Why Does the Severity of COVID-19 Differ With Age? 
Understanding the Mechanisms Underlying the Age Gradient in Outcome Following SARS-CoV-2 Infection

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Although there are many hypotheses for the age-related difference in the severity of COVID-19, differences in innate, adaptive and heterologous immunity, together with differences in endothelial and clotting function, are the most likely mechanisms underlying the marked age gradient. Children have a faster and stronger innate immune response to SARS-CoV-2, especially in the nasal mucosa, which rapidly controls the virus. In contrast, adults can have an overactive, dysregulated and less effective innate response that leads to uncontrolled pro-inflammatory cytokine production and tissue injury. More recent exposure to other viruses and routine vaccines in children might be associated with protective cross-reactive antibodies and T cells against SARS-CoV-2.

There is less evidence to support other mechanisms that have been proposed to explain the age-related difference in outcome following SARS-CoV-2 infection, including pre-existing immunity from exposure to common circulating coronaviruses, differences in the distribution and expression of the entry receptors ACE2 and TMPRSS2, and difference in viral load.

Key Words: 2019 novel coronavirus, ACE2, antibodies, coagulation, endothelium, heterologous, immune system, outcome, pre-existing immunity, severity

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Compared with adults, and in contrast to other respiratory viruses, children infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), generally are asymptomatic or have mild disease with a significantly lower hospitalization rate and mortality.1,2

We have previously reviewed hypotheses for the age-related difference in the severity of coronavirus disease 2019 (COVID-19), separating them into factors that put adults at higher risk and those that protect children.4 Since then, more evidence has become available to support some of the hypotheses and make others less likely.

Here, we provide an updated review of the mechanisms that might explain the marked age gradient in the severity of COVID-19 (Table 1 and Figure 1).

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MECHANISMS WHICH ARE MORE LIKELY TO CONTRIBUTE TO THE AGE-RELATED DIFFERENCE IN SEVERITY OF COVID-19

Differences in Innate Immunity
Mucosal Innate Immunity

The control of SARS-CoV-2 requires an optimal early innate immune response. Children have a more robust innate immune response in their nasal mucosa when infected with SARS-CoV-2.9 Melanoma differentiation-associated protein 5 (MDA5) has been identified as the major pattern recognition receptor for SARS-CoV-2 on epithelial cells.10,11 Retinoic acid-inducible gene (RIG)-I plays an additional minor role.10,12 Children have a stronger innate immune response to SARS-CoV-2 by way of a higher basal expression of MDA5 and RIG-I on nasal epithelial cells, macrophages and dendritic cells.9 The activation of MDA5 and RIG-I leads to the activation of interferon regulatory factor (IRF) 3 which subsequently results in production of interferon (IFN)-alpha.13 Although the expression of these pattern recognition receptors is similar in children and adults after five days of infection, an early response is necessary to quickly control SARS-CoV-2.

Interferon (IFN)-alpha and -gamma are important components of the early innate immune response against SARS-CoV-2.14,15 Children infected with SARS-CoV-2 have a higher expression of genes associated with IFN and NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome signaling in their nasal epithelial cells, particularly in ciliated cells.9,16 The expression of these genes is associated with strong antiviral activity against SARS-CoV-2.17,18 It has been hypothesized that, in contrast to infections with other respiratory viruses such as respiratory syncytial virus or influenza, there is a narrow window of opportunity for cells to express IFNs before SARS-CoV-2 shuts off the antiviral system.9,15,19,20

Compared with adults, healthy children also have much higher numbers of immune cells in their upper respiratory tract, especially cells of the innate immune system, such as neutrophils and natural killer cells.21,22 In adults, infection with SARS-CoV-2 leads to a large influx of immune cells to the upper respiratory tract that is not observed in children.9 However, SARS-CoV-2-infected children have a more pronounced activation of CCL3 and C-X-C chemokine receptor (CXCR) 1/2 expression in neutrophils in the upper respiratory tract.9 Furthermore, children have higher levels of certain cytokines and chemokines (specifically, IFN-alpha 2, IFN-gamma, C-X-C motif chemokine ligand 10 (CXCL10), interleukin (IL)-1beta, IL-8 and IL-17) in their nasal fluid.16,24

