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## Long-term immunological health consequences of COVID-19

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### **Document Version:**

Publisher's PDF, also known as Version of record

### **Queen's University Belfast - Research Portal:**

[Link to publication record in Queen's University Belfast Research Portal](#)

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# Long-term immunological health consequences of COVID-19

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As this has been a rapid review, it is a summary of the research at 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 the British Society for Immunology, its members or the individual members of the advisory group.

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## Executive summary

As the COVID-19 pandemic continues, it has become clear that infection with SARS-CoV-2 may be responsible for previously unexpected long-term immunological health consequences. The UK's immunologists have been at the forefront of researching the phenomena that we are seeing and the mechanisms behind them.

This briefing note aims to summarise what we do and don't currently know about the long-term immunological health consequences of COVID-19 and sets out the key recommendations for future research. An asterisk (\*) denotes words that appear in the glossary (annex 2).

Exposure to the disease, COVID-19, causes symptoms in multiple organ systems across the body, and is not limited to only the lungs and respiratory system as was originally thought. In addition, patients are reporting chronic symptoms, such as fatigue and shortness of breath, that last for months after their original infection.

The immune system's response to the SARS-CoV-2 virus is thought to play a part in the appearance of these symptoms, rather than the virus itself, often through facilitating inflammation. This has the ability not only to exacerbate any secondary conditions the patient already has, but also to cause them, as is the case with other viruses, and these may persist for years.

The full extent of the prevalence of COVID-19 patients who go on to experience longer-term immunological health consequences is not yet fully understood. However, the emerging need for COVID-19 follow-up clinics to treat these chronic symptoms may place an additional burden on the health service.

The briefing note lays out several recommendations to help us understand what SARS-CoV-2 and our immune response to it does to our health over the long term. This includes using large cohort studies over a number of years to follow the health of those have been infected from diverse demographics. This type of longitudinal study is particularly important to aid knowledge on the long-term effects of COVID-19. Failure to seize this opportunity now has the potential to perpetuate chronic ill health in those patients recovering from COVID-19 and to substantially increase the burden on the NHS in the future.

# Introduction to the immune system

The immune system is the body's defence system against invading pathogens, in this case the SARS-CoV-2 virus that causes COVID-19. The first line of defence is termed innate immunity\* – the basic, initial barriers that aim to ensure that not every exposure to a virus always leads to entry into cells and overt infection. If virus gets in, it encounters patrolling white blood cells called B cells\* and T cells\*. B cells\* make highly specific antibodies\* targeted onto the virus for elimination; this is adaptive immunity\*. T cells\* both help stimulate the B cells\* and also kill any cells that do get infected by the virus, so limiting infection. These two cell types keep a memory of the specific infection so that the immune system can respond faster and more effectively if it meets the infection again – the basis for vaccines. Symptoms exhibited during and after an infection may be caused by the pathogen directly, but can also be caused by the body's immune response to the pathogen; unfortunately, the immune system can work against the body itself as well as against the pathogen.

## Symptoms during initial infection

Patients who become infected with SARS-CoV-2 may experience no, mild, or severe symptoms.<sup>1,2,3</sup> A small proportion of patients with severe symptoms require hospitalisation and can die from the infection.<sup>4</sup> Symptoms can be partly due to the virus and partly due to the immune system reacting to the virus.

The median incubation period from initial infection to symptom onset is 5.1 days with the majority (~97.5%) developing symptoms within 11.5 days. The symptoms that occur after infection include fever (72%), shortness of breath (71%), cough (69%), tiredness (46%), coughing up sputum (26%), aching muscles or joints (21%), headache (13%) and sore throat (10%).<sup>5</sup> Other symptoms can include loss of taste (50%) and sense of smell (66%).<sup>6</sup> In patients with mild disease, the fever is likely to settle and patients recover after 7 days. In more severe cases, patients may continue coughing for a couple of weeks. In patients with severe infection, shortness of breath becomes marked 7–10 days after symptom onset as the infection induces inflammation in the lungs which prevents efficient oxygen exchange.

Some patients are now reporting diverse, chronic, ongoing symptoms for three months plus after initial infection. One of the first published datasets indicates about 50% of hospitalised patients are suffering symptoms such as fatigue, shortness of breath and joint pains, two months after hospital discharge.<sup>3</sup>

# What are the underlying immune mechanisms that contribute to people experiencing longer-term health problems after COVID-19 infection?

The term 'cytokine storm'\* has been used to describe the very high levels of inflammatory cytokines\* observed in the blood of hospitalised patients with severe COVID-19. These inflammatory cytokines\* will have long-term consequences, not only for lung health, but also distant organs. This will place additional burden on healthcare services and we are likely to see a significant increase in the global burden of disease.

