

# The ageing immune system and 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

Since the beginning of the COVID-19 pandemic, it has been apparent that this disease affects different people in different ways. One of the starkest contrasts has been how infection with SARS-CoV-2 can affect people dissimilarly across age groups.

This report explores how ageing can affect the immune system's response to the SARS-CoV-2 virus. This includes the role of ageing in susceptibility to infection, immune memory, what role other medical conditions associated with ageing have to play; what this means for the optimal treatment of COVID-19 and the vaccines that are being developed to prevent this disease. An asterisk (\*) denotes words that appear in the glossary (annex 2).

It is well established that the immune system changes as we get older. The balance between immune activation, regulation and resolution can be altered as we age, resulting in inadequate protection against infection, along with a greater risk of inflammatory disease. As with many aspects of the human body, there is no one 'cut off' point for this to occur but instead it is a gradual process. Indeed, the shrinkage of the thymus, an organ that produces a type of immune cell known as T cells\*, begins shortly after birth.

Large studies in the UK have confirmed the positive correlation between increasing age and increasing COVID-19 disease severity. Relative to hospitalised patients under 50 years of age, those aged 60–69 are approximately five times more likely to die from COVID-19, while those aged 70–79 are at 8.5 times greater risk. The reasons for this are numerous. There are, for example, increased and chronic background levels of inflammation in older individuals, referred to as 'inflammaging'\*, which have been linked to increased risk of disease and increased expression of inflammatory genes is associated with increased all-cause mortality in older individuals.

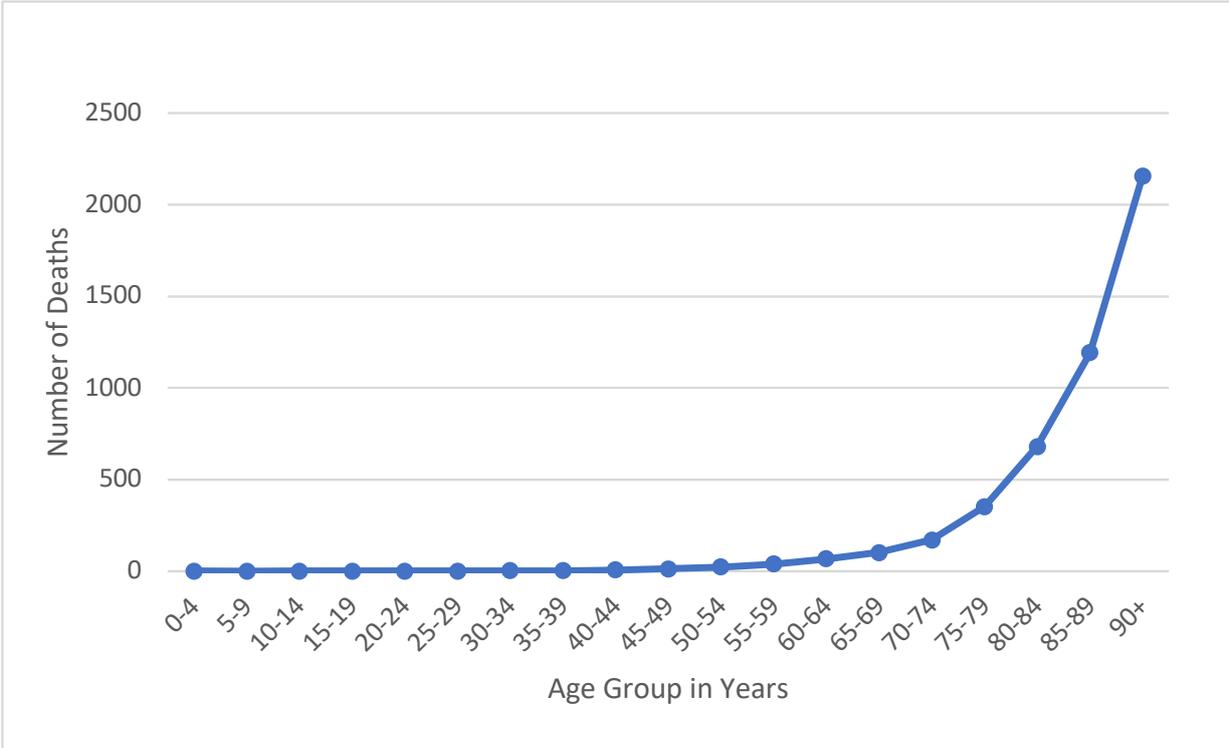
Various factors work in tandem with the ageing immune system to exacerbate effects that are already happening. One feature influencing the age-related severity of COVID-19 is the higher prevalence of chronic disease in this population: by the age of 70 years, 75% of adults have two or more long-term conditions, termed multimorbidity. This can include chronic lung disease, diabetes and hypertension, amongst other conditions, all of which contribute to a greater risk of poor outcomes from COVID-19. More data is needed to be able to confirm if co-infection with either other viruses or bacteria results in an increase in mortality or morbidity.

