

Expert summary - What the latest research on COVID-19 immunology can tell us about responding to the epidemic

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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.

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, the only effective control measure is social (physical) distancing. Studies are underway to discover how many of us have been infected and so have specific antibody to the virus ('sero-prevalence*'). There is still uncertainty about what types of immunity are most protective and for how long, which is essential to know for disease projections and public health.

Elucidating biomarkers to identify which cases 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-moderated organ damage will be vital to manage the disease outbreak and limit mortality. This can be achieved through immune modulators, anti-inflammatory drugs and antiviral therapies.

It is clear that exposure to higher doses of the virus may lead to more severe disease, and so it is crucial to provide adequate personal protective equipment to healthcare workers and learn more about nosocomial* spread in hospital and community settings. People with severe disease may also remain infectious for longer. We do not yet have good tests for infectiousness, but studies suggest even mild cases could be infectious on day 8 after symptom onset.

Physical distancing while antibody tests are developed to determine who has been exposed to SARS-CoV-2* remains crucial. However, scaling lab-based antibody tests to commercial equivalents is challenging; some high-throughput tests may produce false-positives to antibodies against other related coronaviruses such as the common cold. Questions also remain whether any or some of the antibody response mounted by those exposed to SARS-CoV-2* can protect from future infection. This means 'antibody-positive passports' cannot be wholly relied upon at this stage.

Vaccines or effective therapeutics are the only realistic prospect of long-term control and the ultimate lifting of social restrictions. It is absolutely vital these efforts 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 may be less effective in elderly populations.

Key unknowns:

- The role of antibody vs. cellular immunity in immune protection and disease
- Whether, and how, the immune response may enhance disease
- Why the disease is often severe in older people, and rarely in children
- The immune biomarkers that predict severe disease and treatment response

Background to this report

In early April 2020, the Academy of Medical Sciences (AMS) and the British Society for Immunology (BSI) established an expert advisory group chaired by the BSI President, Professor Arne Akbar FMedSci. Focussing on immunology and COVID-19, the expert advisory group has completed this rapid review of the relevant immunology research and what it can tell us about responding to the COVID-19* epidemic. The composition of the advisory group is provided in Annex 4. SAGE are welcome to consult the advisory group on immunology issues in future.

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 AMS, the BSI or the individual members of the group.

Text in **bold** highlights key messages. An asterisk (*) denotes words that appear in the glossary (Annex 3).

Introduction

In December 2019, a new type of viral pneumonia appeared in Hubei Province, China. It seemed highly infectious and resistant to therapy, infecting medical staff and other patients. There was initial delay in recognising the seriousness of disease, but early reports showed it to be very similar to the SARS1* coronavirus outbreak of 2002–04. SARS1* caused over 8,000 infections with approximately 10% mortality. The new disease, called COVID-19* and caused by a virus termed SARS-CoV-2* (more about the virus can be found in Annex 1), seemed milder, but still with 1% mortality. The initial cases were associated with the Huanan seafood market, in which exotic animals were sold for food, but it was soon clear that person to person transmission was occurring. By February 2020, outbreaks appeared outside China, most notably in Italy and Iran. Soon after, the World Health Organization (WHO) declared a pandemic.

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
- 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

What happens when a person is exposed to the virus, and during early infection?

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 (R_0)* is estimated at between 2.5-3.5¹ – 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 supports the case that people with persistent symptoms should self-isolate for longer than 7 days.

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**

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).

infections arise from asymptomatic spread.⁸ This is likely to play a more significant role in transmission of COVID-19 than '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 and plentiful personal protective equipment (PPE) is paramount to limiting transmission.

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 cellular 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.

⁸ Ibid., 3. 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.

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

The ability to manipulate the immune response is vital to prevent death from COVID-19*. Many NIHR national priority trials include immune modulators*. A group of anti-inflammatories, known as glucocorticoids, were somewhat successful in treating SARS1*. **However, better understanding of disease progression is key to choosing the correct immunological pathway to modulate and when to do so.**

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.**¹³ Viral-RNA* in non-respiratory tissues may reflect killed or inactivated virus that has been cleared from the airway and is no longer infectious.¹⁴ Pathologies in other sites are likely secondary results of inflammation and blood clotting.

Why are older people and men more severely affected?

Ageing has a negative impact on the immune system, airways and lungs (see Annex 2 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 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 T cell responses.

The impact of ageing on the immune system also has implications for the efficacy of SARS-CoV-2* vaccines for older individuals. **Older people only rarely respond to vaccines as well as younger individuals. This highlights the importance of anti-inflammatory drug intervention and antivirals in addition to vaccines, particularly for older groups.**

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.

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

¹³ Ibid., 3. Woelfel R, *et al.* (2020).

