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## VIRIOLOGY

# SARS-CoV-2 in children: spectrum of disease, transmission and immunopathological underpinnings

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## Summary

As the SARS-CoV-2 pandemic unfolds across the globe, consistent themes are emerging with regard to aspects of SARS-CoV-2 infection and its associated disease entities in children. Overall, children appear to be less frequently infected by, and affected by, SARS-CoV-2 virus and the clinical disease COVID-19. Large epidemiological studies have revealed children represent less than 2% of the total confirmed COVID-19 cases, of whom the majority experience minimal or mild disease that do not require hospitalisation. Children do not appear to be major drivers of SARS-CoV-2 transmission, with minimal secondary virus transmission demonstrated within families, schools and community settings. There are several postulated theories regarding the relatively low SARS-CoV-2 morbidity and mortality seen in children, which largely relate to differences in immune responses compared to adults, as well as differences in angiotensin converting enzyme 2 distribution that potentially limits viral entry and subsequent inflammation, hypoxia and tissue injury. The recent emergence of a multisystem inflammatory syndrome bearing temporal and serological plausibility for an immune-mediated SARS-CoV-2-related disease entity is currently under investigation. This article summarises the current available data regarding SARS-CoV-2 and the paediatric population, including the spectrum of disease in children, the role of children in virus transmission, and host-virus factors that underpin the unique aspects of SARS-CoV-2 pathogenicity in children.

**Key words:** SARS-CoV-2; COVID-19; paediatrics; transmission; ACE2; multisystem inflammatory syndrome.

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## INTRODUCTION

Since its identification in January 2020 to the time of writing, SARS-CoV-2 has caused coronavirus disease (COVID-19) in almost 10 million people worldwide and resulted in 500,000 deaths.<sup>1</sup> However, COVID-19 morbidity and mortality exhibits significant variation across age groups. Early publications revealed SARS-CoV-2 could cause a wide spectrum of illness in adults, and children were seemingly under-represented with regard to both the total number of cases as well as the likelihood of experiencing severe disease.<sup>2,3</sup> Comprehensive population-based epidemiological studies have confirmed this finding, revealing a lower prevalence of SARS-CoV-2 infection in children compared to adults.<sup>4–6</sup> Furthermore, if children do acquire SARS-CoV-2, the vast majority experience mild disease not requiring hospitalisation,<sup>3,7–9</sup> and as SARS-CoV-2 disseminates globally and chains of transmission are becoming increasingly recognised, children do not appear to be efficient transmitters of infection.<sup>10–13</sup>

There are a number of hypotheses postulated to explain children's lower risk of being infected by, and affected by, SARS-CoV-2. These include differences in viral kinetics, a mucosal burden of competing pathogens, and alterations in their immune response including vascular susceptibility to SARS-CoV-2 infection. Most notably, a hyperinflammatory state, with features of acute respiratory distress syndrome (ARDS), appears to be a central feature of the pathogenesis of acute severe disease in adults. Children are seemingly acutely protected from this state for reasons that are as yet unclear, yet one of the leading hypotheses regarding their protection from acute illness and transmission relates to age-related differences in expression of angiotensin converting enzyme 2 (ACE2) in different tissue types. ACE2 is a key mediator of SARS-CoV-2 host cell entry and plays an integral role in the

endothelial inflammatory response. However, with the recent recognition of potential late multisystem inflammatory sequelae from SARS-CoV-2 infection, differences in the immune-mediated response to SARS-CoV-2 is also of interest.

This article presents an overview of SARS-CoV-2 infection in children based on the available data to date, including the spectrum of disease, transmission and immunopathological underpinnings, as well the possible multi-system inflammatory sequelae that may ensue.