Immunity to SARS-CoV-2 is not fully understood at any age and more work needs to be done here to determine the correlates of protection and then carry out follow-up studies to determine the lifespan of immunity. Looking at immunity in older people we can, however, look to prior knowledge on other infections and vaccine studies, which could suggest that raising robust immunity may be more difficult or may take longer.

A key aspect of an ageing immune system is a change in its response to vaccines. The decline in immune function in older adults can lead to both a reduced initial response to vaccination and/or reduced efficacy of the vaccine response. Continuing to work on the development of therapeutics for those who have contracted COVID-19 is vitally important because of concerns over the ability of older people to develop effective immunity or to respond to a vaccine.

It is as yet unknown whether older people will require different vaccines or an altered dosing schedules, but this will have real consequences for the public health response to this pandemic. Such knowledge will affect the deployment of vaccines once one or more is proven to be safe and effective. It is therefore of the utmost urgency that those making policy decisions have an understanding of age differences in immunity and a clear plan for action, including public information and education.

# COVID-19 Deaths Per 100,000 Population



**Figure 1**  
As depicted in this graph, the relative risk of dying from COVID-19 increases exponentially with age.  
Source: ONS and O'Driscoll *et al* 2020 Age-specific mortality and immunity patterns of SARS-CoV-2. *Nature* DOI: <https://doi.org/10.1038/s41586-020-2918-0>

# Introduction to ageing and the immune system

The immune system is a complex organisation of cells and molecules acting together to protect us from harmful infectious agents, aid recovery from injury and eliminate abnormal or cancerous cells. If the immune system overreacts and is poorly regulated, inflammatory disease can occur. Conversely if it doesn't react enough, and in the right way, it fails to protect us against a multitude of dangers including infections. In young healthy people there is generally a good balance between immune activation, regulation and resolution. However, this balance can be lost as we age. In older people, the immune system can fail to protect effectively against infection, and the risk of inflammatory disease rises.

Most aspects of the immune system deteriorate with age, a process known as immune senescence\*. This process can be identified as early as 55 years of age.<sup>1</sup> The abundant innate 'first responder' cells and blood-based molecules of the immune system are intrinsically altered and respond are slower and/or less efficiently.<sup>2</sup> The adaptive 'fine-tuned, highly specific' elements of the immune system, the T and B lymphocytes, would normally have the capacity to recognise and respond to a very broad range of foreign molecules without inappropriately recognising self-molecules; this self-recognition when it occurs is termed autoimmunity and causes harm. The immune balance is altered as we age as the functional types of T cells\* and B cells\* change; notably as we age we produce fewer cells that are able to recognise and deal with new infections such as SARS-CoV-2 or to respond adequately to vaccines.<sup>3, 4</sup>

