Why is COVID-19 less severe in children? A review of the proposed mechanisms underlying the age-related difference in severity of SARS-CoV-2 infections

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ABSTRACT

In contrast to other respiratory viruses, children have less severe symptoms when infected with the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In this review, we discuss proposed hypotheses for the age-related difference in severity of coronavirus disease 2019 (COVID-19).

Factors proposed to explain the difference in severity of COVID-19 in children and adults include those that put adults at higher risk and those that protect children. The former include: (1) age-related increase in endothelial damage and changes in clotting function; (2) higher density, increased affinity and different distribution of angiotensin converting enzyme 2 receptors and transmembrane serine protease 2; (3) pre-existing coronavirus antibodies (including antibody-dependent enhancement) and T cells; (4) immunosenescence and inflammaging, including the effects of chronic cytomegalovirus infection; (5) a higher prevalence of comorbidities associated with severe COVID-19 and (6) lower levels of vitamin D. Factors that might protect children include: (1) differences in innate and adaptive immunity; (2) more frequent recurrent and concurrent infections; (3) pre-existing immunity to coronaviruses; (4) differences in microbiota; (5) higher levels of melatonin; (6) protective off-target effects of live vaccines and (7) lower intensity of exposure to SARS-CoV-2.

What is already known on this topic?

- Compared with older adults, severe or fatal COVID-19 disease is much less common in infants, children and young adults.
- This pattern is strikingly different to that for infection with most other respiratory viruses, for which both the prevalence and severity are higher in children.

What this study adds?

- A number of factors have been proposed to explain the difference between children and adults in the severity of COVID-19, which can be categorised into those that put adults at higher risk and those that protect children.
- Although, there are several hypotheses for the age-related difference in the severity of COVID-19, the observed age-gradient seems to most closely parallel changes in immune and endothelial/clotting function.

INTRODUCTION

The novel SARS-CoV-2, which causes the disease called COVID-19, has rapidly spread across the globe. A striking and consistent observation has been the difference in severity of COVID-19 at different ages: severity, the need for hospitalisation and mortality rise steeply with older age while severe disease and death are relatively rare in children and young adults.[1–3] Most children infected with SARS-CoV-2 are asymptomatic or have mild symptoms, most commonly fever, cough, pharyngitis, gastrointestinal symptoms and changes in sense of smell or taste.[4 5]

Whether children are also less often infected by SARS-CoV-2 is an ongoing debate. Large epidemiological studies suggest that children comprise only 1 to 2% of all SARS-CoV-2 cases.[6–8] However, these numbers heavily depend on testing criteria and, in many reports, testing was done only in individuals who were symptomatic or required hospitalisation, which is less often the case for children. Some studies suggest that children are just as likely as adults to become infected with SARS-CoV-2.[9] However, more recent studies report that children are less likely to get infected after contact with a SARS-CoV-2-positive individual.[10–14] It has been suggested that children and adolescents have similar viral loads[15 16] and may therefore be as likely to transmit SARS-CoV-2 as adults.[17 18] In addition, the viral load may be similar in asymptomatic and symptomatic individuals.[19–21] However, reassuringly, transmission in schools from children either to other children or to adults has been rare.[22–24]

The observation that children are less often infected with SARS-CoV-2 and that they have less severe symptoms is similar to that reported for SARS-CoV-1 and Middle East respiratory syndrome (MERS)-CoV.[25–27] However, this pattern is strikingly different to that for infection with most other respiratory viruses (eg, respiratory syncytial virus (RSV), metapneumovirus, parainfluenza or influenza viruses), for which the prevalence and severity are both higher in children.[28]

It remains uncertain whether the age-related difference in clinical features of COVID-19 is due to risk factors for severe COVID-19 that increase with age or due to factors that protect younger age groups. Here, we critically review proposed hypotheses for the age-related difference in severity of COVID-19 (table 1).