## SPECTRUM OF DISEASE

Since the emergence of SARS-CoV-2 as a human pathogen in the Hubei Province of China, it has become evident that children are largely spared the acute severe features of COVID-19. China was the first country to experience intense community transmission, and a review of 72,314 cases by the Chinese Center for Disease Control (CDC) revealed that less than 1% of cases occurred in children aged less than 10 years, and the vast majority of these cases were well enough to be managed in the community.<sup>14</sup> The United States (US) has subsequently emerged as the nation with the highest rates of infection and less than 2% of affected cases are in the paediatric age range,<sup>15</sup> which is in keeping with data collated in Italy<sup>16</sup> and Spain.<sup>17</sup> In New South Wales, Australia, where community testing rates have been high, children contribute only 4% of the known COVID-19 cases in the community, despite comprising 23% of the population.<sup>18</sup>

Alongside a low prevalence of diagnosed disease, children also consistently exhibit mild (if any) illness following infection with SARS-CoV-2, including some traditionally 'high risk' children such as those with cancer,<sup>19</sup> bone marrow transplant recipients,<sup>20</sup> immunosuppressed children on biological agents,<sup>21</sup> and those with cystic fibrosis.<sup>22</sup>

The most common symptom reported in children is fever, with rhinorrhoea, cough, gastrointestinal symptoms, headache and myalgia also reported.<sup>15,23–25</sup> However, a proportion of children with SARS-CoV-2 detected by real time polymerase chain reaction (RT-PCR) have no clinical or radiological features of disease.<sup>24,26</sup> Mild bronchial thickening and ground-glass opacities are the main radiological findings on chest X-ray or computed tomography studies, and can be evident in asymptomatic children.<sup>24,27</sup> While there are still limited data available regarding COVID-19 in infants, case reports regarding infants with SARS-CoV-2 infection (horizontally or otherwise acquired) have predominantly described asymptomatic or paucisymptomatic disease, with mild shortness of breath the most commonly reported symptom.<sup>28</sup> Outcomes have been favourable in the vast majority of infants with SARS-CoV-2 infection, including those presenting with less common and potentially more severe signs, including encephalopathy.<sup>29</sup> While vertical transmission has been postulated to occur,<sup>30</sup> there is evidence suggesting perinatal acquisition is unlikely in the context of appropriate hygiene measures (adequate hand-hygiene and the use of a surgical mask in mothers positive for SARS-CoV-2) at delivery.<sup>31</sup> Therefore, it is recommended that infants should continue to room-in with their mothers and breastfeeding should be encouraged, with these hygiene measures in place.<sup>32</sup>

Severe disease requiring admission to intensive care units (ICUs) in the acute phase of infection is rare in children. Of 1391 children assessed and tested for SARS-CoV-2 at Wuhan

Children's Hospital, only 12.3% ( $n=171$ ) were positive, of whom just three children (1.8%) required ICU admission.<sup>24</sup> However, as has been evident in other reports (including a prospective surveillance study of paediatric oncology units in France),<sup>33</sup> it is uncertain as to whether these children required ICU admission due to COVID-19 or their comorbid conditions. Whilst a review of 41 children with COVID-19 in Spain demonstrated a relatively high proportion requiring hospitalisation (25/41, 61%), only four required admission to ICU (4/41, 9.8%).<sup>17</sup> In North America, the majority of paediatric cases have not required hospitalisation,<sup>8,34</sup> and those requiring ICU admission frequently have a number of comorbidities and complex medical backgrounds that dictate their need for intensive care.<sup>35</sup>

Therefore, extrapolating conclusions from the observational data available on children who develop moderate to severe COVID-19 globally is difficult due to possible confounding by other factors. Published detailed clinical information is often lacking with regard to whether these children required high-level care due to COVID-19, or were simply RT-PCR SARS-CoV-2 positive and admitted due to an alternative diagnosis or active comorbidity at a time when community transmission of the virus in their geographic settings was high.<sup>27</sup> Furthermore, a vast array of (not yet evidence-based) therapeutic options have been utilised in many of these descriptive studies, including antiviral agents, traditional medicine, antibiotics, and immunomodulatory agents, many of which have known adverse effects, further complicating the ability to ascertain whether complications in these cases were due to SARS-CoV-2 or other factors implicated in these presentations.<sup>36,37</sup>