One major change that occurs at a variable rate with ageing is an increase in the resting state of general immune activation, referred to as the inflammatory status and reflected by increased blood levels of so-called inflammatory markers (for example, C reactive protein or CRP). While acute inflammation is necessary for triggering an immune response, chronically increased background levels of inflammation in older individuals, referred to as 'inflammaging\*', have been linked to increased risk of disease and increased expression of inflammatory genes is associated with increased all-cause mortality in older individuals.<sup>5</sup> This chronic inflammation also reduces the ability to respond to infections or vaccinations. For example, increased systemic inflammation may be associated with impaired efficacy of influenza vaccination;<sup>6</sup> excessive inflammation can inhibit immunity to many viruses in older humans, an effect that can be reversed by short-term inhibition of inflammation with anti-inflammatory drugs,<sup>7</sup> which might explain part of the benefit of dexamethasone in treating COVID-19.

Obesity also increases systemic inflammation, even in younger subjects, and men in general have higher levels of inflammation than women.<sup>8</sup> This increased inflammation with age, male sex and obesity may contribute to the increased severity of COVID-19 in adults with these characteristics. However, it is not yet entirely clear that the propensity of older individuals to exhibit high baseline inflammation is associated with the heightened inflammatory response observed in older patients with severe COVID-19. Nevertheless, the constitutive elevated inflammatory state in this group of individuals may hamper the effectiveness of the immune response to the initial encounter with SARS-CoV-2 and also the efficacy of vaccination against the virus.

## Are older people more susceptible to SARS-CoV-2 infection?

Studying susceptibility to infection in the community is complicated by several factors. The different age groups may have different social behaviours with respect to compliance with social distancing measures. Limiting testing to symptomatic individuals will also skew infection rates in favour of older people since they are more likely to be symptomatic than younger groups.<sup>9, 10</sup> Estimating the relative risk of infection following exposure between older and younger people is therefore complex. Random sampling of the population to estimate infection rates in the REACT-1 study did not show any consistent difference in infection rates in the different age groups from age 5 onwards.<sup>11</sup>

## Do older people experience more severe COVID-19 disease or experience different symptoms?

Large, robust studies have now confirmed the strong association between increasing age and COVID-19 disease severity.<sup>12</sup> Older people are more likely to be hospitalised than younger, with a median age of hospital admission in the first wave of 73 years<sup>10</sup>. Relative to hospitalised patients under 50 years of age, those aged 60–69 years are approximately five times more likely to die from COVID-19, while those aged 70–79 are at 8.5 times the risk.<sup>10</sup> These studies have demonstrated that, in hospitalised patients, age is the major factor associated with risk of death.<sup>13</sup> Mortality in care homes and the community adds to these data, resulting in the striking age-related mortality figures illustrated in figure 1.

## Summary of different symptoms in older adults

Emerging data suggest that older people may also experience different symptoms from younger people during COVID-19. Older adults hospitalised with COVID-19 more commonly have symptoms of confusion and a productive cough, in addition to the common symptoms of shortness of breath and fever.<sup>14, 15</sup> Younger people are, by contrast, more likely to present to hospital with gastrointestinal symptoms.<sup>14</sup> Neurological symptoms in older adults may indicate delirium,<sup>15</sup> possibly resulting from the indirect effect of inflammatory mediators arising from the respiratory site of infection and/or confusion due to low oxygen status. Additionally, neurological symptoms could result from direct infection of the central nervous system as some studies have documented the presence of replicating virus in brain tissue at post-mortem.<sup>16</sup> However, the consequences of viral replication outside the respiratory tract are not well understood.

# How does the immune response to COVID-19 differ in older people compared with younger people?

Some measures of SARS-CoV-2 adaptive immunity\* are shown to be increased with age yet, paradoxically, severity of disease also increases with age. Thus, it is clear that we do not yet have a complete understanding of the role of the immune system in the balance between protection versus pathology.

