

## SYMPOSIUM REPORT

# Hide and seek in a pandemic: review of SARS-CoV-2 infection and sequelae in children

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**Abstract**

Children infected with SARS-CoV-2 have a clinical phenotype that is distinct from that observed in adult cases. They can present with a range of respiratory, gastrointestinal and neurological symptoms, or with a delayed hyperinflammatory syndrome (paediatric multisystem inflammatory system temporally associated with SARS-CoV-2; PIMS-TS) that frequently requires treatment in an intensive care unit. These manifestations may be related to unique expression of transmembrane receptors and immune physiology in children. The clinical features and inflammatory profile of PIMS-TS are similar to other inflammatory disorders that occur in children such as Kawasaki disease, macrophage activation syndrome and sepsis. Given children are infected less frequently and have less severe disease due to COVID-19 compared to adults, their physiological profile is of great interest. An understanding of the unique mechanisms of infection and disease in children could aid the identification of potential therapeutic targets. Like adults, children can have long-term complications of SARS-CoV-2 infection, including neurological and cardiac morbidity. Vaccination against SARS-CoV-2 is not yet authorised in children aged <12 years, and hence we anticipate ongoing paediatric presentations of COVID-19 in the coming months.

**KEYWORDS**

COVID-19, COVID-19 related, paediatric multisystem inflammatory disease, pediatrics

## 1 | INTRODUCTION

Since the first case of infection due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Wuhan, China on 31 December 2019, the world has felt the impact of this highly communicable virus which has infected >180 million individuals as of 1 July 2021 (European Centre for Disease Prevention & Control, 2021). Whilst our attention was initially focused on the high incidence of respiratory failure occurring in infected adults (Ruan et al., 2020), it became evident that a small proportion of children in China were infected but with milder symptoms (Bi et al., 2020). Subsequent reports in June 2020 emerged from centres in the UK and the USA that a

severe inflammatory syndrome was being found in children that had recent SARS-CoV-2 infection (Feldstein et al., 2020; Whittaker et al., 2020). This syndrome is often referred to as Paediatric multisystem inflammatory syndrome temporally associated with COVID-19 (PIMS-TS) in the UK (Royal College of Paediatrics & Child Health, 2020), or multisystem inflammatory syndrome in children (MISC) in North America (Centers for Disease Control & Prevention, 2020). Here we review the potential mechanisms of unique presentations in children; phenotypic and immune characteristics of children infected with SARS-CoV-2; the similarities with Kawasaki disease and known inflammatory disorders; and the longitudinal morbidity and outcomes of COVID-19 in children.

## 2 | SARS-CoV-2 RT-PCR POSITIVE DISEASE IN CHILDREN AND COMPARISONS TO ADULT PATIENTS

Symptoms of children with SARS-CoV-2 infection are wide ranging and can include respiratory, gastrointestinal and neurological problems. Of those that have positive screening tests <2% require hospitalisation in high-income countries (American Academy of Pediatrics & the Children's Hospital Association, 2021; Ibrahim et al., 2020) and on a global scale <6% have severe disease or require intensive care (Bailey et al., 2021; Tsankov et al., 2021). The exact rates of hospitalisation and severe disease are challenging to measure due to regional variation in the threshold for screening for SARS-CoV-2, diagnostic criteria and hospital resources that are available. Presence of pre-existing health condition/s, such as chronic respiratory or cardiovascular disease, in children with active SARS-CoV-2 infection increases risk of severe disease or paediatric intensive care unit (PICU) admission significantly (relative risk 1.79; 95% CI: 1.27–2.51) (Tsankov et al., 2021). Children infected with SARS-CoV-2 who do not develop PIMS-TS are less likely to require PICU than those who do (Tripathi et al., 2021). In developed countries, COVID-19 was responsible for a mean 0.48% of all-cause deaths in children between 1 March 2020 and 1 February 2021 (Bhopal et al., 2021).