The direct long-term outcomes for children from SARS-CoV-2 infection remains to be seen. Aside from the multi-system inflammatory sequelae potentially associated with SARS-CoV-2 (see section [Multisystem inflammatory sequelae](#)) there are no outcome data for children with SARS-CoV-2 infection beyond acute infection. There are preliminary adult data that raise concerns for the longer-term respiratory, cardiac and neurological sequelae. Observations from China in non-critical hospitalised SARS-CoV-2 adult survivors demonstrated persisting pulmonary function defects on discharge; the most common being diffusion capacity, followed by restrictive ventilatory defects, both of which correlated with the severity of acute infection.<sup>38</sup> Myocardial involvement (as evidenced by elevated troponin levels) has been reported in up to 30% of adults hospitalised with SARS-CoV-2 infection, which may be related to myocarditis, myocardial ischaemia/infarction, cardiomyopathy or coronary vasculitis.<sup>39</sup> The long-term prognosis for such patients is extrapolated from the long-term outcomes of other viral-associated myocardial injury (myocarditis, cardiomyopathy and vasculitis) and general myocardial insults (e.g., myocardial ischaemia/infarction). One concern that requires consideration is the long-term cardiac outcomes for children with SARS-CoV-2 who develop coronary artery abnormalities in the context of the suspected SARS-CoV-2 associated multisystem inflammatory conditions (see section [Multisystem inflammatory sequelae](#)). As may occur in other viral illnesses, there have been case reports of neurological complications in adults with SARS-CoV-2 including neuroinflammatory syndromes (such as encephalitis and acute demyelinating encephalomyelitis), stroke and peripheral nervous disorders (including Guillain-Barré syndrome,

plexopathies, and cranial nerve palsies) that may lead to long-term morbidity (with prognoses extrapolated from other viral-associated and general neurological insults).<sup>40–46</sup> However, as demonstrated in the differences regarding how children are affected by acute SARS-CoV-2 infection compared to adults, identifying and prognosticating the long-term outcomes for children must be independently evaluated to that of adults, and in the literature to date, there has not been a clear indication that these neurological complications predominate in children infected with SARS-CoV-2.

## THE ROLE OF CHILDREN IN TRANSMISSION

By analogy to influenza, for which children are known to be major transmitters, there was initial concern regarding the potential role of children as ‘silent spreaders’ of SARS-CoV-2.<sup>47,48</sup> and occasional early studies supported this perspective.<sup>49</sup> As SARS-CoV-2 spreads globally, the transmission chains of SARS-CoV-2 are becoming apparent. Collectively, data suggest that children with SARS-CoV-2 acquire their infection from an adult contact, with minimal secondary transmission from children.<sup>50</sup> Droplets are the main mechanism of transmission of SARS-CoV-2, and while some studies have revealed the presence of SARS-CoV-2 RNA detected in the stool of patients<sup>51</sup> and on environmental surfaces,<sup>52</sup> confirmation of viable virus of sufficient load to produce infection in other individuals has not yet been documented. To date, there are no published data confirming faecal-oral transmission of SARS-CoV-2, despite detectable virus genetic material documented in the stool of paediatric patients.<sup>53,54</sup>

Isolated case reports have suggested transmission from symptomatic children to household contacts,<sup>10,11</sup> however these are rare. Simultaneously, other case reports support an absence of transmission even amongst symptomatic children, including one paediatric index case for whom not one of 172 contacts tested positive for SARS-CoV-2.<sup>55</sup> One case series of household contacts revealed 3/31 (9.6%) clusters involved a child as a possible source case, compared to H5N1 avian influenza in which 54% of family clusters had a paediatric source case.<sup>12</sup> Similarly, in school-based transmission studies in Australia involving 18 index COVID-19 cases, only two of 735 (0.3%) students became secondarily infected: one from an adolescent student, and another from an infected teacher.<sup>13</sup> A systematic review on school closures for coronavirus control has found no conclusive evidence for a convincing impact on population-level viral transmission dynamics,<sup>56</sup> and in Sweden (where schools and childcare centres have remained open throughout the pandemic) the prevalence of SARS-CoV-2 in children has remained very low.<sup>57</sup>