## Innate response of the airway epithelium\*

Epithelial cells, the front-line cells of the body release immune messengers when they are challenged by infection. While COVID-19 manifests with more severe symptoms in older people, young people and children shed virus during SARS-CoV-2 infection at levels equivalent to older adults.<sup>17</sup> This may indicate that high viral loads are better tolerated in younger people, that the virus more rapidly colonises regions of the lower airways where it is not easy to quantify in older people; or that the immune response to infection in older people is a greater determinant of severity and symptoms.<sup>18</sup> This difference in manifestation across age groups may result from lower expression of the SARS-CoV-2 cell entry receptor, ACE-2\*, in younger people.<sup>17</sup> Respiratory epithelial cells are considered to be the main cell type infected by SARS-CoV-2 and the inherent antiviral responses of these cells alter with age.<sup>16</sup> Senescence of respiratory epithelial cells in older age may support viral infection and contribute to local tissue inflammation but is a relatively understudied area.

## Macrophages\*

Macrophages\* are an important immune cell type involved in the protection of tissues. In COVID-19, blood monocytes\* are activated and have an atypical morphology, indicating that this cell type may contribute to antiviral defence, as well as tissue injury.<sup>19,20</sup> Macrophages\* are implicated in many of the co-morbidities associated with more severe COVID-19 infection, including diseases such as diabetes and cardiovascular disease, but whether this is a consequence of an age-related change in their biology is not well defined. Macrophages are highly responsive to their extracellular environment, which is affected to various degrees by the ageing process. Inflammatory monocytes\*/macrophages\* are recruited to the sites of even mild tissue damage in healthy older adults and these cells can inhibit virus-specific immunity.<sup>21</sup> These cells may also contribute to the rise in basal levels of inflammation with age, predisposing older SARS-CoV-2-infected patients to dysregulated production of mediators of the life-threatening inflammatory response.<sup>22</sup>

## Neutrophils\*

It is known that neutrophils\* of older people with respiratory diseases are not as effective at making their way to sites of injury in a direct and timely fashion.<sup>23</sup> We do not know whether this functional difference also exists in COVID-19 but, given the substantial increase of neutrophils\* in the blood during a COVID-19 response,<sup>24</sup> this would be an important point to consider.

## T cells\*

We know that T cells\* are critical components of the adaptive immune system required to attack infected cells and to help other cells mount an effective immune response. They are reduced in the blood of infected individuals, although we do not know whether this is due to a loss of cells or represents a relocation into tissues. T cells\* may be involved in inducing some of the pathology in the disease.<sup>25</sup> Old (end-stage) T cells\* accumulate during ageing and have altered function. They have also been shown to be increased during SARS-Cov-2 infection<sup>26, 27</sup> and therefore the increase of old T cells\* with altered functional activity coupled with excessive inflammation may be detrimental for the outcome of SARS-CoV-2 infection.

## B cells\* and antibodies\*

The most effective, and longest lived, antibodies\* are made by B cells\* that have been through a process of affinity maturation in specialised structures called germinal centres. This process also selects the cells making antibodies\* that have been through 'quality control' to make sure they do not accidentally bind to any self-molecules (i.e. become autoreactive). In older age these selective processes are reduced and there is more evidence of autoreactive antibodies\*.<sup>28</sup> In COVID-19 there is a rapid expansion of the types of B cells\* that secrete antibodies\* – plasma cells – and the levels of antibody\* correlate with levels of disease severity.<sup>29</sup> Questions therefore arise as to the protective versus pathological nature of these antibodies\* and whether this is related to age-related changes in antibody\* quality, especially considering the reported lack of germinal centres<sup>30</sup> and increased levels of autoreactive antibodies\* in first responses to COVID-19.<sup>31, 32</sup>

## What is the effect of multimorbidity on COVID-19 risk in older people?

One factor influencing the age-related severity of COVID-19 is the higher prevalence of chronic disease in this population: by the age of 70 years, 75% of adults have two or more long-term conditions, termed multimorbidity. So, while there are indications that age on its own is the strongest risk factor for mortality,<sup>10</sup> the prevalence of morbidity in the older population will exacerbate this.