Systemic Innate Immunity

In comparison to children with other common respiratory viral infections, those with COVID-19 have a greater change in innate and T cell-mediated immune responses over time.25 Children with SARS-CoV-2 infection show a marked reduction in myeloid cells.26 They have low levels of dendritic cells, natural killer cells and classical (CD14+CD16-) intermediate (CD14+CD16+) and non-classical (CD14+CD16+) monocytes in blood.26 Adults with COVID-19, especially severe COVID-19, also have low levels of dendritic and
TABLE 1. Summary of Mechanisms Proposed to Contribute to the Age-Related Difference in the Severity of COVID-19

| Mechanisms with the strongest supporting evidence to date | Differences in innate immunity | Differences in adaptive immunity | 3. Heterologous immunity and off-target effects of vaccines | Differences in the endothelium and clotting function | Mechanisms with less supporting evidence to date |
|----------------------------------------------------------|--------------------------------|--------------------------------|-------------------------------------------------------|-------------------------------------------------|-----------------------------------------------|
| In response to SARS-CoV-2, children have: | • a stronger mucosal innate immune response, which helps clear the virus\(^a,4,25,20,24\) | • higher lymphocyte counts with a higher proportion of naïve T cells, T regulatory cells and T follicular helper cells\(^{30,32}\) | • more recently been vaccinated with BCG, MMR, Tdap and other vaccines which might offer indirect protection against COVID-19\(^{4,38,70,75,76,86,97}\) | • less prone to endothelial damage and abnormal clotting\(^{128}\) | 1. Pre-existing immunity from exposure to commonly circulating human coronaviruses |
| • lower levels of neutrophils, which have been associated with microangiopathy and thrombosis\(^{27,29}\) | • differences in cytokines levels with a lower tendency to develop a cytokine storm\(^{26,29,32,35}\) | • frequent recurrent or concurrent infections which might induce an enhanced state of activation of the immune system\(^{101}\) | 2. ACE2 and TMPRSS2 | 2. ACE2 and TMPRSS2 |
| • differences in cytokines levels with a lower tendency to develop a cytokine storm\(^{26,29,32,35}\) | 3. A stronger mucosal innate immune response, which helps clear the virus\(^a,4,25,20,24\) | • higher lymphocyte counts with a higher proportion of naïve T cells, T regulatory cells and T follicular helper cells\(^{30,32}\) | • higher lymphocyte counts with a higher proportion of naïve T cells, T regulatory cells and T follicular helper cells\(^{30,32}\) | • differences in cytokines levels with a lower tendency to develop a cytokine storm\(^{26,29,32,35}\) |

**Mechanisms with the weakest supporting evidence to date**

1. **Pre-existing immunity from exposure to commonly circulating human coronaviruses**
   - Although antibodies against HCoVs can be cross-reactive, they might not be cross-neutralizing\(^{20,25,49,58,115–118}\)
   - Role of cross-reactive T cells in relation to SARS-CoV-2 also remains unclear\(^{21,122,126}\)
   - There is conflicting evidence on whether children or adults have higher levels of antibodies and T cells cross-reactive between HCoVs and SARS-CoV-2\(^{25,118,129–130}\)

2. **ACE2 and TMPRSS2**
   - There is conflicting evidence on whether children have lower numbers and different distribution of ACE2 and TMPRSS2 across body sites\(^{2,9,23,24,57,49,106–108}\)
   - ACE2-angiotensin system is affected by many factors other than age\(^{16,40,137,160,166–170}\)
   - ACE2-angiotensin system is complex and also involved in regulating immune responses\(^{171}\)

3. **Viral load**
   - Children and adults have similar viral loads and shedding from the respiratory tract\(^{24,20,101}\)
   - Children and adults have similar viral loads and shedding from the respiratory tract\(^{24,20,101}\)

**Differences in Adaptive Immunity**

**Mucosal Adaptive Immunity**

SARS-CoV-2-specific immunoglobulin (Ig) A and IgG levels in nasal fluid have mostly been reported to be similar in children and adults.\(^{16}\) However, one study in adults reported that specific IgA levels in nasal fluid were inversely correlated with age.\(^{4,38}\) A small study showed that children can have IgA in their saliva without having had a positive respiratory SARS-CoV-2 polymerase chain reaction, which raises the possibility that a local immune response might prevent the establishment of an infection.\(^{45}\) One hypothesis for this is that individuals might be protected from SARS-CoV-2 due to pre-existing immunity to commonly circulating human coronaviruses (HCoVs).\(^{46}\) Adding to the evidence that mucosal immunity is important for controlling SARS-CoV-2 are the results from a study showing that adults who remain seronegative after mild COVID-19 have IgA antibodies with neutralizing activity in nasal fluid and saliva.\(^{44}\)