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Table 1 Proposed hypotheses for the age-related difference in severity of COVID-19

Hypothesis Key factors	Proposed mechanism	In support of hypothesis	Against hypothesis
(A) FACTORS INCREASING RISK IN ADULTS			
(1) Endothelium and clotting function			
Endothelial damage and hypercoagulable state	► Increased endothelial damage with age ► Susceptibility to excessive coagulation increases with age	► Importance of endotheliitis and microthrombi in pathogenesis of COVID-19[29 30] ► Association between conditions that affect the endothelium, such as diabetes and hypertension, and severe COVID-19[35–37] ► Age-related changes in coagulation consistent with age gradient of severe COVID-19[38] ► Thrombotic complications, such as heart attacks and strokes, in COVID-19[29 31–34] ► Vasculitic skin manifestations in COVID-19[39–44 53 223]	
(2) ACE2 receptors and TMPRSS2			
Viral entry	► Age-related differences in expression, affinity and distribution facilitate SARS-CoV-2 entry into cells	► Expression and affinity of ACE2 increase with age[55 57–59] ► Variants in the ACE2 gene are linked to severity of COVID-19[68] ► Pneumonia caused by CoV NL63 (that also binds to ACE2) is more common in adults compared with young children[224] ► TMPRSS2 expression on nasal and lung epithelial cells likely increases with age[58 59 71]	► ACE2 has anti-inflammatory properties that protect against ARDS, as well as SARS-CoV- and influenza-associated lung injury in animal studies[64 65] ► Less ACE2 leads to higher levels of angiotensin II which is positively correlated with viral load and organ injury in SARS-CoV-2-infected patients[67]
(3) Pre-existing immunity			
Cumulative exposure to commonly circulating HCoVs (229E, HKU1, NL63, OC43)	► Non-neutralising HCoV antibodies facilitating cell entry and viral replication (antibody-dependent enhancement)	► Reinfection with commonly circulating HCoV is frequent[76 77] ► Higher levels of neutralising and non-neutralising CoV antibodies have been found in adults, especially elderly compared with children[78 79 148] ► Cellular immunity to SARS-CoV-2 found in some non-exposed individuals[88–90] ► Higher numbers of cross-reactive T cells found in elderly[80] ► Children with COVID-19 have a less robust T cell response to spike protein (lower frequency of $CD25^+$ and IFN-γ-producing $CD4^+$ T cells), lower neutralising antibody levels and less antibody-dependent enhancement[78]	
(4) Immunosenescence and inflammaging			
Age-related changes in the immune system including chronic CMV infection	► Decline in innate and adaptive immune function in elderly leads to reduced SARS-CoV-2 clearance ► Chronic proinflammatory state associated with age predisposes to cytokine storm ► CMV's effect on T cells leading to reduced capacity for immune responses to novel viral infections such as SARS-CoV-2	► Increase in abundance and activity of NLRP3 inflammasome with age might be associated with severe COVID-19[99 100] ► Diseases associated with inflammaging (eg, cardiovascular, diabetes, obesity) are risk factors for severe COVID-19[97] ► CMV causes clonal T cell proliferation and a reduction in naïve T cell diversity[103] ► CMV increases inflammatory-mediated cytokines such as TNF-α and IL-6[106]	
(5) Comorbidities			
Obesity, diabetes, hypertension, chronic lung, heart and kidney disease, and smoking	► Likely related to endothelial damage	► Younger age groups less often suffer from the comorbidities that have been associated with severe COVID-19 in adults[36]	► Younger age groups with these conditions do not appear to develop severe COVID-19[7 107–109]
(6) Vitamin D			
Anti-inflammatory and anti-oxidative properties	► Lower vitamin D levels	► Vitamin D is reduced in older age groups, as well as in obesity and chronic kidney disease, both of which are associated with more severe COVID-19[117 118 120] ► Vitamin D levels lower in SARS-CoV-2-positive individuals and negatively correlated with severity of radiological findings[124 125] ► Infants less likely to be vitamin D deficient than older age groups, as supplemented in many countries[225]	