Several countries have reported increased severity of COVID-19 disease in multimorbid adults. A study of 1,590 Chinese COVID-19 patients revealed that 8.2% had two or more conditions. Moreover, risk of poor outcomes was 2.5 times higher in multimorbid patients, with chronic obstructive pulmonary disease (COPD), diabetes and hypertension giving higher risk of severe COVID-19 or death.<sup>33</sup> Analysis of UK Biobank\* participants revealed that, among those aged 65 or over, those who had been hospitalised with COVID-19 were more likely than other participants to have pre-existing dementia, COPD, depression, type 2 diabetes, chronic kidney disease and atrial fibrillation\*.<sup>34</sup> Interestingly coronary artery disease prevalence was similar in COVID-19 patients and other biobank participants.

It is perhaps not surprising that chronic lung diseases such as COPD are a common comorbidity in hospitalised UK COVID-19 patients, with a prevalence of 17%. These patients are already known to have an increased risk of developing pneumonia and poor long-term outcomes, irrespective of exposure to SARS-CoV-2.<sup>35</sup> Similarly, patients with interstitial lung diseases such as pulmonary fibrosis\* are at increased risk of death from COVID-19.<sup>36</sup>

Frailty\* is a distinct age-related condition that can co-exist with multimorbidity but there are also older adults who are frail without chronic disease. The importance of frailty\* as a risk factor in COVID-19 is indicated by the use of the Clinical Frailty Scale in the UK guidelines for escalation of patients to critical care.<sup>37</sup> However, studies to date on the impact of frailty\* have produced mixed findings, suggesting that frailty\* was,<sup>38</sup> and was not<sup>39</sup> associated with increased COVID-19-related mortality.

As susceptibility to COVID-19, prevalence of multimorbidity, and frailty\* all have advanced age in common, one possibility is that the severity of COVID-19 symptoms relates to the biological rather than chronological age of the individual. One recent paper used pre-COVID data from over 340,000 UK Biobank\* subjects to estimate their biological age (Pheno-Age) and has shown that those who were biologically 10–14 years older than their chronological age had a significantly higher risk of contracting the infection and higher mortality.<sup>40</sup>

# Does co-infection affect susceptibility to SARS-CoV-2 infection and COVID-19 disease in older people?

The advent of molecular diagnostics has confirmed that co-infections (i.e. being infected by more than one pathogen at the same time) are common. The consequences of such co-infections in the context of the SARS-CoV-2 pandemic are poorly understood. Co-infections may be acute, where another pathogen is encountered in the same time frame as SARS-CoV-2, or chronic where patients living with chronic infections are then infected with SARS-CoV-2.

The frequency of acute co-infections varies between studies, ranging from 3% to >20% of COVID-19 patients.<sup>41, 42</sup> The most common viral co-infections include rhinovirus, RSV, endemic coronaviruses, influenza virus, bocavirus and human metapneumovirus. All of these viruses cause greater morbidity and mortality in the elderly compared with healthy young adults. The clinical consequences of viral co-infections in COVID-19 patients remain unclear, with some studies suggesting increased morbidity and mortality, while others do not. A pre-clinical study using a mouse model demonstrated that infection with influenza virus followed by SARS-CoV-2 resulted in more severe respiratory symptoms, increased weight loss and more rapid mortality, compared with mice infected with either influenza virus or SARS-CoV-2 alone.<sup>43</sup> More research is needed to understand the consequences of acute viral co-infections on COVID-19 disease morbidity and mortality, especially in the elderly. Because of social restrictions introduced to mitigate SARS-CoV-2 circulation during the southern hemisphere 2020 winter, influenza virus and other respiratory virus circulation was much lower than previous years, thereby diminishing the capacity to study co-infections in COVID-19 patients.

Data from Brazil indicated slightly but significantly lower odds of morbidity and mortality among COVID-19 patients who received influenza vaccine.<sup>44</sup> These data suggest potential benefits of the 'flu vaccine in diminishing COVID-19 disease severity', although the mechanisms of action remain to be explained.