### 2.1 | Respiratory manifestations

Of all children with COVID-19, 54% have had signs of upper respiratory tract infection and 25% have lower respiratory infection (Götzinger et al., 2020). Of children that require hospitalisation, cough (39%; Swann et al., 2020) and shortness of breath (30%; Swann et al., 2020) are common presenting symptoms. Just 3.8% of those hospitalised have severe pneumonia (Wu et al., 2020c). The majority of children with respiratory manifestations of SARS-CoV-2 infection have been found to have pathognomonic features on chest CT, which is classically a ground-glass appearance of the lungs (Li et al., 2020a,b).

### 2.2 | Gastrointestinal morbidity following SARS-CoV-2 infection

It is estimated that 20% of lymphocytes are found in the gut (Ganusov & De Boer, 2007), and given the relatively high expression of viral entry mediating proteins for SARS-CoV-2 in the epithelium of the distal gastrointestinal tract (Lee et al., 2020), it is not surprising that gastrointestinal symptoms are common in both adults and children with COVID-19. Of those with COVID-19, up to 50.5% of adults and 22% of children have at least one gastrointestinal symptom such as loss of appetite, diarrhoea, vomiting or abdominal pain (Götzinger et al., 2020; Pan et al., 2020). A higher mean viral load in the nasopharynx 10 days after symptom onset is associated with greater incidence of diarrhoea in SARS-CoV-1 infection (Cheng et al., 2004), with potential for SARS-CoV-2 having a similar correlation. There are a number

### New Findings

- **What is the topic of this review?**

A description of the current literature relating to COVID-19 infection in children and the associated inflammatory condition, paediatric multi-inflammatory syndrome temporally associated with SARS-CoV-2 (PIMS-TS).

- **What advances does it highlight?**

Children with SARS-CoV-2 infection have a distinct clinical phenotype when compared to adults. This may relate to relative differences in their adaptive immunity and in the degree and distribution of expression of the SARS-CoV-2 receptor (angiotensin-converting enzyme 2). There are several similarities between PIMS-TS, Kawasaki disease shock syndrome and other known inflammatory disorders such as macrophage activation syndrome. Few data are available to date regarding vaccination responses of children against COVID-19.

of reports of appendicitis-type presentations in children that have COVID-19 (Malhotra et al., 2021; Tullie et al., 2020). Appendicitis has previously been attributed to luminal obstruction secondary to mesenteric adenopathy (inflamed lymphoid tissue) and infection, but interestingly there is a potentially higher rupture rate in children with COVID-19 (Bhangu et al., 2015; Malhotra et al., 2021).

In as many as 80% of children that have COVID-19, rectal swab PCR tests are positive after nasopharyngeal swabs begin to test negative. This persists in 31% at 2 weeks (De Ioris et al., 2020), continuing for a mean 28 days in asymptomatic children and 31 days in symptomatic children (Cai et al., 2020). It is unclear whether these detections represent viable virus or remnants of detectable RNA. In adults, viable virus may be isolated between 7 and 15 days after an initial positive nasopharyngeal PCR test (Murata et al., 2021). This is correlated with a cycle threshold ( $C_t$ ) of 24.6 (IQR: 20.4–25.8) (Murata et al., 2021). The  $C_t$  indicates the number of PCR amplification cycles required for detection of viral RNA. In this case, the  $C_t$  is significantly lower than typical diagnostic thresholds for SARS-CoV-2.

### 2.3 | Acute neurological manifestations of SARS-CoV-2

Acute neurological disease in children with SARS-CoV-2 fortunately appears to be uncommon. Case series describe encephalitis in SARS-CoV-2 PCR positive infants under 3 months of age having hypotonia

and drowsiness in the absence of an alternative central nervous system infection (Nathan et al., 2020). Reported findings on neuroimaging include acute disseminated encephalomyelitis (ADEM) like changes and myelitis (Lindan et al., 2021). ADEM is a serious disorder in which children may present with altered conscious state and coordination problems after a preceding infection, usually of the upper respiratory tract (Menge et al., 2005). In some children that have COVID-19, enhancement of the cranial nerves has been identified, but this does not always correlate with a neurological deficit (Lindan et al., 2021).

In children with PIMS-TS the picture is more concerning, with up to 22% having neurological involvement (LaRovere et al., 2021). Of these, 12% have life-threatening neurological problems including severe encephalopathy, stroke, ADEM, acute fulminant cerebral oedema and Guillain-Barré syndrome (LaRovere et al., 2021).