Concordant with these epidemiological findings, a recent modelling study demonstrated that susceptibility to SARS-CoV-2 infection in people under the age of 20 years is around half that of adults.<sup>58</sup> Additionally, only 21% of infections are symptomatic in adolescents (aged 10–19 years), compared to 69% in older adults (>70 years). As a result, transmission-based interventions aimed at children, including school closures, are projected to have a relatively small impact of SARS-CoV-2 transmission dynamics.<sup>58</sup>

Indeed, there are now data from many geographic settings across Europe, Asia and America confirming that the proportion of children infected with SARS-CoV-2 in the community is low (varying from 1% in young children to 6% in

older children),<sup>54</sup> although further adequately powered seroprevalence studies are necessary to more clearly establish the transmission dynamics in children.

Despite the weight of evidence suggesting children are not major drivers of transmission of SARS-CoV-2 at a population level, children in many geographic areas have been subject to the same social isolation rules as adults, including widespread school closures. These policies have significant repercussions for education, development and wellbeing.<sup>59</sup> Furthermore, reduced economic productivity at household as well as national levels, and negative impacts on the psychosocial wellbeing of parents and/or caregivers may be expected corollaries. Limiting transmission from adult source cases is essential through prioritisation of optimal hygiene and physical distancing measures; yet the need to enforce physical distancing in children with the same rigour (including universal school closures or restrictions) poses a risk of marked social and emotional morbidity which is not proportionate to the existing evidence for the role of children in the transmission of SARS-CoV-2.<sup>60</sup>

## DIAGNOSTIC CONSIDERATIONS

As with other human coronaviruses, the diagnostic gold standard for SARS-CoV-2 is via RT-PCR, commonly utilising genes encoding the internal RNA-dependent RNA polymerase and surface spike glycoprotein.<sup>61–63</sup> Higher viral loads have been documented in the lower respiratory tract,<sup>64</sup> consistent with what has been observed for SARS-CoV and Middle East respiratory syndrome (MERS).<sup>65</sup> In some settings, where there is a strong clinical suspicion of SARS-CoV-2 yet a negative result on nasopharyngeal or throat swab, lower respiratory tract sampling is recommended;<sup>66</sup> however, this should be reserved for the most unwell children in light of the risks associated with obtaining lower respiratory tract samples.

Buccal swabs have been explored as a more tolerable sampling method than the currently recommended nasopharyngeal or oropharyngeal specimens,<sup>67</sup> yet studies investigating this method have included very small numbers of children and have revealed higher cycle thresholds when compared with nasal nasopharyngeal specimens, indicating a lower viral load assessed via this sampling method. Although saliva specimens have been investigated in studies involving small numbers of adults with SARS-CoV-2 infection,<sup>68</sup> this has not been evaluated in the paediatric population. Most of the available data regarding the timing of viral detection via PCR is based on evidence obtained from the adult population, and indicates that viral detection via PCR tends to decline more quickly in upper respiratory tract samples than lower respiratory tract samples.<sup>63</sup> SARS-CoV-2 RNA can be detected for longer periods in patients with more severe disease than in patients with mild illness.<sup>69</sup>

SARS-CoV-2 infection can also be ascertained by the detection of antibodies to SARS-CoV-2, which may be helpful in aiding in the diagnosis of post-infectious inflammatory syndromes in children. The first detectable serological marker is total antibodies,<sup>70</sup> although IgM and IgG enzyme-linked immunosorbent assay (ELISA) have been documented as positive as early as four days after symptom onset.<sup>63</sup> Seroconversion typically occurs in the third to fourth week after illness and ELISA-based IgM and IgG antibody tests have revealed a high specificity for the diagnosis of SARS-