¹⁴ Ibid., 3. Woelfel R, *et al.* (2020).

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.¹⁵

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.^{16,17} However, secondary bacterial infections has 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 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 be faring 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.

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,¹⁸ and so help discern infectious patients from resolved cases that continue to shed viral-RNA*. ^{19,20} However, even this test is not definitive.

¹⁵ The European Centre for Disease Prevention and Control (2020). Coronavirus disease 2019 (COVID-19) in the EU/EEA and the UK – eighth update

¹⁶ 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.

¹⁷ 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.

¹⁸ Ibid., 3. Woelfel R, et al. (2020)

¹⁹ 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.

²⁰ Ibid., 3. Woelfel R, et al. (2020)

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,²¹ yet a small screen of asymptomatic blood donors found 70% carried SARS-CoV-2* antibodies.²² This knowledge can help calculate when we have attained protective 'herd immunity.'

On the basis of an R_0^* 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.

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.²³ Low antibody levels may correlate with very different states; e.g. lethal or near-lethal

²¹ 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

²² Yang T, et al. (2020). *Combining Point-of-Care Diagnostics and Internet of Medical Things (IoMT) to Combat the COVID-19 Pandemic*. *Diagnostics*, **10(4)**, 224

²³ Tan W, et al. (2020). *Viral Kinetics and Antibody Responses in Patients with COVID-19*. medRxiv preprint.

infection, old age, or having only had a mild infection. However, for MERS*²⁴ 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 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?

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.**^{25,26,27,28} Plasma from recovered SARS1* patients was effective in treating new cases, indicating it contained durable protective antibodies*.²⁹

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.

²⁴ Zhao J, et al. (2017). Recovery from the Middle East respiratory syndrome is associated with antibody and T-cell responses. *Science Immunology* **2**(14).

²⁵ Wu LP, et al. (2007). Duration of antibody responses after severe acute respiratory syndrome. *Emerging Infectious Diseases* **13**(10), 1562-1564.

²⁶ Mo H, et al. (2006). Longitudinal profile of antibodies against SARS-coronavirus in SARS patients and their clinical significance. *Respirology* **11**(1), 49-53.

²⁷ Guo X, et al. (2020). Long-Term Persistence of IgG Antibodies in SARS-CoV Infected Healthcare Workers. medRxiv preprint.

²⁸ Liu W, et al. (2006). Two-year prospective study of the humoral immune response of patients with severe acute respiratory syndrome. *Journal of Infectious Disease* **193**(6), 792-795.

²⁹ Mair-Jenkins J, et al. (2015). The Effectiveness of Convalescent Plasma and Hyperimmune Immunoglobulin for the Treatment of Severe Acute Respiratory Infections of Viral Etiology: A Systematic Review and Exploratory Meta-analysis. *Journal of Infectious Disease* **211**(1), 80-90.

What are the opportunities and challenges for new vaccines?

What makes a successful vaccine?

Multiple promising COVID-19* vaccines are now entering development pipelines. However, it is too early to say if their effects will be protective, or safe. To develop an effective vaccine, we need to better understand the required CoP*

Notwithstanding the urgent timeline, vaccine selection requires rigorous efficacy and safety testing. Some components of immunity seem to be associated with poorer disease outcomes, so are best avoided as vaccine candidates. It is also essential that vaccines do not cause antibody dependent enhancement (ADE*), whereby some antibodies actually facilitate rather than block carriage of virus into human cells.³⁰ 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. Animals receiving SARS1 vaccines developed immune-mediated lung or liver damage.^{31,32,33,34,35,36} This negative effect was in some cases reduced by using adjuvants* (used to stimulate a stronger response to vaccines),³⁷ but there is no consensus about why this damage occurs.

What vaccine strategies are being explored?

As SARS-CoV-2* has only recently emerged, the strategies currently being explored are mostly based on experimental findings from preclinical SARS1* vaccines. A recent Coalition for Epidemic Preparedness Innovations (CEPI) report identified over 100 vaccine candidates in preparation, a number in Phase I clinical trials. These candidates will be diverse in the type, size and durability of immune response they induce, the doses per person required and ease of manufacture at scale. Most target the spike protein receptor binding domain (RBD*).³⁸ In animal studies on the SARS1* virus, this approach induced strong protection against infection.³⁹ However, similar vaccines against coronaviruses in other species proved mostly ineffective and may have selected for new virus variants (i.e. led to new mutations).⁴⁰

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

³⁰ Takano T, et al. (2019). Pathogenesis of oral type I feline infectious peritonitis virus (FIPV) infection: Antibody-dependent enhancement infection of cats with type I FIPV via the oral route. *Journal of Veterinary Medical Science* **81**(6), 911-915.