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Table 1 Continued

Hypothesis Key factors	Proposed mechanism	In support of hypothesis	Against hypothesis
(B) FACTORS PROTECTING CHILDREN			
(1) Immune system			
Age-related differences in immune response	► Stronger innate, trained immune response leading to more effective virus containment/clearance ► Weaker adaptive immune response and therefore less hyperinflammation ► Lower proinflammatory cytokine responses (cytokine storm)	► Children with COVID-19 have higher levels of IL-17A and IFN-γ[78] ► Some other infections are also less severe in children, for example, dengue, Epstein-Barr virus, hepatitis A, measles, Legionnaires' disease, polio, varicella	► Age-related difference in immune response does not mirror age gradient in COVID-19 in which lower severity extends into early adulthood ► Differences in the immune response do not protect against other respiratory viruses to which children are generally more commonly and more severely affected[28] ► Stronger innate immune response may be both protective but may also worsen cytokine storm[32 136 138 139] ► Children are not less prone to develop a cytokine storm leading to ARDS with RSV and influenza infections[138 140] ► Immunocompromised not at as high risk of severe COVID-19 as would expect if this were principal mechanism[226]
(2) Recurrent and concurrent infections			
Viral and mycoplasma infections	► More frequent infections with other pathogens may help fight SARS-CoV-2	► Children infected with SARS-CoV-2 often have co-infections with other viruses or mycoplasma[141 142] ► Recurrent viral infections could lead to epigenetic changes in trained immunity making it more effective in clearing SARS-CoV-2[134]	
(3) Cross-reactive coronavirus antibodies and T cells			
Exposure to commonly circulating HCoV (229E, HKU1, NL63, OC43)	► Pre-existing neutralising antibodies and T cell immunity to commonly circulating HCoV in younger age groups cross protect against SARS-CoV-2		► Antibodies to commonly circulating CoV2 are cross-reactive with SARS-CoV-2, but rarely cross-neutralising[146–148] ► No difference in antibody levels against HCoVs between children infected with SARS-CoV-2 and those who are not[150] ► Higher levels of neutralising CoV antibodies have been found in adults compared with children[78] ► Higher numbers of cross-reactive T cells found in eldery[80] ► The role of cross-reactive T cells remains unclear[88–90] ► Unlikely to explain lower severity extending into early adulthood
(4) Microbiota (nasopharyngeal, oropharyngeal, lung and/or gastrointestinal)			
Colonising microbial flora	► Differences in the microbiota might influence susceptibility to SARS-CoV-2	► Microbial interactions and competition might limit colonisation and growth of SARS-CoV-2[154 155] ► ACE2 highly expressed in the nasopharynx and gastrointestinal tract[152 153] ► Observed differences in the gastrointestinal microbiota between patients infected with SARS-CoV-2 and healthy controls[160–162] ► Administration of probiotics leads to quicker improvement of COVID-19-related symptoms[227]	
(5) Melatonin			
Anti-inflammatory and anti-oxidative properties	► Higher melatonin levels	► Children have higher levels of melatonin[190 191] ► Bats, which suffer from minimal or no symptoms of CoV infection, have higher levels of melatonin compared with humans[189] ► Melatonin inhibits calmodulin which increases ACE2 expression and retention on cell surface[180 181] ► In silico studies suggest that melatonin inhibits SARS-CoV-2's main protease[185]	

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Table 1 Continued

(6) Off-target effects of live vaccines			
Trained immunity from BCG, MCV, OPV	► More recent vaccination with live vaccines that have off-target effects	► Trials show BCG-induced protection against viral infections[194 195] ► Possible correlation between different BCG countries' vaccination policies and severity of COVID-19[200–202] ► More recent BCG, MMR and OPV vaccination in younger age groups might protect against severe COVID-19[199 208 209]	► Off-target immunomodulatory effects are unlikely to be long lasting[205 206] ► Many other explanations for differences between countries' rate and severity of COVID-19[203 205]
(7) Exposure			
Intensity of viral exposure	► Severity of COVID-19 associated with initial viral load	► Children are predominantly infected by transmission from adults[6 208 209] ► Children have less workplace, shopping, travel and nosocomial exposure to SARS-CoV-2 ► For SARS-CoV and MERS-CoV, subsequent generations of virus with reduced pathogenicity reported[217 218]	► No evidence for reduced virulence of SARS-CoV-2 in second-generation infections[219 220]

ACE2, angiotensin converting enzyme 2; ARDS, acute respiratory distress syndrome; CMV, cytomegalovirus; HCoV, human coronavirus; IFN, interferon; IL, interleukin; MCV, measles-containing vaccine; MERS-CoV, Middle East respiratory syndrome coronavirus; MMR, measles-mumps-rubella; NK, natural killer; NLRP3, NOD-containing, LRR-containing and pyrin domain-containing protein 3; OPV, oral polio vaccine; RSV, respiratory syncytial virus; TMPRSS2, transmembrane serine protease 2; TNF, tumour necrosis factor.