While COVID-19 was initially considered a respiratory syndrome, it is now clear that damaging fibrosis\* (scarring) and inflammation can be found in multiple organs including lung, heart, kidneys, liver, adrenal glands and gastrointestinal tract, although these phenomena vary widely between individuals. The extent of disease partly reflects the wide distribution of the cellular receptor for SARS-CoV-2, angiotensin-converting enzyme 2 (ACE-2\*), but also the indirect effects of inflammatory mediators. Other viral infections can trigger a range of autoimmune diseases, (e.g. Guillain-Barré syndrome), so follow-up studies for these and other conditions will be needed for COVID-19 patients. For the inflammatory effects, disproportionate activation of the complement system\* can lead to excessive coagulation in the blood and thrombotic complications, pulmonary embolism, cardiac injury and stroke.

In general, inflammation may worsen pre-existing conditions, but equally may cause them. Some secondary illnesses may persist for years, such as inflammation-induced cognitive decline, psychosis, mood disorder and fatigue. Respiratory viruses with pandemic potential continue to emerge and so it is vital that we learn as much as possible from the current crisis. The clinical trials of anti-inflammatory therapeutics provide real potential to discover immune modulators that will benefit not just COVID-19 but also immune-mediated injuries to distant organs.

Therefore, it appears that SARS-CoV-2 can likely do long-term damage in different parts of the body, through direct effects of viral infection and tissue damage (fibrosis\*), through collateral damage from excessive inflammation, through post-viral autoimmunity, and through the consequences of thrombotic complications.

# What are the longer-term immunological health consequences of COVID-19 infection?

In addition to respiratory symptoms (e.g. cough), COVID-19 may also involve acute cardiac, renal and hepatic injury in some patients as well as cardiac arrhythmias\*, rhabdomyolysis\*, coagulopathy\*, and shock.<sup>7,8,9</sup> As previously mentioned, such disseminated effects are accompanied by raised cytokine\* levels in blood serum or plasma. The systemic COVID-19 syndrome is usually accompanied by mild lymphopaenia\*, neutrophilia\*, fever, thrombocytopenia\*, hyperferritinaemia\*, and elevation of other inflammatory and clotting factors.<sup>10</sup> Severe pathology is thought to be due to reduced anti-viral immune defence in conjunction with overexuberant cytokine\* responses.<sup>11</sup> Severe disease and disease affecting multiple organs has a poor short- and long-term outcome.

## Lungs

One possible consequence of severe acute inflammation is scarring or fibrosis\*, which may be irreversible and lead to long-term health problems. In the lungs, this may lead to pulmonary fibrosis\*, leaving patients breathless with a reduced lung capacity. In one study, 94% of hospitalised patients showed residual abnormalities on CT scans at time of discharge following severe COVID-19,<sup>12</sup> with abnormalities also being identified in CT scans of asymptomatic patients.<sup>13</sup> However, the disease often has characteristics of organising pneumonia, a disease that is normally steroid responsive. The optimal therapy for this condition following COVID-19 is currently unknown. A particularly worrying aspect is that CT lung abnormalities ('ground-glass appearance') are not limited to severe, hospitalised cases, but can also be found in people who had asymptomatic or mild infections.<sup>10</sup>

A longitudinal study of SARS1\* patients from 2003 to 2018 found that more than a third had reduced lung capacity.<sup>14</sup> Similarly, with MERS\*, a third of survivors had long-term lung damage.<sup>15</sup> These studies were small but indicate that it will be necessary to follow COVID-19 survivors long term to determine whether lung function abnormalities are persistent, and how they should be managed.

## Circulatory system

Abnormal clotting and microthrombi\* are a feature of COVID-19 infections with as many as 31% of ICU patients experiencing thrombotic complications, which may lead to stroke.<sup>16</sup> A third of patients in one study showed neurological symptoms, including acute cerebrovascular events, impaired consciousness and muscle injury. These effects are more frequent in patients with severe respiratory impairment, affecting up to 45.5% of such cases.<sup>17</sup>

## Cardiovascular system

The cardiovascular system is also affected, with complications including myocardial injury, myocarditis, acute myocardial infarction (heart attack), heart failure, dysrhythmias\*, and venous thromboembolic events. Chronic cardiac disease was the most commonly identified co-morbidity in COVID-19 patients.<sup>5</sup> Follow-up studies have determined that SARS patients may exhibit lipidaemia, cardiovascular system abnormalities or glucose metabolism dysfunction.<sup>18,19</sup> Defects in lipid metabolism remained 12 years after clinical recovery in a metabolomic study among 25 SARS1 survivors.<sup>20</sup> Acute kidney injury is an independent risk factor for patient in-hospital mortality.<sup>21</sup> The mechanisms are unclear, but may derive from fluid restriction, drug toxicity, hypoxia, hypotension or hypercytokinaemia\*. It is possible that SARS-CoV-2 is present in kidney, liver, heart, brain and blood,<sup>22</sup> but these findings require validation. The Post-hospitalisation COVID-19 study (PHOSP-COVID) is a consortium of leading researchers and clinicians from across the UK working together to understand and improve long-term health outcomes for COVID-19 patients. It aims to recruit 10,000 patients to follow up with clinical assessments over 12 months.