CoV-2,<sup>63</sup> although false positive results have been described<sup>71</sup> and cross-reactivity between other coronaviruses may occur.<sup>72</sup> While specific sensitivity quantification is difficult to delineate with regard to serology in children, it is known that paucisymptomatic patients (which describes the vast majority of paediatric cases) may have low antibody concentrations and in these circumstances, false negative results are more likely to occur.<sup>73</sup>

## MECHANISMS OF DISEASE

### Immune response

Similar to SARS-CoV, which caused the 2003 SARS epidemic, several features of SARS-CoV-2 suggest the immune response is central to disease pathogenesis. For both viruses, the delay to onset of significant symptoms points to the priming of an immune response and high levels of inflammatory markers supports an inflammatory pathogenesis, while the worsening of disease in the presence of decreasing viral titres suggests that direct viral cytopathic effects may no longer be of relevance at that time.<sup>74</sup>

In adults, it has been established that infection with SARS-CoV-2 results in a robust antiviral CD4 and CD8 T cell response<sup>75</sup> as well as generation of virus-specific antibodies, including neutralising antibodies.<sup>76</sup> Using single cell ribonucleic acid sequencing (scRNA-seq) several studies have now established the immune profile of adult patients with COVID-19. One study found that in hospitalised adults with COVID-19, especially those with ARDS, there is depletion of natural killer (NK) cells, dendritic cells and CD16+ monocytes, but expansion of plasmablasts.<sup>77</sup> Further analysis revealed that type I interferon induced signatures were strong (but not universal) in all patients, although cytokine expression was not elevated in peripheral blood immune cells, suggesting an alternative source of inflammatory cytokines in COVID-19.<sup>77</sup> Indeed, scRNA-seq of bronchoalveolar lavage immune cells has revealed the presence of aberrant pro-inflammatory macrophages, especially in patients with severe COVID-19,<sup>78</sup> suggesting that perhaps the immune cells of resident tissues are the source of inflammatory cytokines. Another study focused on the early recovery phase of COVID-19 and identified a prominent population of CD14IL1 $\beta$  monocytes in the peripheral blood of adults seven days after showing a negative PCR for SARS-CoV-2, which was associated with increased signalling by inflammatory cytokines (such as type 1 interferons and IL-6 in several immune cell subsets, including monocytes, T cells and B cells).<sup>79</sup>

Very little research currently exists regarding the immune response to SARS-CoV-2 in children. Data from New York city has shown that severe disease is associated with obesity in older children, and a pro-inflammatory profile demonstrated by a high C-reactive protein (CRP) and IL-6 levels at admission.<sup>80</sup> Therefore, it seems that a pro-inflammatory state in predisposed children may be associated with severe adult-like COVID-19. Indeed, a key unanswered research area regarding SARS-CoV-2 is how the immune response in children differs from adults, and whether this difference may explain the spectrum of disease susceptibility and severity associated with COVID-19. Postulated reasons as to why most children appear to be protected from an acute hyper-inflammatory response to SARS-CoV-2 include: (i) the capacity to mount a more controlled and efficient immune response; (ii) relatively fewer co-morbidities that predispose

to a pre-existing pro-inflammatory state; and (iii) relatively lower viral loads that may not trigger as intense an inflammatory response.