### 3 | POSSIBLE MECHANISMS OF DISTINCT COVID-19 PRESENTATIONS IN CHILDREN

#### 3.1 | Viral entry mediating proteins

Spike protein is one of four structural proteins found in SARS-CoV-2. This protein mediates entry of coronavirus into host cells in the airway as it contains a receptor-binding domain that recognises angiotensin-converting enzyme 2 (ACE-2), a type I membrane protein (Shang et al., 2020; Zhao et al., 2020). ACE-2 is expressed predominantly in the respiratory tract but also the heart, gut, neurons, prostate, testes, bladder and kidneys (Donoghue et al., 2000; Muus et al., 2021; Penninger et al., 2021; Zubair et al., 2020). The affinity of the virus for ACE-2 is much higher than previously studied human coronaviruses (Wu et al., 2020b). The nasal epithelium is the site of greatest expression of ACE-2 in the respiratory tract with a decreasing gradient down to the peripheral lung (Hou et al., 2020). The expression of nasal epithelium and alveolar type 2 cell ACE-2 increases with age in humans (Bunyavanich et al., 2020; Muus et al., 2021). The downstream signalling cascade of ACE-2 expression, incorporating angiotensins 1–7, results in anti-inflammatory effects (Benter et al., 2008; Khajjah et al., 2016). Lower ACE-2 expression in children might thus plausibly account for the lower prevalence and severity of COVID-19 related disease in children when compared to that in adults.

Transmembrane protease, serine 2 (TMPRSS2) is co-expressed alongside ACE-2. It primes the spike protein and hence facilitates, but is not essential to, entry of SARS-CoV-2 into host cells (Hoffmann et al., 2020; Tao et al., 2021). There is conflicting evidence as to whether, like ACE-2, TMPRSS2 expression differs with age (Bunyavanich et al., 2020; Li et al., 2018; Muus et al., 2021; Saheb Sharif-Askari et al., 2020). One group identified that TMPRSS2 was lower in both the nasal and the bronchial airways in children compared to adults, and was more highly expressed in patients that had asthma or smoked (Saheb Sharif-Askari et al., 2020). In mouse models, expression of ACE-2<sup>+</sup>TMPRSS2<sup>+</sup> cells increases between 2 and 4 months of age, supporting this conclusion (Muus et al., 2021). Reduced TMPRSS expression in children has thus

been suggested as contributing to the fact that severe COVID-19 is less prevalent in this age group (Schuler et al., 2021).

Within the cleavage site of the S-protein is a cleavage site for furin, a protease enzyme. The presence of this site is unique in SARS-CoV-2 and not present in other coronaviruses of similar phylogenetic lineage, hence speculated to be a reason for its high infectivity (Wu et al., 2020a). Inactivation of this enzyme results in reduced viral replication in human respiratory cells (Johnson et al., 2021). There has been one small study comparing adult and paediatric lung biopsy samples for the measurement of furin expression (Tao et al., 2021). Whilst there appears to be greater expression of furin in the lungs of children compared to adults, the data did not reach statistical significance (Tao et al., 2021). Circulating furin is greater in children that are overweight or obese compared to children with low-to-normal weight, a potential reason that obese children are more likely to have severe COVID-19 (Svärd et al., 2021; Tsankov et al., 2021).

#### 3.2 | A highly responsive immune system

Children have a strong innate immune system, due to the time taken to develop adaptive immunity. Newborns have a high concentration of maternally derived IgG antibodies but this declines over the first 6 months of life (Bayram et al., 2019). Concurrently IgA in infants increases, with breast milk being a key source of this antibody (Bayram et al., 2019). CD4<sup>+</sup> T cells are white blood cells matured in the thymus that have a CD4 co-receptor which assists these cells to communicate with antigen presenting cells. From birth, CD4<sup>+</sup> T cells decline from 52% of total lymphocytes to 41% in adolescence (Shearer et al., 2003). Regulatory T cells comprise 30–40% of CD4<sup>+</sup> cells in paediatric tissue but this proportion declines to 1–10% in adulthood (Thome et al., 2016). Regulatory T cells have key roles in identifying cells that belong to an individual's immune system versus a potential pathogen (self vs. non-self) (Vignali et al., 2008). This overall composition makes children well suited to responding to viral infection, whilst limiting maladaptive inflammatory processes (Vignali et al., 2008).