## Fatigue

Many patients who recover from severe infection can exhibit a variety of symptoms for weeks after the virus has been cleared such as fatigue, pain, sleep disruption and neurological symptoms including memory loss, delirium and hallucinations. This bears some outward similarities to chronic fatigue syndrome although we do not yet understand the underlying pathology. Three possibilities have been suggested for long-term effects after infection by scientists at Yale. Patients with long-term symptoms might still harbour infectious virus in some reservoir organ, not identified by nasal swabs. Also, persistent fragments of viral genes, though not infectious, may still be triggering a violent immune overreaction. Alternatively, although the virus is cleared, the immune system continues in an overactive or perturbed state, analogous to the long-term debilitation after glandular fever. It is not yet known how the immune system is altered in patients who have chronic symptoms after infection and those that have none. However, if the immune system is involved in the neurological symptoms then there must be an interaction between the immune and neuroendocrine systems.

## Other

Some patients with mild or asymptomatic disease may suffer long-term inflammatory consequences. Over 1,000 cases of paediatric inflammatory multisystem syndrome associated with SARS-CoV-2 have now been reported globally,<sup>23</sup> but it is not yet clear how common such syndromes are in adults. We currently do not know what the long-term health impact of COVID-19 will be, but detailed follow-up will be necessary to support patients beyond the acute phase of infection.

# How do longer-term immunological health effects post-COVID-19 infection vary from person to person?

The body's immune system for responding to infection is a complex network of many types of interacting white blood cells and molecules. Every individual's immune system is as unique as their fingerprints, and so different people can respond to a virus in different ways, for example with greater or lesser collateral damage through inflammation. It has become clear from many studies that people have different risks for severe or lethal infection with SARS-CoV-2 – among factors associated with higher risk are age, male sex, obesity, diabetes, occupational exposure and ethnicity.<sup>2</sup> Each of these factors is likely to contribute to this raised risk in a variety of ways, but differential immunity to the virus is one important aspect. As longer-term studies progress, we are starting to understand the associations between the spectrum of disease severity (from asymptomatic, to mild, to severe) and the long-term immunity that is elicited.

## What is the effect of individual variation on any potential longer-term immunity to COVID-19?

The immunological responses detected post-SARS-CoV-2 infection are incredibly variable, from lots to virtually none, even between people who are demographically similar and clearly PCR-positive. It is a basic truth that people with more severe disease (perhaps with a higher 'viral burden' to stimulate immunity) tend to have higher levels of antibody\*. People who have been very mildly affected or completely asymptomatic can also make an antibody\* response, though levels are sometimes low or absent. One recent study showed that in an asymptomatic group, 40% had lost detectable antibodies\* within two months.<sup>10</sup> The effect of this on the potential for re-infection is presently unknown. It should be noted that, even without detectable levels of antibodies\*, there can still be memory B cells which are able to produce antibodies\* in an accelerated reaction to re-infection. Memory T cell responses persisted much longer following SARS than neutralising antibody\* responses, and are detectable in patients who have recovered from COVID-19, which may also offer protection.<sup>24</sup>

People with different demographic characteristics have different long-term immunity to pathogens, aside from their differences during the acute infection. We think of the ageing immune system as being functionally impaired, for example often showing poorer vaccine responses and higher levels of potentially autoreactive antibodies\*. Simple measures of SARS-CoV-2 immunity, such as antibody\* levels, show that older people do not lack for *quantity* of antibody\*.<sup>25</sup> We do not yet know how the *quality* of the antibody\* in terms of function and durability may differ. Cellular immunity (T cells\*) in older people can be numerically or functionally lower. However, no studies have yet looked at long-term perturbations of immune function or organ damage by COVID-19-induced immune inflammation in older people.

Immunity to SARS-CoV-2 has been compared between male and female patients, seeking explanations for why men are more likely to suffer severe disease. The general pattern seen is that men are disadvantaged by starting out at a higher pro-inflammatory set-point, while women make higher specific T cell\* responses to the virus.<sup>26</sup> The level of the T cell\* response seems important, as poor T cell\* immunity correlates with poorer outcome and potentially shorter-lived immunity. The effect of obesity is in some ways similar to the effect of being male – a greater skewing to a pro-inflammatory set-point. COVID-19 is characterised by inflammation and is more severe in obese and older people. In this context it is pertinent to note that adipose tissue in obesity can cause increased inflammation, older people have higher background levels of inflammatory cytokines\* (inflammaging), and obesity in conjunction with older age exacerbates inflammaging.<sup>27</sup>

The study of immune and inflammatory parameters in the blood in patients with or without long-term symptoms after infection may identify the correlation between immunity and longer-term symptoms in COVID-19 patients. These include specific antibody\* levels and SARS-CoV-2-specific T lymphocytes\*, markers of T\* and B cell\* activation and proliferation, and serum levels of inflammatory markers such as CRP, IL6 and TNF- $\alpha$ . Investigations of immune/neural interactions would be ideal but difficult to perform. Damage or scarring of lungs or other organs may also contribute to continued symptoms but this will be difficult to quantitate. Senescent cells that are inflammatory accumulate during tissue damage and may participate in continued tissue dysfunction.