Common acute bacterial co-infections in COVID-19 patients include *Mycoplasma pneumoniae*, *Pseudomonas aeruginosa* and *Haemophilus influenzae*.<sup>45</sup> There is some evidence of increased mortality in COVID-19 patients with bacterial co-infections. Further data are needed to confirm these observations. Interestingly, in some studies >90% of COVID-19 patients received antibiotics, whether or not they had confirmed bacterial co-infections. This raises concerns about the propensity of the pandemic to accentuate the development of antimicrobial resistance.

Fungal co-infections have been reported more rarely in COVID-19 patients, with *Candida albicans* and *Aspergillus spp* being the most frequent.<sup>45</sup> Further investigation of fungal co-infections in COVID-19 patients is needed.

The consequences of chronic infections in COVID-19 patients also remain poorly understood. Reports of CMV\*/SARS-CoV-2 co-infection are rare. However, CMV\* has the unusual property of skewing the cellular immune system to a more mature state, essentially prematurely ageing the immune system and altering the response to vaccination and infection. The prevalence of CMV\* infection increases with age such that approximately 85% of elderly UK residents are CMV\* infected.<sup>46</sup> Given its high prevalence in the elderly, CMV\* infection is a major cause of immune ageing but its impact on COVID-19 disease is currently unknown.

It has been suggested that the immune system of patients with HIV is prematurely aged;<sup>47</sup> in this context it is interesting to note that the median age of HIV+ COVID-19 patients was 55 years, compared with 74 years for non-HIV patients in a large UK study.<sup>48</sup> There is no evidence that antiretroviral drugs used for treatment of HIV protect against SARS-CoV-2 infection.

HBV or HCV patients do not appear to be at higher risk of severe COVID-19 unless they also have advanced liver cirrhosis. However, those with severe cirrhosis, including when caused by HBV or HCV infection, were almost 30 times more likely to die from COVID-19 than people with chronic liver disease without cirrhosis.<sup>49</sup>

# Age and development of protective immunity against SARS-CoV-2

There is an incomplete understanding of what constitutes a good measure of immune protection against SARS-CoV-2 at any age. Neutralising antibodies\* do appear to correlate with protection in animal studies, but the assays to measure this are complex, not standardised and not suited to mass testing. Memory T cells with specificity for SARS-CoV-2 have been found in convalescent patients and, while the methodology is not currently tractable for testing at scale, they are a good candidate for a measure that would correlate with protective immunity. In time we may be able to identify tractable correlates of protection with more certainty and will be able to carry out follow-up studies to determine the lifespan of immunity.

In the meantime, we can look to prior knowledge on other infections and vaccine studies for information on the effects of age. It is well accepted that a vaccine designed for healthy young adults may not perform as well in an older person and this holds true for many vaccines. This could indicate that raising robust immunity in older individuals is more difficult. Some studies indicate that the dynamics of an immune response are different in older versus younger people. For example, it has been shown that for hepatitis A<sup>50</sup> and for pneumococcal vaccine responses<sup>51</sup> older people can mount an effective high-affinity antibody\* response equivalent to that of younger people, but it requires a longer time frame. So, some of the observed differences in levels of immunity might be due to the timings of immunological measurements rather than to any meaningful difference in functional immunity. In a situation of natural infection, a delayed response would be critical, but if older people could make effective immune memory given a little more time there is hope that vaccinations would be effective. Nevertheless, we need to consider the fact that older people may not make as good a memory response in the first instance. It has been shown, for example, that the antibodies\* made in large quantities in the early stages of severe COVID-19 are likely from a pathway that does not provide long-lasting high-affinity antibody production.<sup>27</sup>

There is little evidence to suggest that immune memory after infection or vaccination does not last as long in older people, although since the quality of immune memory raised is often poor in the first place, recalling an effective response later is less likely. There is a functional difference in T cell\* immunity between old and young.<sup>52</sup> Similarly, there is evidence to suggest that memory B cells\* persist in older people, but their ability to develop into antibody\*-secreting cells upon re-challenge is compromised.<sup>53</sup>