³¹ Weingartl H, et al. (2004). Immunization with modified vaccinia virus Ankara-based recombinant vaccine against severe acute respiratory syndrome is associated with enhanced hepatitis in ferrets. *Journal of Virology* **78**(22), 12672-6.

³² Czub M, et al. (2005). Evaluation of modified vaccinia virus Ankara based recombinant SARS vaccine in ferrets. *Vaccine*. **23**(17-18), 2273-9.

³³ Liu L, et al. (2019) Anti-spike IgG causes severe acute lung injury by skewing macrophage responses during acute SARS-CoV infection. *JCI Insight*. **4**(4).

³⁴ Deming D, et al. (2007). Correction: Vaccine efficacy in senescent mice challenged with recombinant SARS-CoV bearing epidemic and zoonotic spike variants. *PLoS Medicine* **4**(2), e80.

³⁵ Yasui F, et al. (2008) Prior immunization with severe acute respiratory syndrome (SARS)-associated coronavirus (SARS-CoV) nucleocapsid protein causes severe pneumonia in mice infected with SARS-CoV. *Journal of Immunology* **181**(9), 6337-48.

³⁶ Tseng C-T, et al. (2012). Immunization with SARS Coronavirus Vaccines Leads to Pulmonary Immunopathology on Challenge with the SARS Virus. *PLoS ONE* **7**(4), e35421.

³⁷ Ibid., Tseng C-T, et al. (2012).

³⁸ Thanh Le T, et al. (2020). The COVID-19 vaccine development landscape. *Nature Reviews Drug Discovery* Epub ahead of print.

³⁹ Jiang S, et al. (2012). Roadmap to developing a recombinant coronavirus S protein receptor-binding domain vaccine for severe acute respiratory syndrome. *Expert Reviews Vaccines* **11**(12), 1405-13.

⁴⁰ Fehr AR & Perlman S (2015). Coronaviruses: an overview of their replication and pathogenesis. *Methods in Molecular Biology* **1282**, 1-23

Annex 1: 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* virus⁴¹ 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 receptor binding domain (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.⁴²

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.⁴³ 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.

⁴¹ Zhang YZ & Holmes EC (2020). *A Genomic Perspective on the Origin and Emergence of SARS-CoV-2*. Cell, In Press, Corrected Proof.

⁴² Ibid., Zhang YZ & Holmes EC (2020).

⁴³ Rambaut A, Holmes EC & Pybus OG. *A dynamic nomenclature for SARS-CoV-2 to assist genomic epidemiology*. Virological

Annex 2: Infection and the life course

Infection in children

There have been a very small number of paediatric cases of COVID-19*.⁴⁴ Children are at reduced risk of disease and severe complications, but can be asymptomatic carriers. As in adults, underlying conditions increase susceptibility.⁴⁵ In one study, 11% of children admitted to hospital with respiratory infections had COVID-19; all had good outcomes.⁴⁶

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.^{47,48} 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.⁴⁹ 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,⁵⁰ so this aspect of immunity does not appear to be an issue.

⁴⁴ Liu W, et al. (2020). *Detection of Covid-19 in Children in Early January 2020 in Wuhan, China*. The New England Journal of Medicine **382(14)**, 1370-1371.

⁴⁵ Rasmussen SA & Thompson LA (2020). *Coronavirus Disease 2019 and Children What Pediatric Health Care Clinicians Need to Know*. JAMA Pediatrics

⁴⁶ Tagarro A, et al. (2020). *Screening and Severity of Coronavirus Disease 2019 (COVID-19) in Children in Madrid, Spain*. JAMA Pediatrics

⁴⁷ Vukmanovic-Stejic M, Akbar AN, et al. (2017). *Enhancement of cutaneous immunity during aging by blocking p38 mitogen-activated protein (MAP) kinase-induced inflammation*. J Allergy Clin Immunol **17**, 31766-9.

⁴⁸ De Maeyer RPH, et al. (2020). *Blocking Elevated p38 MAPK Restores Efferocytosis and Inflammatory Resolution in the Elderly*. Nature Immunology Epub ahead of print.

⁴⁹ Zhao J, et al. (2011). *Age-related increases in PGD(2) expression impair respiratory DC migration, resulting in diminished T cell responses upon respiratory virus infection in mice*. The Journal of Clinical Investigation **121(12)**, 4921-4930.

⁵⁰ Wu F, et al. (2020). *Neutralizing antibody responses to SARS-CoV-2 in a COVID-19 recovered patient cohort and their implications*. medRxiv preprint

Annex 3: 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.

Adjuvant - are a substance frequently used in vaccines which enhances the body's immune response to an antigen.

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.

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 4: Advisory group membership

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