## What is the effect of individual variation on the longer-term effects of COVID-19 infection and its clinical management?

There is currently much interest in characterisation of diverse manifestation of a post-COVID-19 syndrome. While some facets of this are likely a result of direct virus damage to organs, some are likely to be an effect mediated through the immune system: results of inflammation, of a perturbed immune system (as can happen following glandular fever), or of autoimmunity. We know from similar viral infections that severe disease can leave the body vulnerable to infection by other pathogens – this is akin to the body putting the brakes on too hard and slowing the ability to respond to new pathogens too much. This can manifest quickly in secondary bacterial infections (which seem uncommon in COVID-19), or more slowly in an increased susceptibility to infections over the weeks and months following disease. This is an area we will need to monitor in COVID-19 patients.

Disease mechanisms and treatments will need to be worked out over the next few months in COVID-19 follow-up clinics. From the above, it's highly likely that the immune mechanisms may differ to some extent between the different groups.

# Recommendations

- 1** Research into COVID-19 has in some respects been impeded by the lack of adequately funded long-term follow-up studies during SARS and MERS outbreaks. To properly understand the long-term immunological health consequences of COVID-19, learn from the current situation and be better prepared for any future pandemics, we need to urgently establish long-term (5–10 years) cohort studies and research programmes to track durability of the immune response (both antibody and T cells) and long-term disease consequences in COVID-19 patients. These cohorts should include representation from groups whose immune response may vary (e.g. older individuals).
- 2** Datasets are still emerging, but there appears to be a sizeable subset of people recovered from the acute infection, who continue to suffer chronic symptoms. These people range from asymptomatic to severe infections – as such, many may not even have had a PCR test and may not be known to the NHS as positive cases. Their COVID-19 status may in some cases only be established by screening for B or T cell memory to the virus. The chronic symptoms are diverse, affecting different parts of the body and may have different underlying causes. At a clinical and at a research level, understanding these pathologies will require a multidisciplinary approach with input from immunology, respiratory medicine, cardiology, vascular biology, renal medicine, liver medicine, neurology, endocrinology and rheumatology.
- 3** Research to better understand the underlying biological mechanisms that drive the longer-term immunological health consequences of COVID-19 should be a high priority in order to establish new therapeutic options that may alleviate or cure the diverse chronic symptoms. Failure to do so would not only perpetuate the burden of chronic disease in this large group, it would also perpetuate a substantial, new, long-term care-burden on the NHS, requiring extensive COVID-follow-up clinics stretching forward for years to come.

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## Annex 2: Glossary

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

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

**Antibodies** – large Y-shaped proteins produced by B cells. They act to neutralise invading pathogens such as the SARS-CoV-2 virus.

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

**Cardiac arrhythmias** – a group of conditions that results in the heart beating irregularly, e.g. too slowly or too quickly.

**Coagulopathy** – a condition in which the ability of blood to clot is impaired.

**Complement system** – the part of the immune system that, through a cascade of reactions, enhances its ability to remove pathogens from the body.

**Cytokines** – 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** – 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.

**Dysrhythmias** – see cardiac arrhythmia.

**Fibrosis** – the replacement of normal functional tissue with connective tissue, which can lead to permanent scarring.

**Hypercytokinaemia** – a severe immune reaction in which the immune system releases too many cytokines into the blood too quickly (see cytokine storm).

**Hyperferritinaemia** – the presence of too much ferritin, an iron storing protein, in the blood.

**Innate immunity** – the immune system's defences that are non-specific to any pathogen.

**Lymphopaenia** – a deficiency of lymphocytes, a type of white blood cell.

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

**Microthrombi** – a microscopic blood clot.

**Neutrophilia** – accumulation of neutrophils, a type of white blood cell mostly involved in the innate immune system.

**Rhabdomyolysis** – the breakdown of damaged skeletal muscle which releases myoglobin into the blood. Excess levels of myoglobin in the blood can lead to kidney damage.

**SARS1** – Severe Acute Respiratory Syndrome caused by the coronavirus known as SARS-CoV, which caused two outbreaks between 2002 and 2004.

**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.

**Thrombocytopenia** – a platelet (thrombocyte) deficiency in the blood.

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