## Treatments and prophylaxis

### Vaccines

The ability to respond to infections declines in ageing populations. This is primarily due to a decline in the body's ability to mount effective immune responses. This provides challenges for vaccination where the decline in immunity in older adults can lead to a reduced response to vaccination.<sup>54</sup>

Vaccinations are generally given to older people in order to boost pre-existing immune responses to common endemic pathogens and thus restore immunity that has waned over time; several vaccines have been developed specifically to protect older populations against these infections. For example, the shingles (varicella zoster virus; VZV) vaccine, Shingrix®, uses a novel subunit glycoprotein E antigen\* administered with a potent adjuvant\* to overcome age-related reduction in vaccination responses. This has much improved vaccine efficacy in older individuals compared with Zostavax®, which uses a live attenuated strain of VZV. Similarly, influenza vaccines use an increased antigen\* dose or the addition of a powerful adjuvant\* to increase immunogenicity in older people.<sup>55</sup>

More problematic, potentially, is the reduced ability of older individuals to make an entirely new immune response to an infection that they have not encountered before. This occurs because immune cells that are needed to initiate an entirely new immune response, termed naïve T cells\*, decline with age due to the shrinking of the thymus which produces them. For instance, studies with a live, attenuated yellow fever virus vaccine, one of the most effective vaccines currently available, demonstrated that older individuals have slower generation of antibodies\* and lower virus neutralising capacity as compared with young adults.<sup>4</sup> Given that SARS-CoV-2 is a new infection, older people will not have encountered it before, potentially making vaccination even more challenging. However, applying existing vaccination strategies for the older population to COVID-19 vaccines may ensure acceptable vaccine efficacy for the population at highest risk of disease. Design of these vaccines should take into consideration the features of the ageing immune system.<sup>56</sup>

To date there are limited data on how the COVID-19 vaccines will perform in older populations. Moderna have expanded their Phase 1 trial to include 40 older adults with ages 56 to 70 years or  $\geq 71$  years. Although the sample sizes and duration of follow-up were limited, their data suggest that a second dose of vaccine will be needed to achieve neutralising antibodies\* in those aged 56 and older.<sup>57</sup> In addition, Sinovac Biotech, following their Phase I/II clinical trials of the inactivated COVID-19 vaccine candidate has an ongoing study to assess their CoronaVac vaccine in healthy adults aged 60 years and above.<sup>58</sup> Similarly, assessment of the AstraZeneca/University of Oxford ChAdOx1 nCoV-19 vaccine is currently being undertaken in older individuals in the UK (ClinicalTrials.gov Identifier: NCT04400838), but there have been no results published from older age groups to date. However, RNA vaccines developed in Germany by BioNTech and Pfizer have demonstrated lower neutralising antibody\* titres in older adults compared with younger adults in a Phase 1 trial.<sup>59</sup>

In summary, there are multiple aspects of COVID-19 vaccine development for older adults that will require attention. These may include different routes of immunisation, different vaccine formulations, additional vaccine doses for initial vaccination and/or more frequent boosting after initial vaccination. Further clinical development and optimised vaccination protocols for older adults will be essential for the toolbox of COVID-19 vaccines soon to be licensed.

## Therapeutics

Given the concerns over the ability of older people to develop effective immunity through vaccination, discovery of therapeutics to treat COVID-19 remains an important goal.

Many clinical trials are evaluating drugs that may provide benefit either through antiviral actions (e.g. Remdesivir, Favipiravir), through modulation of the immune response (e.g. dexamethasone, Tocilizumab REGN-COV2) or through other mechanisms (e.g. aspirin, statins).<sup>60</sup>

Following preliminary results of the RECOVERY trial, and several other trials worldwide, dexamethasone has been widely instituted as treatment for patients with features of severe COVID-19 disease.<sup>61</sup> The RECOVERY trial demonstrated a significant reduction in 28-day mortality in patients who were ventilated or receiving oxygen therapy who received dexamethasone compared with those who did not receive dexamethasone. The median age of patients in the analysis was 66.9 years, although the median age in the cohort receiving invasive mechanical ventilation (who saw the most benefit) was 59 years.<sup>59</sup>