Interesting comparisons have been made between children hospitalised with respiratory syncytial virus (RSV), one of the commonest respiratory infections of childhood and COVID-19 pneumonia. Children that have COVID-19 have greater total circulating CD3<sup>+</sup>8<sup>+</sup> lymphocytes, and a greater proportion of CD3<sup>+</sup> and CD3<sup>+</sup>8<sup>+</sup> lymphocytes than those that have RSV (Li et al., 2020a). CD3<sup>+</sup>8<sup>+</sup> lymphocytes are also referred to as cytotoxic T-cells, as they are able to kill infected cells once activated and hence are central to the adaptive immune response. The CD8<sup>+</sup> T cell response may signify the virus is a more severe infection due to the proportionate increase in host response. There is an established correlation between disease severity and increased lymphocytes and reduced neutrophils (Wu et al., 2020c; Stephenson et al., 2021).

Cytokines are small proteins produced by cells that are important for cell signalling. They include the interleukins (IL), tumour necrosis factors (TNF), and interferons (IFN). Serum IL-10 is found in lower concentration in children that have SARS-CoV-2 pneumonia than RSV

pneumonia (Li et al., 2020a). Whilst this is an anti-inflammatory cytokine, it is produced alongside pro-inflammatory cytokines in response to infection potentially preventing harm to the host (Saraiva & O'Garra, 2010). Pro-inflammatory cytokines including IL-2, IL-4, IL-6, TNF- $\alpha$  and IFN- $\gamma$  are found at similar concentrations (Li et al., 2020a). This suggests that there is impaired efficacy of immune regulators including regulatory T cells in maintaining this balance (Asseman et al., 1999).

By 12 years of age children have had a mean 21.9 (SD 9.0) episodes of respiratory infection (Grüber et al., 2008). This frequent exposure to respiratory pathogens, most of which are viral in origin (Drummond et al., 2000), primes the immune system to respond to environmental pathogens (Aranburu et al., 2017). Cross-immune responses have been identified between viral respiratory pathogens such as RSV and human parainfluenza virus, and occur more strongly with closely related serotypes (Bhattacharyya et al., 2015). Prior to 2019, coronavirus infection was common in the community, being responsible for many cases of 'the common cold' (McIntosh et al., 1970). Hence, children may have a greater degree of cross-immunity to SARS-CoV-2.

Dendritic cells are antigen presenting cells that can activate T cells to undertake their specialised functions (Patente et al., 2019), whilst natural killer (NK) cells are white blood cells that are able to trigger the death of cells that are under stress without requiring involvement of the adaptive immune system (Paul & Lal, 2017). Children that have mild SARS-CoV-2 infection have reduced levels of dendritic and natural killer cells in the acute phase of their illness whilst this is not the case in adults (Neeland et al., 2021). This is thought to be due to these cells migrating to the site of infection, in keeping with the increases in dendritic cells, NK cells and expression of TNF, IL-12 and IL-23 in the lungs of adults that have COVID-19 (Liao et al., 2020; Stephenson et al., 2021; Tang et al., 2011).

Exploration of other inflammatory mediators in children remains of interest. Circulating concentrations of macrophage inflammatory protein-1 $\beta$  (MIP-1 $\beta$ ), C-X-C motif chemokine ligand 10 (CXCL10), IL-7 and IL-1 $\alpha$  in adults correlate with COVID-19 disease severity and are consistent with monocyte and NK cell recruitment and T cell activity (Stephenson et al., 2021). The drug anakinra is an IL-1 receptor antagonist which was trialled in adults with COVID-19 pneumonia but did not change outcome in mild to moderate disease (Tharaux et al., 2021). Children in the second stage intervention phase of the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial are also being randomised to anakinra treatment as well as tocilizumab, an IL-6 blocker (Nuffield Department of Population Health University of Oxford, 2021). Further understanding of the inflammatory profile in children, taking into account the variable expression of cytokines across bodily compartments (Stephenson et al., 2021), is key to unlocking novel therapeutic options.