FACTORS LEADING TO ADULTS BEING AT HIGHER RISK

Differences in the endothelium and clotting function

SARS-CoV-2 can infect endothelial cells and cause vasculitis.[29 30] Activation of coagulation pathways and formation of microthrombi, as a result of endothelial damage, as well as angiogenesis play an important part in the pathogenesis of COVID-19 and can lead to thrombotic complications such as heart attacks and strokes.[29 31–34] This could also explain why patients with conditions that affect the endothelium, such as diabetes and hypertension, are at greater risk for severe COVID-19.[35–37]

The endothelium in children is less 'predamaged' compared with adults and the coagulation system also differs, which makes children less prone to abnormal clotting.[38] Of note, the age profile of severe COVID-19 (and the increased risk in men) mirrors that of thrombotic diseases such as deep vein thrombosis.

Reports of children presenting with a more serious Kawasaki disease/toxic shock-like illness ('Paediatric Inflammatory Multisystem Syndrome Temporally associated with SARS-CoV-2 [PIMS-TS]' in Europe; also known as Multisystem Inflammatory Syndrome in Children [MIS-C] in the USA) might seem to also support the concept that vascular function plays an important role in the pathogenesis of COVID-19.[39–47] However, the pathogenesis of PIMS-TS, which usually presents 4–6 weeks after infection, differs from acute COVID-19, as it is likely to be an autoimmune phenomenon.[48] In addition, the hyperinflammation underlying PIMS-TS is different to that observed in adults with severe COVID-19, which includes higher levels of IL-7 and IL-8 and lower levels of effector $CD4^+$ T cells.[48]

Another intriguing observation is that chilblain-like skin lesions (usually on the lower extremities) in association with COVID-19 have been described more often in children and young adults.[49–53] The pathology underlying these lesions has been identified as endothelial viral invasion leading to vasculitis or thrombotic vasculopathy.

Angiotensin converting enzyme 2 receptors and transmembrane serine protease 2

Angiotensin converting enzyme 2 (ACE2) is the main receptor for the entry of SARS-CoV-2 into human cells.[54] This receptor is present on many cells including epithelial cells of the nasopharynx, lungs, heart, kidney, intestine, liver, testis, placenta, central nervous system and blood vessels, as well as macrophages.[55 56] The expression of ACE2 in nasal and lung epithelium increases during childhood and further during adulthood.[57–59] Furthermore, it has also been postulated that children have ACE2 receptors with a lower affinity for SARS-CoV-2 and a different distribution across body sites, making the entry of SARS-CoV-2 into cells more difficult.[55] However, while the number and affinity of ACE2 receptors on epithelial cells increases with age and is influenced by other factors, such as smoking, diet, diabetes mellitus, drugs, gender and genetics,[37 55–57 60 61] it has not been shown that this leads to differences in the manifestations of COVID-19. Furthermore, ACE2 receptor abundance decreases in the elderly, the age group that is most susceptible to COVID-19. In contrast, in patients who are taking ACE inhibitors or angiotensin receptor blockers for arterial hypertension, ACE2 is overexpressed and it has been postulated that this renders these individuals more susceptible to severe COVID-19.[62 63] However, this is controversial, partly explicable by the complexity of the regulation of the ACE2-angiotensin system, which is important in regulating the immune response, especially in the lungs, where it plays a role in protecting against acute respiratory distress syndrome (ARDS). In animal studies, ACE2 protects against SARS-CoV-2 and influenza-associated lung injury.[64 65] After SARS-CoV-2 gains entry into cells through the ACE2 receptor, ACE2 expression is downregulated, which prevents it from exerting its anti-inflammatory properties and 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,[66] 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.[67] This fits with the finding that in patients with diabetes mellitus, in whom ACE2 expression is reduced (likely due to glycosylation), COVID-19 is associated with severe lung injury and ARDS.[35 36]

While variants in the gene which encodes for ACE2 are linked to the risk of severe COVID-19,[68] it is still unclear if there is an association between the level of circulating ACE2 and severity of COVID-19. Nevertheless, it is possible that higher circulating levels of ACE2 in blood might neutralise virus and protect against lung damage through inactivation of circulating angiotensin II. In mice, treatment with human ACE2 mitigates lung injury during

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influenza infection.[69] Moreover, serum ACE2 levels are negatively correlated with body mass index and oestrogen levels,[70] which could contribute to the association between obesity and male sex with severe COVID-19.