### Other host-virus factors

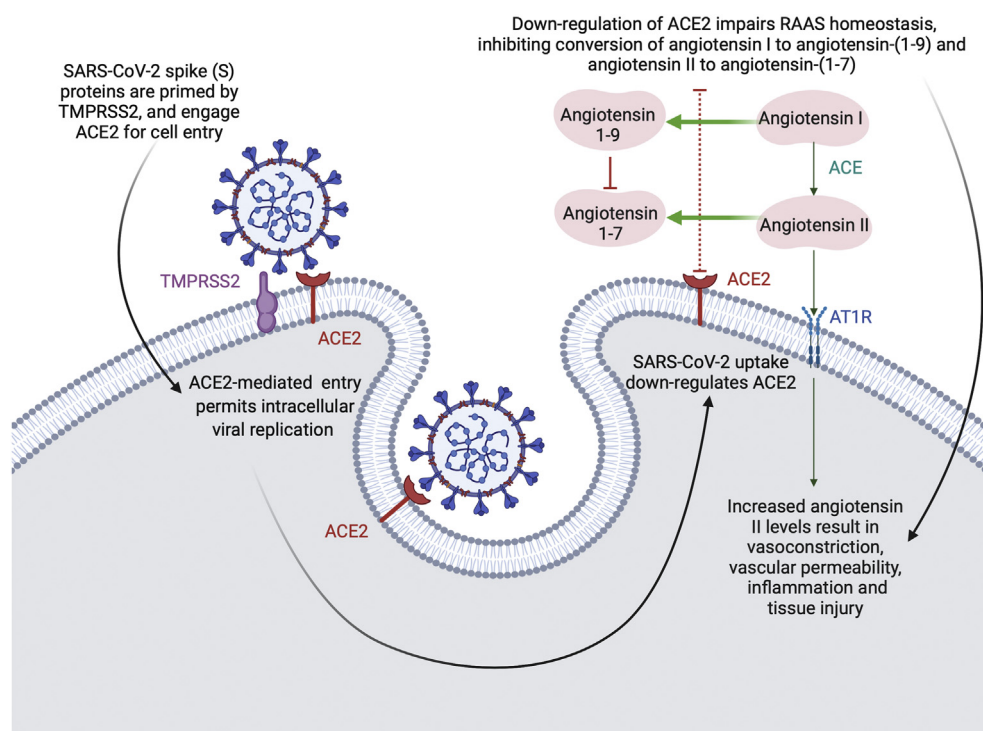
One of the most consistent and biologically plausible theories emerging in the literature regarding the mild (if any) disease SARS-CoV-2 causes in children surrounds age-related differences in ACE2. Cell entry of coronaviruses depends on the binding of the viral spike (S) protein to cellular receptors, as well as the cleavage or priming of this S protein by host cell proteases (Fig. 1).<sup>81</sup> SARS-CoV-2 (and its predecessors SARS-CoV and the seasonal coronavirus, CoV-NL63) engage ACE2 for cell entry, and utilise the transmembrane protease serine 2 (TMPRSS2) for S protein priming.<sup>82,83</sup> In the previous SARS-CoV epidemic, the efficiency of ACE2 usage in viral cell binding was found to be a key determinant of SARS-CoV transmissibility.<sup>84</sup>

ACE2 is an enzyme that functions to convert angiotensin II to its metabolite angiotensin-(1–7), particularly within the lung microenvironment, where ACE2 levels are intrinsically elevated.<sup>85</sup> Angiotensin-(1–7) has a homeostatic role in the regulation of the renin-angiotensin-aldosterone system (RAAS), a finely tuned cascade of vasoactive peptides that orchestrates key processes of human physiology.<sup>86,87</sup> The RAAS is an important regulatory pathway for the cardiovascular system and the counter-regulatory enzymes ACE and ACE2 have been identified as key elements of the inflammatory processes established in conditions such as cardiac hypertrophy, pulmonary hypertension, lung injury and sepsis.<sup>88</sup> Diminished expression of ACE2 can result in chronic heart failure and pulmonary compromise, implying a protective mechanism of ACE2 and alluding to a mechanism whereby dysregulated ACE2 in COVID-19 may imbalance the angiotensin-II/angiotensin-(1–7) equilibrium to tend towards inflammation and hypoxia.<sup>85</sup>

After gaining entry to the host cell, SARS-CoV-2 appears to down-regulate ACE2 expression on cell surfaces, thereby minimising the ability of the enzyme to exhibit its protective effects on organs.<sup>87,89,90</sup> While ACE2 expression has been found throughout the cardiorespiratory and gastrointestinal systems (with TMPRSS2 expressed even more broadly), nasal epithelial cells exhibit the highest expression of ACE2/TMPRSS2 within the entire respiratory tract, which may explain the prominence of the symptom of anosmia in patients with COVID-19.<sup>91–93</sup>