**Systemic Adaptive Immunity**

In relation to adaptive immunity, rapid and coordinated appearance of SARS-CoV-2-specific CD4+ and CD8+ T cells in blood is associated with faster clearance of SARS-CoV-2 and milder COVID-19.\(^{4,38}\) Children with COVID-19 have higher lymphocyte counts, with a higher proportion of innate lymphoid and non-clonally expanded naïve T cells in the blood.\(^{5,49}\) Children also have higher numbers of T follicular helper cells, which are important for an early antibody response.\(^{5,49}\) Furthermore, they have lower T cell responses to S and ORF1 proteins and reduced CD4+ T cell effector memory.\(^{46,35,49,50}\) Results of T cell responses against N and spike proteins are conflicting with some studies showing lower levels in children\(^{36}\) and others higher levels.\(^{16,35,49}\)

Adults infected with SARS-CoV-2 typically have a decreased lymphocyte count, with reduced numbers of naïve CD4+ and CD8+, T regulatory and memory T cells.\(^{31–35}\) One study reported that acute and memory SARS-CoV-2-specific CD4+ cells increase with age.\(^{40}\) T cell exhaustion with impaired effector activity has been observed in adults with severe COVID-19.\(^{24,34}\) Poor and uncoordinated T cell responses, in addition to a scarcity of naïve T cells have been found in elderly adults and are associated with poor outcomes from COVID-19.\(^{24,54,55}\)

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\(^{a}\) ACE2, angiotensin-converting enzyme 2; BCG, Bacillus Calmette-Guerin; COVID-19, coronavirus disease 2019; HCoVs, human coronaviruses; MMR, measles-mumps-rubella; ORF, open reading frame; SARS-CoV-2, severe acute respiratory tract coronavirus 2; Tdap, tetanus-diphtheria-pertussis; TMPRSS2, transmembrane serine protease 2.
In children, during COVID-19, genes associated with B cell activation are expressed earlier. In relation to differences in levels of SARS-CoV-2-specific antibodies between children and adults, the evidence is conflicting. An early increase of IgA, IgM and, to a lesser extent IgG, is associated with asymptomatic and mild SARS-CoV-2 infection. An early rise in antibodies is observed in children. One study reported that infants have lower serum SARS-CoV-2-specific IgG levels compared with older children, another that children have lower serum SARS-CoV-2 neutralizing antibody levels compared with adults and one that adults with severe COVID-19 have higher levels of specific IgA antibodies. Another study reported children were less likely than adults to seroconvert to SARS-CoV-2. However, there are also studies which report higher levels of specific IgG in children compared with adults. 

**Figure 1.** Mechanisms proposed to contribute to the age-related difference in the severity of COVID-19.

**Heterologous Immunity and Off-Target Effects of Vaccines**

Heterologous immunity describes immune responses generated by an antigen providing immunity against other (unrelated) pathogens. This includes innate and adaptive immune responses and can result from natural infection or vaccination. COVID-19 severity is reported to be lower in individuals who have been vaccinated with measles-mumps-rubella (MMR) or tetanus-diphtheria-pertussis (Tdap) vaccine. As children have generally been more recently vaccinated with these vaccines, this might contribute to the age-related difference in COVID-19 severity.

MMR vaccines contain attenuated enveloped ribonucleic acid (RNA) viruses that have glycoprotein spikes, similar to SARS-CoV-2 and also share other sequence homologies. Cross-reactive epitopes have also been found between antigens included in Tdap and SARS-CoV-2. It has therefore been hypothesized that MMR and Tdap vaccination might lead to cross-protective antibodies and T cells that protect against COVID-19. In one small prospective study, MMR-vaccinated participants who later developed COVID-19, all had a mild course. Another, much larger case-control study, showed that MMR vaccination might have a protective effect against COVID-19 in males but not females. A case-control study in children also showed that children vaccinated with a measles-containing vaccine had lower infection rates with SARS-CoV-2 and, if infected, had milder symptoms. Another study found that the outcome of COVID-19 inversely correlated with levels of rubella-specific antibodies and another with levels of mumps-specific antibodies. An interim analysis of an ongoing randomized control trial (RCT) of MMR to reduce SARS-CoV-2 infection and severity in health care workers reported that MMR reduces the risk of symptomatic infection.