In addition to the ACE2 receptor, SARS-CoV-2 entry into cells involves transmembrane serine protease 2 (TMPRSS2), which cleaves the viral spike protein. Like ACE2, TMPRSS2 has been reported to increase with age on nasal and lung epithelial cells.[58 59 71] However, two recent studies did not confirm these findings.[72 73]

Pre-existing immunity from coronavirus antibodies and T cells

Commonly circulating human coronaviruses (HCoV)-229E, HCoV-HKU1, HCoV-NL63 and HCoV-OC43 are responsible for approximately 6%–8% of acute respiratory tract infections.[1] Most individuals develop antibodies to HCoVs during childhood.[74 75] However, despite seroconversion at an early age, re-infection with HCoVs later in life is common[76 77] and levels of neutralising and non-neutralising cross-reactive antibodies, as well as cross-reactive T cells increase with age.[78–80]

Pre-existing non-neutralising antibodies can bind to virions, which can then more easily enter macrophages and granulocytic cells, a mechanism called antibody-dependent enhancement (ADE). Such virions covered in antibodies can also more easily replicate, leading to higher viral loads.[81] Children with COVID-19 have lower neutralising antibody levels and less ADE than adults.[78] Higher levels of non-neutralising cross-reactive HCoVs antibodies might partly explain increased susceptibility to severe COVID-19 in older adults.[79] ADE is a phenomenon that also needs to be considered in the development of vaccines, as enhanced disease after viral challenge postvaccination has been observed after vaccination against SARS-CoV and MERS-CoV in animal models,[82–86] and in the use of convalescent plasma as a treatment option.[87]

Infection with commonly circulating coronaviruses leads to long-lasting T cell immunity to spike (S) protein, nucleocapsid (N) protein and non-structural NSP7 and NSP13 of *ORF1*. However, the role of cross-reactive T cells in relation to SARS-CoV-2 remains unclear.[88–90] It has been suggested that pre-existing T cells with low avidity, which are often usually present in higher numbers in the elderly, negatively impact T cell responses to SARS-CoV-2.[80] Children with COVID-19 have been shown to have a less robust T cell response to the spike protein.[78]

Immunosenescence, inflammaging and chronic CMV infection

Ageing is associated with immunosenescence, a gradual decline in innate immunity, exemplified by ineffective pathogen recognition, macrophage activation, reduced neutrophil activity and natural killer [NK] cytotoxic activity and in adaptive immunity, associated with thymic atrophy, lymphopenia, a decrease in naïve T cells and an increase in anergic memory lymphocytes leading to an exhaustion of helper T cells, cytotoxic T cells and B cells.[91–96] Immunosenescence likely contributes to reduced SARS-CoV-2 clearance.

A second age-related change in the immune system is inflammaging, a chronic pro-inflammatory state that develops with advanced age and has been associated with inflammatory diseases such as atherosclerosis and diabetes, which are associated with severe COVID-19.[97 98] The predisposition to cytokine storm in the elderly could be explained by an increase in abundance and activity of the NOD-containing, LRR-containing and pyrin domain-containing protein 3 (NLRP3) inflammasome, which has been associated with severe COVID-19.[99 100]

Another immunological mechanism that might contribute to the age gradient in COVID-19 severity is the age-related increase in auto-antibodies against type I interferon (IFN) (especially IFN-α and IFN-ω), which are associated with severe COVID-19 pneumonia.[101] IFN type plays an important role in the innate antiviral response.[102]

Chronic cytomegalovirus (CMV) infection, which increases with age, may be a significant driver of inflammaging and immunosenescence.[103] Chronic CMV causes clonal T cell proliferation and a reduction in naïve T cell diversity, and also leads to an advanced differentiation status of CMV-specific CD8 T cells associated with either increased expression or downregulation of surface receptors, cytokine and transcription factors.[103 104] These effects of CMV on T cells may lead to a reduced capacity for immune responses to novel viral infections such as SARS-CoV-2.[105] CMV also increases inflammatory-mediated cytokines such as tumour necrosis factor (TNF)-α and interleukin (IL)-6,[106] making the elderly with clinically silent CMV infection more susceptible to the cytokine storm associated with severe COVID-19.