In the lower respiratory tract, where both SARS-CoV and SARS-CoV-2 appear to have their most acute pathogenic effects, ACE2/TMPRSS2 expression has been identified in both type I and type II pneumocytes.<sup>83,94,95</sup> In children, a higher concentration of ACE2 in pneumocytes has been documented, which may explain the protection for this age group against the severe clinical manifestations of COVID-19.<sup>85,96</sup> Age-dependent ACE2 gene expression has also been documented in the nasal epithelium, with the lowest gene expression evident in younger children and increasing expression evident with age.<sup>97</sup> As this is the first point of contact for SARS-CoV-2 in the human body, lower ACE2 expression in the nasal epithelium of children may explain the infrequent infectivity in this age group.

The RAAS derangement that is evident in many underlying chronic cardiovascular conditions, which normally do not



**Fig. 1** Host cell interaction with SARS-CoV-2. ACE, angiotensin converting enzyme; AT1R, angiotensin 1 receptor; RAAS, renin-angiotensin-aldosterone system; TMPRSS2, transmembrane protease serine 2.

affect paediatric populations, may be implicated in the severity of COVID-19 seen in older populations. It is becoming evident that while age is the strongest predictor of COVID-19-related death, in keeping with findings revealed by prior coronavirus epidemics, the presence of coexisting conditions—particularly chronic cardiovascular disease and obesity—are proving key prognostic determinants for COVID-19.<sup>98–101</sup>

It has been hypothesised that SARS-CoV-2 may directly attack vascular endothelial cells expressing high levels of ACE2, resulting in abnormal coagulation and a sepsis-like picture.<sup>102</sup> Dysfunction of the vascular endothelium tends to result in organ ischaemia via a shift in the vascular equilibrium towards vasoconstriction, which further exacerbates tissue inflammation.<sup>103,104</sup> SARS-CoV-2 may facilitate induction of endotheliitis, as autopsy evidence has revealed the presence of viral inclusion bodies within endothelial cells alongside an accumulation of inflammatory cells, impairing microcirculatory function and resulting in clinical ischaemia of multiple organs.<sup>103</sup> Once again, this may explain a pre-disposition for patients with pre-existing endothelial dysfunction (as is associated with hypertension, diabetes, established cardiovascular disease and obesity) to have the highest risk of adverse outcomes in COVID-19.<sup>103</sup>

Finally, modified endovascular responses due to developmental differences in clotting factors and endothelial cells have also been proposed as an explanation for the attenuated response to SARS-CoV-2 in children.<sup>103,105</sup> Indeed, there is clear evidence that haemostasis is a developmental continuum, with reduced vitamin K dependent coagulation factors and antithrombin evident in neonates, while lower protein C and S levels persist throughout childhood.<sup>106</sup> This contrasts to the prothrombotic milieu evident in elderly populations,

which may serve as yet another mechanism for driving severe disease in this population.<sup>107</sup>

## MULTISYSTEM INFLAMMATORY SEQUELAE

In April 2020, several severely unwell children with fever and shock were described in the United Kingdom (UK) in association with SARS-CoV-2 infection.<sup>108</sup> No such cases had been reported prior to this from China, and a solitary case from the US of Kawasaki disease (KD) with concurrent detection of SARS-CoV-2 infection had been published.<sup>109</sup> Further cases were later identified in the UK and the condition was labelled 'paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2' (PIMS-TS).<sup>108</sup> Reports subsequently emerged from other high-burden settings regarding children with fever, shock, rash and abdominal pain, some of whom met diagnostic criteria for KD;<sup>110–113</sup> many of these children were seropositive for prior SARS-CoV-2 infection and a minority showed concurrent detection of SARS-CoV-2 via RT-PCR.<sup>108,110,111</sup> The US Centers for Disease Control and Prevention (CDC) has named the syndrome 'multisystem inflammatory syndrome in children associated with COVID-19' (MIS-C).<sup>114</sup>