### 3.3 | Composition of the gastrointestinal microbiota

The microbiota refers to the community of micro-organisms present in an environment. In the last decade advances have been

made in understanding that the gut microbiota and immune system have close interaction, with the adaptive immune system regulating microbiota composition and diversity (Zhang et al., 2015). The composition of the gastrointestinal microbiota is altered in adult patients that have COVID-19 compared to healthy controls, with reduced commensals such as *Faecalibacterium prausnitzii*, *Eubacterium rectale* and bifidobacteria up to 30 days following disease resolution (Yeoh et al., 2021). These organisms are likely to have important roles in immune modulation given their reduced abundance in problems such as inflammatory bowel disease (Matsuoka & Kanai, 2015). There are not yet any reports relating to the paediatric microbiome in COVID-19 (Yamamoto et al., 2021). There are well established changes that occur in the microbiome throughout childhood, which correlate with the transition from breast feeding to solid food intake (Milani et al., 2017; Stewart et al., 2018). The links between age, gastrointestinal microbiota and illness severity may aid the explanation of children's presentations in the setting of COVID-19.

## 4 | PIMS-TS PROFILING AND COMPARISONS TO KNOWN INFLAMMATORY CONDITIONS

The definition of PIMS-TS by the Royal College of Paediatrics & Child Health (2020) (Figure 1) is similar to the post-COVID-19 inflammatory syndrome descriptions by the Centers for Disease Control & Prevention (2020) and World Health Organisation (2020). The common criteria are previous exposure to SARS-CoV-2, that the disorder is a diagnosis of exclusion, and the presence of a range of inflammatory symptoms. The median age of onset is 8.3–11 years (Davies et al., 2020), and the condition occurs more frequently in boys (Davies et al., 2020; Dufort et al., 2020; Feldstein et al., 2020; Whittaker et al., 2020). Common presenting symptoms are fever (90.6–100%) (Davies et al., 2020; Tripathi et al., 2021), tachycardia (97%) (Dufort et al., 2020), gastrointestinal symptoms (80–98%) (Davies et al., 2020; Dufort et al., 2020; Penner et al., 2021) such as vomiting, abdominal pain and diarrhoea, rash (52–60%) (Dufort et al., 2020; Tripathi et al., 2021; Whittaker et al., 2020), neurological abnormalities (52%) (Penner et al., 2021), conjunctival injection (45–56%) (Dufort et al., 2020; Whittaker et al., 2020) altered cardiac function (33%) (Penner et al., 2021) and mucosal changes (27%) (Dufort et al., 2020). These symptoms classically appear 4–6 weeks after SARS-CoV-2 infection (Consiglio et al., 2020).

### 4.1 | Comparisons of PIMS-TS with Kawasaki disease

PIMS-TS has many similarities to Kawasaki disease (KD), a medium-vessel vasculitis seen not infrequently by paediatricians, which can in rare cases cause a shock syndrome (Kanegaye et al., 2009). The exact aetiology of KD is unclear, but is likely an infectious trigger with pre-2019 human coronaviruses being among the pathogens previously investigated (Esper et al., 2005).

Criteria 1: Features	Criteria 2: Diagnosis of exclusion	Criteria 3: Confirmatory testing not required
<ul style="list-style-type: none"> <li>A child presenting with persistent fever, inflammation (neutrophilia, elevated CRP and lymphopaenia) and evidence of single or multi-organ dysfunction (shock, cardiac, respiratory, renal, gastrointestinal or neurological disorder)... this may include children fulfilling full or partial criteria for Kawasaki disease</li> </ul>	<ul style="list-style-type: none"> <li>Exclusion of any other microbial cause, including bacterial sepsis, staphylococcal or streptococcal shock syndromes, infections associated with myocarditis such as enterovirus</li> </ul>	<ul style="list-style-type: none"> <li>SARS-CoV-2 PCR testing may be positive or negative</li> </ul>