Comorbidities

Children have a lower prevalence of the comorbidities that have been associated with severe COVID-19 in adults, such as obesity, diabetes, hypertension and chronic kidney, lung and heart disease.[36] Even though, no definite risk factors have been identified in children, those with chronic lung disease (including asthma), cardiovascular disease and immunosuppression more often require hospital compared with previously healthy children.[7 107–109] However, intriguingly, even children with serious medical conditions, who are on immunosuppressive or cancer treatment, are much less affected by COVID-19 than adults.[110–113]

Lower levels of vitamin D

Vitamin D has anti-inflammatory and anti-oxidative properties,[114] and vitamin D deficiency has been associated with an increased risk for the development of respiratory tract infections.[115] Mechanisms by which vitamin D might protect against respiratory viruses include increasing viral killing, reducing synthesis of pro-inflammatory cytokines and protecting the integrity of tight junctions thereby preventing infiltration of immune cells into lungs.[116]

The overlap between risk factors for severe COVID-19 and vitamin D deficiency, including obesity,[117] chronic kidney disease[118] and black or Asian origin,[119] suggests that vitamin D supplementation may play a role in prophylaxis or treatment of COVID-19.[114] In many countries, vitamin D is routinely supplemented in infants younger than 1 year of age and in some countries even up to the age of 3 years. Furthermore, vitamin D levels are lower in older age groups, especially in men, in whom suplementation is less frequent.[120] Several studies report a negative correlation between estimates of average vitamin D levels in the population and the incidence and mortality from COVID-19.[121–123] One study found lower vitamin D levels in SARS-CoV-2-positive individuals compared with SARS-CoV-2-negative individuals, even after stratifying for age over 70 years.[124] Another study found lower vitamin D levels in patients with COVID-19 compared with sex-matched, age-matched and season-matched controls.[125] Furthermore, the level of vitamin D was negatively correlated with the severity of radiological

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findings. Two other studies also found a correlation between low vitamin D levels and COVID-19 severity and mortality.[126 127]

In vitro studies show that calcitriol, the active form of vitamin D, has antiviral activity against SARS-CoV-2.[128] A further important finding from a study in rats shows that vitamin D alleviates lipopolysaccharide-induced acute lung injury via the renin-angiotensin system (RAS),[129] which is important in the pathogenesis of COVID-19, in which the degree of overactivation of the RAS is associated with poorer prognosis. Low vitamin D levels lead to higher RAS activity and higher angiotensin II concentrations.[130]

FACTORS PROTECTING CHILDREN

Differences in innate and adaptive immunity

In addition to direct cytotoxic effects of the virus, immune-mediated mechanisms play a crucial role in the pathogenesis of COVID-19.[131] There are important differences in the immune system between children and adults, which might contribute to the different manifestations of COVID-19.[78 132]

Children have a stronger innate immune response, which is the first-line defence against SARS-CoV-2, with a higher number of NK cells. Another important factor is 'trained immunity' which involves epigenetic reprogramming of innate immune cells (including NK cells) after exposure to certain stimuli, including infections and vaccinations, leading to 'memory'.[133 134] These trained cells react faster and more strongly to subsequent pathogen challenge providing enhanced protection. However, this hypothesis would not explain, why this mechanism does not protect children against other respiratoryviruses.[28] It is likely that immune responses, including IFN production, on mucosal surfaces are also important in the defence against SARS-CoV-2.[135] To date, no studies have compared IFN production by SARS-CoV-2 challenged epithelial or dendritic cells of children and adults.

In relation to adaptive immunity, children also have a higher proportion of lymphocytes and absolute numbers of T and B cells,[136] while ageing is associated with a reduction in thymic activity and a reduction in naïve T cells.[96] Adults infected by SARS-CoV-2 typically have decreased lymphocyte counts[137] and it could be that higher numbers of lymphocytes, especially the large repertoire of naïve T cells which enables a strong T cell-mediated immune response, play a role in protecting children against SARS-CoV-2.