A second RCT to investigate the influence of MMR on the severity of COVID-19 is also ongoing. In individuals after SARS-CoV-2 infection or after COVID-19 vaccination, enhanced in vitro T cell responses to components of the MMR and Tdap vaccine have been found. Identical
T cell receptor clonotypes can be found on T cells activated by SARS-CoV-2, Tdap or MMR antigens, consistent with heterologous immunity. Another study reports that antibodies induced by inactivated poliovirus vaccination bind the RNA-dependent RNA polymerase of SARS-CoV-2 and inhibit infection of Vero cells in vitro.

Another vaccine proposed to provide beneficial effects against COVID-19 is Bacillus Calmette-Guérin (BCG). Ecologic studies claim to identify an association between countries’ BCG vaccination policy and their COVID-19 rates and severity. But such studies are subject to confounding by timing of the study in relation to the epidemic in each country, lockdown and other mitigation measures, testing and reporting rates, and are also limited by inaccurate BCG vaccination status reporting. Furthermore, it is unlikely that the beneficial effects of BCG vaccination last for many years as they are likely abrogated by the impact of intervening vaccines and other factors that also modulate the immune system. Consistent with this, some ecologic studies and retrospective case-control studies have not found any protection against COVID-19 from BCG given many decades earlier. One RCT in the elderly reported that BCG reduced the incidence and severity of COVID-19. Larger RCTs of BCG to reduce the severity of COVID-19 are ongoing.

Children infected with SARS-CoV-2 often have co-infections with other viruses (including commonly circulating HCoVs). Frequent recurrent or concurrent infections could induce an enhanced state of activation of the immune system, including epigenetic changes inducing trained immunity, making it more effective in clearing SARS-CoV-2.

**Differences in the Endothelium and Clotting Function**

Widespread endothelial injury and coagulation activation by SARS-CoV-2 is a key feature of severe COVID-19. This is associated with thromboembolisms, such as deep vein thrombosis and pulmonary emboli, as well as arterial thrombosis or microvascular thrombosis. When SARS-CoV-2 binds to the ACE2 receptor, the expression of the receptor is downregulated, resulting in increased levels of angiotensin II, which is associated with inflammation, endothelial dysfunction and a procoagulant state. Endothelial damage leads to the release of plasminogen activator inhibitor 1 and to the activation of tissue factor, which leads to further inflammation and induction of the thrombotic cascade. This increases endothelial damage and platelet activation. Platelets express both ACE2 and TMPRSS2 and can therefore be directly activated by SARS-CoV-2.

The endothelium in children is less “pre-damaged” compared with adults and the coagulation system also differs, which makes children less prone to abnormal clotting. In adults with COVID-19, the overall rate of venous thrombosis is approximately 14 to 20%, and of arterial thrombosis 2%. Higher rates are observed in adults admitted to intensive care. Thrombotic coagulopathy has been observed in SARS-CoV-2-infected children of all age groups, often occurring during hospitalization and despite thromboprophylaxis, and is associated with a high mortality of up to 28%. Although the incidence is less well described in children, it is much lower than in adults. One study reports rates of 2% in children with COVID-19 and 7% in children with PIMS-TS. Children above the age of 12 years, those with cancer or a central venous catheter are at higher risk for thromboembolic events. Of note, however, thromboembolic events have also been observed in children with asymptomatic SARS-CoV-2 infections.

**MECHANISMS WHICH ARE LESS LIKELY TO CONTRIBUTE TO THE AGE-RELATED DIFFERENCES IN SEVERITY OF COVID-19**

**Pre-existing Immunity from Commonly Circulating Human Coronaviruses**

Commonly circulating human coronaviruses (HCoV-229E, -HKU1, -NL63 and -OC43) are responsible for approximately 6 to 8% of acute respiratory tract infections and most individuals develop immunity to HCoVs during childhood. Individuals who have not been infected with SARS-CoV-2 can therefore have cross-reactive, neutralizing and non-neutralizing antibodies, and T cells against the S protein (up to 5%), N protein (up to 24%) and ORF regions of SARS-CoV-2. Seroprevalence depends on geographical location.

Despite seroconversion at an early age, re-infections with HCoVs later in life are common. There is conflicting evidence on whether children or adults have higher levels of cross-reactive antibodies and T cells. Some studies report that levels of neutralizing and non-neutralizing cross-reactive antibodies, as well as cross-reactive T cells, increase with age, while other studies report higher levels of these antibodies in SARS-CoV-2-uninfected children and adolescents or no differences between age groups. One study found higher cross-reactive IgA and IgG levels in healthy elderly adults and higher IgM levels in healthy children, suggesting that children have a less-experienced but more polyreactive humoral immunity.