**FIGURE 1** RCPCH case definition of PIMS-TS

**TABLE 1** Comparison of PIMS-TS with Kawasaki disease shock syndrome

Characteristic	PIMS-TS	Kawasaki disease shock syndrome
Age of onset (mean/median)	8.3–11 years	2.8–3.8 years
Comorbidity	17–33.3%	Unconfirmed
Ethnicity	More frequent in Black, Hispanic and ethnic minority populations	More frequent in Chinese, Hispanic, Taiwanese and Japanese populations
Coronary artery abnormality	9–14%	62–77.8%
Need for inotropes or vasopressors	47–83%	54%
Need for extra-corporeal membrane oxygenation	2.9–4%	Case reports only
Mortality	2–4.7%	6.8%
References	Davies et al. (2020), Dufort et al. (2020), Feldstein et al. (2020), Penner et al. (2021), Tripathi et al. (2021), Whittaker et al. (2020)	Best et al. (2017), Chen et al. (2015), Cohen et al. (2012), Gamez-Gonzalez et al. (2018), Kanegaye et al. (2009), Li et al. (2019, 2020a), McCrindle et al. (2017), Whittaker et al. (2020)

Subtypes of PIMS-TS have been described, relating to the similarity of presentation to Kawasaki disease shock syndrome (KDSS) (Whittaker et al., 2020). It is rare that KD manifests as shock, with this occurring in as few as 1.45–7% of diagnoses (Kanegaye et al., 2009; Lin et al., 2013). Those patients that do develop KDSS have a number of similar features to PIMS-TS (Table 1), but the exact mechanism causing transition into the shocked state is unknown (Kanegaye et al., 2009). When children with KDSS are assessed with echocardiography they frequently have impaired left ventricular systolic function and dilated coronary arteries, suggesting their shocked state primarily relates to cardiac contractility rather than the filling or tone of the peripheral vasculature (Kanegaye et al., 2009).

In KD, IL-17A is increased, whilst this is not the case in PIMS-TS (Consiglio et al., 2020). IL-17A expression is increased in autoimmune disease such as multiple sclerosis and rheumatoid arthritis (Iwakura et al., 2008), and although it has functions in immune defence its role in mediation in autoimmune disease is not fully understood (Monin & Gaffen, 2018).

Interestingly, there has been a fall in the number of children receiving a diagnosis of KD (Bailey et al., 2021), which could reflect reclassification of cases as PIMS-TS, or a true reduction of cases possibly due to reduced transmission of other pathogens that contribute to KD due to social distancing measures.

## 4.2 | Inflammatory syndromes

The 'cytokine storm' produced by PIMS-TS has similarities with a number of other conditions including haemophagocytic lymphohistiocytosis (HLH), macrophage activation syndrome (MAS), toxic shock syndrome and sepsis (Feldstein et al., 2020). HLH and MAS are both rare life-threatening multisystemic problems, although MAS most commonly occurs in children with systemic juvenile idiopathic arthritis. In both conditions patients commonly experience high fever, enlargement of the lymph nodes, liver and spleen, and bleeding problems (Bracaglia et al., 2017; Janka, 1983). Toxic shock syndrome