Remdesivir is the first antiviral drug to be used in the UK outside of a clinical trial for COVID-19, following a positive Scientific Opinion from the Medicines and Healthcare Products Regulatory Agency (MHRA) in May 2020.<sup>62</sup> However, data from the WHO-led open-label randomised SOLIDARITY trial suggests that Remdesivir has no benefit on mortality, or on the initiation of ventilation or length of hospital stay.<sup>63</sup>

Trials looking at the repurposing of existing drugs and treatments for therapeutic options in COVID-19 in older adults include the PRINCIPLE trial led by the University of Oxford, which aims at treatment of milder forms of infection in a primary care setting.<sup>64</sup>

# Recommendations

**1 Studies on the symptoms and clinical progression of COVID-19 infection should include non-hospitalised individuals and be large enough to determine ages at which critical changes occur.** Studies should identify correlates that affect initial infection, progression to severe disease, recovery and re-infection. This information is essential to determine which age groups need which interventions, enabling targeting of interventions to specific groups. For example, at what age – and with which additional risk factors – is shielding required? What role do antivirals and anti-inflammatory drugs have at different ages?

**2 Identification of the extent of the immune system contribution to the symptoms and pathology** of the disease is required in order to identify areas for possible intervention without compromising anti-infection activity.

**3 We urgently need to establish reliable and tractable methods to measure immune responses in patients** following infection or vaccination with a specific focus on different age groups. We must include measures of cellular immunity as well as humoral immunity\*. More studies are needed in the community setting to capture different degrees of disease severity, to identify what 'good' looks like in an asymptomatic immune response. Studies should extend into the convalescent period and beyond to establish factors that affect the duration of effective immunity.

**4 Studies are needed to determine the effect of other challenges to the immune system during COVID-19 infection.** This includes studies of co-infection, in particular because older people often live with, for example, bacterial urinary tract infections or CMV\* infections. Similarly, the consequences of acute co-infections with other respiratory viruses, such as influenza virus and RSV, on COVID-19 disease severity needs to be examined. Finally, the effect of vaccination against other pathogens, such as influenza, pneumococcal disease or TB, on the response to SARS-CoV-2 requires clarification.

**5 Vaccine protocols need to be optimised for older adults** by investigating dose, formulation, boosting and vaccination routes. Different groups of people, by age or by comorbidity, may require different types of vaccine or vaccine formulations.

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## Annex 2: Glossary

**ACE-2** – angiotensin-converting enzyme 2. The receptor for this has been identified as what the SARS-CoV-1 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.

**Adjuvant** – an agent that boosts the immune response to a vaccine.

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

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

**Atrial fibrillation** – an irregular and often rapid heart rate when the two upper chambers of the heart (atria) experience chaotic electrical signals.

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

**CMV** – human cytomegalovirus is a virus causing lifelong infection in humans, with a prevalence of 55–100% depending on different socioeconomic and geographic factors. Infection is mostly asymptomatic in healthy hosts but can cause severe and sometimes fatal disease in immunocompromised individuals.

**Epithelium** – a thin, continuous, protective layer of cells often lining the outer surfaces of blood vessels and organs.

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

**Frailty** – a measure of a person's physical resilience and indicated by unintentional weight loss, lack of physical activity, exhaustion, weakness, and/or a slow walking speed.

**Humoral immunity** – immunity that is mediated by macromolecules in extracellular fluid such as antibodies.

**Inflammaging** – a chronic low grade inflammation that develops with advancing age, thought to accelerate the process of biological ageing.

**Immune senescence** – the decline in immune function with increasing age.

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

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

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

**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.

**UK Biobank** – a large long-term biobank study in the United Kingdom begun in 2006 which is investigating the respective contributions of genetic predisposition and environmental exposure to the development of disease.

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