two main types of lymphocytes are B lymphocytes and T lymphocytes.

Macrophages - are specialised cells involved in the detection, phagocytosis and destruction of bacteria and other harmful organisms. They can also present antigens to T-cells and initiate inflammation by releasing cytokines that activate other cells.

MERS - stands for Middle East Respiratory Syndrome, caused by the coronavirus MERS-CoV, which was identified in Saudi Arabia in 2012.

Neutralising antibody - a neutralizing (or protective) antibody is an antibody that defends a cell from a pathogen or infectious particle by neutralizing any effect it has biologically. Neutralizing antibodies are part of the humoral response of the adaptive immune system against viruses, intracellular bacteria and bacterial toxins.

Nosocomial - infections originating, taking place or acquired in a hospital.

SARS1 - Severe Acute Respiratory Syndrome caused by the coronavirus known as SARS-CoV, which caused two outbreaks between 2002-04.

SARS-CoV-2 - the name of the coronavirus that emerged in 2019 and causes the disease COVID-19.

Sero-prevalence is the number of people in a population who test positive for a specific disease based on blood serum specimens, usually based upon the presence of antibodies for that disease.

Spike antigen - the spike protein (see below), particularly the receptor binding domain (RBD), is a target for neutralising antibodies and is being used as a target or 'antigen' during vaccine design.

Spike protein or S protein is one of 4 structural proteins of SARS-CoV-2. This protein is responsible for cell entry by binding to the human receptor ACE2 on the cell surface of human cells via the receptor binding domain (RBD) contained within the spike protein.

Subgenomic-RNA - When it infects host cells, SARS-CoV-2 replicates its genomic RNA (gRNA) and produces many smaller RNAs known as subgenomic RNAs (sgRNAs). These sgRNAs are used for synthesizing various proteins.

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.

B-cell - also known as B lymphocytes, B-cells are a type of white blood cell. They function in the humoral immunity component of the adaptive immune system by secreting antibodies.

Viral-RNA - SARS-CoV-2 is a positive sense single stranded RNA virus, which means its genome is encoded on a single strand of RNA. The presence of this viral RNA in a person indicates that person has, or has recently had, an active infection with the virus.

Annex 5: Advisory group membership

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