A further proposed immunological explanation is that children are less capable of mounting the pro-inflammatory cytokine storm, which plays an important role in the pathogenesis of severe COVID-19 and is responsible for multiorgan failure in critically ill patients.[32 136 138 139]

Hospitalised children with COVID-19 have higher serum levels of IL-17A and IFN-γ, but not TNF-α or IL-6.[78] Against this theory, however, is that in RSV or influenza infection, in contrast, children are no less prone than adults to developing a cytokine storm leading to ARDS.[138 140]

More frequent recurrent and concurrent infections

Children infected with SARS-CoV-2 often have co-infections with other viruses (including commonly circulating HCoVs).[141–143] These viruses could interfere with the replication of the SARS-CoV-2.[144] Frequent recurrent viral infections could also induce an enhanced state of activation of the innate immune system, including epigenetic changes in trained immunity, making it easier to clear SARS-CoV-2.[134]

Cross-reactive coronavirus antibodies and T cells

Althoughit has been suggested that children might be protected against SARS-CoV-2 as a result of pre-existing cross-reactive antibodies from more frequent and recent HCoVs infections,[145] preliminary data show that, while antibodies to HCoVs cross-react with the spike protein of SARS-CoV-2 and SARS-CoV, these antibodies are rarely neutralising, as they do not bind to SARS-CoV-2 receptor binding domain.[146–149] In accordance with this, no difference in antibody levels against HCoVs was found between children infected with SARS-CoV-2 and those who were not infected.[150] Furthermore, both neutralising and non-neutralising antibody levels are higher in adults, especially elderly adults compared with children.[78 79] The same is true for cross-reactive T cells to SARS-CoV-2, which are also present in higher numbers in the elderly and might be detrimental.[80] It is likely that IgA on mucosal surfaces is important for defence against SARS-CoV-2.[151] To date, however, no study has compared SARS-CoV-2 IgA levels or avidity between children and adults.

Microbiota

Another potential explanation for the less severe manifestations of COVID-19 in children are the differences in their oropharyngeal, nasopharyngeal, lung and/or gastrointestinal microbiota. The microbiota plays an important role in the regulation of immunity, inflammation, and mucosal homeostasis, as well as in the defence against pathogens. Thus, the microbiota might affect the susceptibility to SARS-CoV-2 infection and severity, or, given that ACE2 is highly expressed in the respiratory and gastrointestinal tract,[152 153] infection with SARS-CoV-2 might affect the microbiota and therefore inflammation.

Children are more heavily colonised with viruses and bacteria than adults, especially in the nasopharynx, where microbial interactions and competition might limit the growth of SARS-CoV-2.[154 155] The association between viral load and COVID-19 severity provides some support for this hypothesis.[156–158] While one small study did not find significant differences in the nasopharyngeal microbiota between patients infected with SARS-CoV-2 and healthy controls,[159] other studies have reported significant differences in the oropharyngeal, lung and gastrointestinal microbiota between these groups.[160–164]

In relation to the gastrointestinal microbiota, patients infected with SARS-CoV-2 have reduced bacterial diversity with a lower relative abundance of certain bacterial phyla including *Faecalibacterium,* and a higher relative abundance of others including *Bacteroides*.[160–162] While *Faecalibacterium* is known to have anti-inflammatory properties,[165] *Bacteroides* has been associated with decreased gastrointestinal ACE2 expression.[166] The gastrointestinal microbiota differs with age, with children generally having higher numbers of *Bifidobacterium*.[167 168] Differences in the gastrointestinal microbiota have also been observed between patients who do or do not excrete SARS-CoV-2 in their stool.[169] However, microbiota findings can be influenced by many different factors, including age, hospital admission, antibiotic administration and diet.[170 171] Therefore, the contribution, if any, of differences in the microbiota to differences in severity of COVID-19 remains unclear and cause versus effect will be difficult to determine.