Delayed production of neutralizing antibodies during a SARS-CoV-2 infection is associated with increased mortality. Antibodies against commonly circulating HCoVs are boosted during a SARS-CoV-2 infection. Importantly, however, although antibodies against HCoVs can be cross-reactive, they do not necessarily protect against SARS-CoV-2, as they are not necessarily cross-neutralizing. One study, however, reported that a recent documented history of a common cold caused by HCoV is associated with lower rate of admission to intensive care unit and lower mortality from COVID-19. Another study showed a correlation between pre-existing antibodies against HCoV-OC43 and COVID-19 severity, but not between antibodies against HCoV-NL63, -229E and -HKU1, indicating that cross-protection might differ between different HCoVs and SARS-CoV-2. Consistent with this, one study found higher antibody levels against HCoV-229E but not -OC43, and higher levels of cross-reactive antibodies in children compared with adults. SARS-CoV-2 and HCoV-NL63 both use ACE2 as an entry receptor. However, sequencing data shows SARS-CoV-2 is more closely related to HCoV-OC43 and -HKU1 than -NL63 and -229E. There is a region coding for 11 amino acids that is highly conserved between SARS-CoV-2 and all four HCoVs, which overlaps with the S2 fusion peptide in SARS-CoV-2. It has been suggested that cross-reactive antibodies against S2 might provide neutralizing activity and protection against SARS-CoV-2. One study reported that pre-existing S2-specific antibodies against HCoV-OC43 are associated with mild COVID-19. These antibodies are more frequently present in children and adolescents. Another study found cross-reactive antibodies against SARS-CoV-2 ORF-1 in pre-pandemic samples, but not against protein S or N. The presence of these antibodies was associated with milder COVID-19. As discussed above, higher antibody levels against ORF (IFN antagonists) are found in children with COVID-19 compared with adults. This could indicate that antibodies against ORF play a role in controlling SARS-CoV-2.
COVID-19 through antibody-dependent enhancement (ADE). In ADE, pre-existing non-neutralizing antibodies can bind to virions, which can then more easily enter and replicate in macrophages and granulocytic cells, leading to higher viral loads. To date, there is scant evidence for ADE in COVID-19.

T cells that are cross-reactive between commonly circulating HCoVs and SARS-CoV-2 have been identified in a number of studies. In one study more than half of participants with no known exposure to SARS-CoV-2 had T cell activity against SARS-CoV-2. There is a correlation between levels of specific IgA and IgG and specific T cell responses. Few studies have compared T cell immunity against HCoVs in different age groups, but one study reported lower levels of T cells against HCoVs in older adults. However, as with cross-reactive antibodies, the role of cross-reactive T cells in relation to SARS-CoV-2 remains unclear.

It has been postulated that different distribution of ACE2 and TMPRSS2 across body sites between children and adults, as well as lower affinity of ACE2 for SARS-CoV-2 in children, contribute to the age-related differences in the severity of COVID-19. However, the many studies on this topic report conflicting results. Some studies report lower expression of ACE2 and TMPRSS2 in the nasal epithelium in children compared with adults, but others did not find age-related differences. One study reported that the expression of neuropilin-1 (NRP1), a protein that promotes virus interaction with ACE2, is lower in the nasal epithelium of children. A study in adults showed that ACE2 and TMPRSS2 in the oral mucosa are higher in elderly compared with young adults. Conflicting results have also been reported for the expression of ACE2 and TMPRSS2 in lungs. Some studies report that the expression of ACE2 and TMPRSS2 in lungs increases with age, while others report a higher expression of ACE2 in lungs in children compared with elderly adults or no difference between the age groups.

Intestinal expression of TMPRSS2 and NRP1 has been reported to be similar between children and adults, while intestinal ACE2 expression might be higher in children, which might explain the higher frequency of gastrointestinal symptoms in this age group.

The conflicting results on the expression of ACE2 and TMPRSS2 reflect the fact that the ACE2-angiotensin system is complex. Apart from age, the ACE2-angiotensin system is affected by many other factors, including genetics, sex, smoking, diet, vitamin D, body-mass index, drugs and comorbidities including diabetes mellitus, chronic obstructive pulmonary disease and hypertension. ACE2 is not only an entry receptor for SARS-CoV-2 but also plays an important role in regulating immune responses, especially in the lungs. After SARS-CoV-2 enters cells, ACE2 receptors are down-regulated, which prevents them from converting angiotensin II to angiotensin (1–7). The consequent excess of angiotensin II might be partly responsible for the organ injury in COVID-19, as serum levels of angiotensin II are significantly elevated in SARS-CoV-2-infected patients and there is a positive correlation with viral load and lung damage.