Inflammatory syndrome	Haemophagocytic lymphohistiocytosis	Macrophage activation syndrome	Kawasaki disease	PIMS-TS	Sepsis
<b>Immune mediators</b>	IL-2, IL-2RA, IL-4, IL-6, IL-10	CXCL9, M-CSF, IL-18, S100 protein	G-CSF, IL-6, IL-8, IL-10, IL-17, IL-17A, IFN- $\gamma$ , MCP-1, sIL-2RA, TNF- $\alpha$	CXCL9, IL-1 $\beta$ , IL-8, IL-10, IL-17, TNF- $\alpha$ , IFN- $\gamma$	IL-6, IL-10, IFN- $\gamma$ , TNF
<b>Haematological changes</b>	Cytopaenia Abnormal coagulation Reduced NK cell activity	Anaemia Thrombocytopaenia	Neutrophilia Lymphopaenia Thrombocytopaenia	Neutrophilia Lymphopaenia	Neutrophilia or neutropaenia Lymphopaenia
<b>Inflammatory markers</b>	D-Dimer + Ferritin ++ Fibrinogen - Triglycerides +	D-Dimer + ESR + LDH + Ferritin ++ Fibrinogen - Triglycerides +	C-Reactive protein + ESR +	C-Reactive protein ++ D-Dimer + Ferritin + pro-BNP ++ hs-Troponin ++	C-reactive protein ++ Procalcitonin ++
References	(Tang <i>et al.</i> , 2008; Lehmborg <i>et al.</i> , 2015)	(Maruyama & Inokuma, 2010; Minoia <i>et al.</i> , 2014; Rodriguez-Smith <i>et al.</i> , 2021)	(Abe, 2014; Chen <i>et al.</i> , 2015; Gamez-Gonzalez <i>et al.</i> , 2018; Li <i>et al.</i> , 2019)	(Waltuch <i>et al.</i> , 2020; Whittaker <i>et al.</i> , 2020; Dufort <i>et al.</i> , 2020; Consiglio <i>et al.</i> , 2020; Tripathi <i>et al.</i> , 2021; Aguilera-Alonso <i>et al.</i> , 2021; Rodriguez-Smith <i>et al.</i> , 2021)	(Doughty <i>et al.</i> , 1998; Hatherill <i>et al.</i> , 2000; Remy <i>et al.</i> , 2018)
<b>Contribution to inflammatory response</b>					

**FIGURE 2** Profiles (Tang *et al.*, 2008) of inflammatory (Lang *et al.*, 2021) diseases in children (adapted from Canna & Behrens, 2012). BNP, brain natriuretic peptide; CSF, colony stimulating factor; ESR, eosinophil sedimentation rate; IFN, interferon; IL, interleukin; LDH, lactate dehydrogenase; M-CSF, macrophage colony stimulating factor; MCP, monocyte chemoattractant protein; PIMS-TS, paediatric multi-inflammatory syndrome temporally associated with SARS-CoV-2; RA, receptor antagonist; TNF, tumour necrosis factor; -, decreased; +, increased; ++, significantly increased

occurs after toxins are released from an antecedent infection or retained tampon, typically by *Staphylococcus aureus* or *Streptococcus pyogenes*.

This spectrum of the role of the host versus infection has previously been conceptualised, with problems such as HLH and MAS being predominantly related to the host, but increasing infection related inflammation in problems such as KD and sepsis (Figure 2) (Canna & Behrens, 2012). Where PIMS-TS sits within this spectrum is still being established and this information is of significance given it provides insight into potential therapeutic targets.

### 4.3 | Profiling of PIMS-TS

Whilst case definitions of PIMS-TS do not require confirmation of previous or current SARS-CoV-2 infection, up to 68–87% of patients with PIMS-TS have detectable IgG against SARS-CoV-2 when measured using a combination of S/N protein and receptor binding domain or N protein based enzyme-linked immunosorbent assay alone (Carter *et al.*, 2020; Whittaker *et al.*, 2020). Of children that have detectable SARS-

CoV-2 IgG antibodies during hospital admission for PIMS-TS, 90% will remain detectable at 6 months (Penner *et al.*, 2021). Seropositivity of patients with PIMS-TS is associated with greater incidence of coronary aneurysms, worse cardiac function and increased prevalence of gastrointestinal symptoms (Carter *et al.*, 2020).

The significant cytokine surge occurring in children with PIMS-TS is distinct from the lesser cytokine release in adults who have COVID-19 (Wilson *et al.*, 2020). PIMS-TS is associated with higher proportion of highly differentiated CD4<sup>+</sup> T cells (Consiglio *et al.*, 2020); CD4<sup>-</sup> T cells and particularly CD8<sup>+</sup> cells are lower than in those children that have mild SARS-CoV-2 infection (Consiglio *et al.*, 2020).

## 5 | NEUROLOGICAL AND LONGITUDINAL OUTCOMES IN CHILDREN FOLLOWING SARS-CoV-2 RELATED ILLNESS

The long term impacts of SARS-CoV-2 in adults include dyspnoea and chest pain, fatigue, sleep difficulties, arthralgia, anxiety and depression, and cognitive disturbance (Huang *et al.*, 2021; Nalbandian *et al.*, 2021).