Higher levels of melatonin

Melatonin has anti-inflammatory and anti-oxidative properties through several different mechanisms.[172 173] For example, this hormone increases proliferation and maturation of NK cells, T

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and B lymphocytes, granulocytes and monocytes in both bone marrow and other tissues,[174] and increases antigen presentation by macrophages.[175] In addition, melatonin decreases serum levels of IL-6, TNF-α and high-sensitivity C reactive protein,[176] and suppresses nuclear factor kappa-B.[177]

Melatonin protects against ARDS and haemorrhagic shock during viral infections.[178 179] Melatonin also inhibits calmodulin, which increases ACE2 expression and retention on the cell surface.[180 181] Melatonin might also block CD147,[182] which is another cellular receptor for of SARS-CoV-2 entry[183] and involved in regulating chemotaxis and lung inflammation.[184] Furthermore, in silico studies suggest that melatonin inhibits SARS-CoV-2's main protease.[185] It has therefore been suggested that melatonin could be used as prophylaxis or treatment in COVID-19.[186 187] A randomised trial to evaluate the efficacy of melatonin for prophylaxis against SARS-CoV-2 infection in healthcare workers is ongoing.[188]

Bats, which are the main reservoir of coronaviruses and suffer from minimal or no symptoms, have higher levels of melatonin compared with humans.[189] In humans, melatonin secretion is negatively correlated with age, with particularly high levels in infants,[190 191] which could contribute to the milder symptoms in this age group.

Off-target effects of vaccines

Many live vaccines have off-target (non-specific) immunomodulatory effects beyond protection against their target disease.[192] For BCG and measles-containing vaccines (MCV), this includes reduced all-cause mortality in high-mortality settings and protection against viral infections.[193–195] The mechanisms underlying the immunomodulatory effects of vaccines are the subject of ongoing investigation. BCG vaccine influences the innate and T cell immunity by epigenetic reprogramming of immune cells and by altering cytokine responses.[196–198]

As children have generally been received BCG and other live vaccines more recently than adults, it has been postulated that this contributes to age-related difference in COVID-19 severity.[199]

Ecological studies identifying associations between countries' BCG vaccination policies and rates and the severity of their COVID-19 outbreak purport to provide evidence in support of this.[200–202] However, association is not the same as causation and there are exceptions to this observation.[203 204] In addition, many of the articles claiming an association do not account for likely confounding factors between countries, such as different diagnostic and reporting procedures, different epidemic curves and different capacity of medical systems.[203 205] It is also 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. It is therefore not unexpected that no difference in COVID-19 infection rate was found decades after vaccination in BCG-vaccinated individuals compared with BCG-naïve individuals.[206] RCTs of BCG to reduce the severity of COVID-19 are ongoing.[207]

Like BCG, MCV and oral polio vaccination has also been suggested to contribute to the difference in the severity of COVID-19.[208 209] Fewer studies have investigated the mechanisms underlying the immunomodulatory effects of MCV, but they have shown an association between MCV and a decrease in circulating leukocytes and lymphocytes, with a decrease in CD4 cells and an increase in CD8 cells.[210 211] An RCT of measles-mumps-rubella vaccine to reduce the severity of COVID-19 is planned.[212]

Intensity of exposure to SARS-CoV-2

Viral load influences the severity of COVID-19[156–158] suggesting that lower intensity of viral exposure might be another factor leading to less severe disease.[213] Children might have less intense exposure to SARS-CoV-2 compared with adults who generally have had workplace, shopping, travel and nosocomial exposure.[6 214–216]

As children are usually infected by an adult, they are infected by a second or third generation SARS-CoV-2. For SARS-CoV and MERS-CoV, subsequent generations of virus were reported with reduced pathogenicity compared with the first-generation virus.[217 218] However, to date, this has not been reported for SARS-CoV-2. In contrast, an antigen drift through a mutation called D614G in the spike protein has been suggested to lead to higher viral loads and viral transmission without changing pathogenicity.[219 220] It is unclear whether this was the result of higher fitness or chance. While the D614 variant of SARS-CoV-2 has been the main driver of the pandemic in China, the G614 variant is the main strain spreadingthrough Europe and the USA.[221]

CONCLUSION

In summary, the observation that, compared with other respiratory viruses, children have less severe symptoms when infected by SARS-CoV-2 is surprising and not yet understood. Furthermore, it is also uncertain why children with the usual risk factors for infections, such as immunosuppression, are not at high risk for severe COVID-19, while previously healthy children can on rare occasions become severely ill.[110–113 222] Although there are several hypotheses for why children are less affected by COVID-19, with the notable exception of age-related changes in immune and endothelial/clotting function, most do not explain the observed age-gradient in COVID-19 with severity and mortality rising steeply after the age of 60 to 70 years. Unravelling the mechanisms underlying the age-related differences in the severity of COVID-19 will provide important insights and opportunities for the prevention and treatment of this novel infection.

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