Viral Load

There is little evidence to support the hypothesis that viral load is responsible for age-related differences in COVID-19 severity. Viral load in the respiratory tract has been associated with transmission risk, disease severity and mortality of COVID-19. Children and adults are mostly reported to have similar viral loads and shedding from the respiratory tract. However, one study found significantly greater viral loads in nasopharyngeal samples from children less than 5 years of age compared with older children or adults, and there are also studies which report lower viral loads in children compared with adults. An increased viral load in blood has also been associated with increased disease severity and increased cytokine storm.

CONCLUSIONS

There are many hypotheses for the age-related difference in the severity of COVID-19, and it is likely that the explanation for the marked age gradient is multifactorial. The proposed mechanisms that relate specifically to the pathogenesis of SARS-CoV-2 seem more likely to be important than those that would also apply to other viral infections for which a similar age gradient is not seen. The latter include, for example, differences in vitamin D and melatonin levels, and chronic cytomegalovirus infection.

Differences in innate, adaptive and heterologous immunity, as well as differences in the endothelial and clotting function, are the most likely mechanisms to explain the observed age gradient in COVID-19. Children have a faster and stronger immune reaction to SARS-CoV-2, especially in the nasal mucosa, involving IFN signaling and the NLRP3 inflammasome, which is able to rapidly control the virus. In contrast, adults can have an overactive, dysregulated and ineffective innate response leading to uncontrolled pro-inflammatory cytokine production and tissue injury. Children also have a higher proportion of innate lymphoid and non-clonally expanded naïve T cells in the blood, while the elderly can have poor and uncoordinated T cell responses with additional scarcity of naïve T cells. More recent MMR and other vaccines might lead to protective cross-reactive antibodies and T cells against SARS-CoV-2, as well as the nasal mucosa, involving IFN signaling and the NLRP3 inflammasome, which is able to rapidly control the virus.

It is likely that the age gradient in severity of COVID-19 is multifactorial. Apart from age, the ACE2-angiotensin system is complex. Differences in innate, adaptive and heterologous immunity, as well as differences in the endothelial and clotting function, are the most likely mechanisms to explain the observed age gradient in COVID-19. Children have a faster and stronger immune reaction to SARS-CoV-2, especially in the nasal mucosa, involving IFN signaling and the NLRP3 inflammasome, which is able to rapidly control the virus. In contrast, adults can have an overactive, dysregulated and ineffective innate response leading to uncontrolled pro-inflammatory cytokine production and tissue injury. Children also have a higher proportion of innate lymphoid and non-clonally expanded naïve T cells in the blood, while the elderly can have poor and uncoordinated T cell responses with additional scarcity of naïve T cells. More recent MMR and other vaccines might lead to protective cross-reactive antibodies and T cells against SARS-CoV-2, as well as the nasal mucosa, involving IFN signaling and the NLRP3 inflammasome, which is able to rapidly control the virus.

Mechanisms which are less likely to explain the age-related differences in COVID-19 are pre-existing immunity from commonly circulating HCoVs and differences in the expression of ACE2 and TMPRSS2, although evidence can be found both for and against these hypotheses. Studies investigating antibodies and T cells against HCoVs in children and adults also report conflicting results. Furthermore, it has not been proven that cross-reactivity between HCoVs and SARS-CoV-2 leads to cross-protection. Studies which have investigated the expression of ACE2 and TMPRSS2 in children and adults also report conflicting results. Moreover, the ACE2-angiotensin system is complex and influenced by many other internal and external factors other than age. Although viral load is associated with COVID-19 severity and mortality, viral load between children and adults is similar, meaning this is also unlikely to contribute to the age-related difference in severity of COVID-19.

It is likely that the age gradient in severity of COVID-19 results from both factors that protect children and factors that make
the elderly more susceptible. It is possible that following exposure to SARS-CoV-2, immunologic factors in children are important in preventing infection or controlling the virus after infection, and age-related differences in endothelial cell clotting function are more important in putting the elderly at risk of the complications of COVID-19 that lead to higher mortality.

SARS-CoV-2 is constantly mutating with new variants becoming better at evading host defenses; understanding the mechanisms underlying the age-related difference in the severity of COVID-19 will provide key insights into its pathogenesis and opportunities for prevention and treatment.

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