Although the link between SARS-CoV-2 and these multisystem inflammatory syndromes requires further elucidation, there is a growing consensus that this syndrome may represent an immune-mediated complication of SARS-CoV-2 infection in children and adolescents, in light of the presence of SARS-CoV-2 antibodies in most cases and 4-week delay in timing between peaks of community SARS-CoV-2 infections and case report clusters of children presenting with inflammatory syndromes in several locations.<sup>110,111</sup>

One of the more comprehensive descriptive studies regarding this inflammatory syndrome depicted 58 children who presented with fever, with half having evidence of rash and gastrointestinal symptoms.<sup>115</sup> Twenty-nine of these cases (50%) developed shock and required intensive care support. Twelve of these children (20%) met the diagnostic criteria for KD, while 24 children (40%) showed no features of KD. However, the patients described were generally older than KD cohorts and showed higher inflammatory markers than is common in KD. Eight (14%) cases developed coronary artery dilation or aneurysms, revealing a possible shared pathogenesis with KD. Almost all children recovered (1 death), with the majority receiving systemic immunomodulatory treatment. Other reports have described a high prevalence of macrophage activation syndrome in PIMS-TS, which is less common in endemic KD than in PIMS-TS.<sup>110</sup>

KD may provide a model for the pathogenesis of PIMS-TS, not least because KD has a strong association with seasonal infections, but also because it is rarely associated with intercurrent infection at the time of manifesting the vasculitic processes (as has been evident in the above described cohorts). A number of surveillance studies have been established to better monitor the emergence of this clinical entity.<sup>116</sup> In Australia, surveillance undertaken by the Paediatric Active Enhanced Disease Surveillance network ([www.paeds.org.au](http://www.paeds.org.au)) has not shown an increased frequency of KD across the period of the COVID-19 epidemic, which may be anticipated in light of the low community prevalence of SARS-CoV-2 to date.

Specific, albeit provisional, recommendations for management of patients with possible PIMS-TS/MIS-C have been published by a group of specialist clinicians and endorsed by the Royal Australasian College of Physicians.<sup>117</sup> SARS-CoV-2 serological testing during the acute presentation, and ideally prior to the administration of intravenous immunoglobulin, is a key priority.

## CONCLUSION

Unlike many respiratory viruses, children have been relatively spared by severe illness in the global pandemic caused by SARS-CoV-2 and appear to be only minor contributors to virus transmission. These aspects of SARS-CoV-2 in children likely result from differences in their immune response to the virus, including a lower predisposition to pro-inflammatory states, fewer co-morbidities, and the differential expression of ACE2 in children, which may attenuate viral entry, as well as ongoing replication and subsequent inflammation, hypoxia and tissue injury.

At the time of writing, the multisystem inflammatory syndromes associated with SARS-CoV-2 (PIMS-TS/MIS-C), which present with KD-like clinical features, remain under investigation. Temporal and serological plausibility of a link with SARS-CoV-2 infection is supported by consistent data, but further studies are required to refine case definitions, establish SARS-CoV-2 as an inciting agent, understand the immune-mediated response to SARS-CoV-2 infection, and determine optimal management strategies.

There remain significant questions needing to be addressed regarding the intricate pathogenic mechanisms underlying the differences in SARS-CoV-2 infection between children and adults. Research to better define the immune response and assess the possibility of altered ACE2 tissue distribution and

affinity for SARS-CoV-2 in the paediatric population should be a focus for future studies. Understanding the nature of host-virus interactions, and particularly which features of the paediatric immune system facilitate protection or (conversely) delayed multi-system inflammation, will shed light on SARS-CoV-2 pathogenesis and may lead to necessary improvements in therapeutic options. Furthermore, it is important that future epidemiological and clinical cohort data describe clinical comorbidities and coinfections in children with more precision, as well as delineating disease findings implicated in severe COVID-19 and potential SARS-CoV-2 multisystem inflammatory sequelae more clearly. This will enable clarification of risk factors for SARS-CoV-2-related disease and its associated disease entities in children.

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