At 6 months from disease onset, as many as 76% of adults that have had COVID-19 continue to experience at least one symptom (Huang et al., 2021).

In children, there are limited data on the chronic impacts of infection. Of children that had positive SARS-CoV-2 tests in an observational study in Melbourne, Australia, 8% had post-acute symptoms at 3–6 months (Say et al., 2021). This only included children that were initially symptomatic. Post-acute symptoms included cough (50%), fatigue (25%), both cough and fatigue (8%), or persistent inflammation related problems (17%) (Say et al., 2021).

Of patients with PIMS-TS, the majority (96%) of children have normalisation of findings on echocardiography, and 98% have resolution of gastrointestinal symptoms (Penner et al., 2021). The most prevalent longstanding symptom is minor abnormalities on neurological examination, which is present in 39% of children at 6 months, although this results in minimal functional impairment (Penner et al., 2021). The most common neurological abnormalities are proximal myopathy or limb weakness, dysmetria and abnormal eye movements (Penner et al., 2021).

These neurological changes may relate to viral neuro-invasion and mechanisms such as trans-synaptic and blood–brain barrier spread following entry via the olfactory nerve (Zubair et al., 2020).

## 6 | VACCINATION

The role of children in the transmission of SARS-CoV-2 has been heavily debated and has impacted on government social distancing policies. Although COVID-19 vaccinations are not yet being offered routinely to people aged <18 years in the UK, 47.7% are estimated to have detectable antibodies (Office for National Statistics, 2021). Children that have minimal or no symptoms of COVID-19 maintain seropositivity for at least 6 months, with no statistically significant difference compared to SARS-CoV-2 positive adults (Toh et al., 2021). The secondary attack rate within households is lower in children than adults (0.15 (95% CI: 0.05–0.27) vs. 0.38 (95% CI: 0.32–0.45) (Galow et al., 2021). This finding was based on a SARS-CoV-2 PCR positive member of the household, with the serology status of the majority (88%) of the household being known (Galow et al., 2021). Children appear to be less likely to test positive for SARS-CoV-2 if asymptomatic than adults, with asymptomatic carriage estimated at 54.6% (Allan-Blitz et al., 2021; Milani et al., 2021).

SARS-CoV-2 vaccinations have now been licensed for use in children aged 12 years and above in the USA (Pfizer, 2021a). Peer review publications are not yet available; with data provided by companies submitted for emergency authorisation, however, this has been endorsed by the Centers for Disease Control & Prevention (2021).

Following two doses of the Pfizer-BioNTech mRNA BNT162b2 vaccine, it is reported that 100% of children aged 12–15 years have a neutralising antibody response to SARS-CoV-2 at 1 month following completed vaccination (Pfizer, 2021b). There is ongoing data collection for children aged between 6 months and 11 years (Pfizer, 2021a). On 25 May 2021, Moderna Inc. published a press release advising that its

phase 2/3 study of two-dose administration of mRNA-1273 vaccine in 12–18 year adolescents had 93% efficacy in preventing SARS-CoV-2 infection after 14 days (Moderna, 2021).

The Oxford ChAdOx1 vaccine trial cohort inclusive of 300 children aged 6–17 years is ongoing as of June 2021, following a delay that occurred after investigation by the Medicines and Healthcare products regulatory agency for the association with venous thrombosis in adults (University of Oxford, 2021).

Children of Black, Hispanic and Asian ethnicity are more likely to test positive when screened for SARS-CoV-2 on a population level, and hence these groups should be prioritised in any vaccination program (Bailey et al., 2021).

## 7 | CONCLUSION

Children may have severe illness secondary to SARS-CoV-2, but this is an infrequent occurrence, and their overall mortality is low. An understanding of why only some children develop severe symptoms in SARS-CoV-2 and why this is distinct from adult presentations of COVID-19 could assist our development of potential therapies and disease prevention strategies.

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## COMPETING INTERESTS

None.

## AUTHOR CONTRIBUTIONS

Both authors contributed to the content of this review including conceptualisation, review of papers and preparation of this manuscript. Both authors have read and approved the final version of this manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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