COVID-19 in children: what did we learn from the first wave?

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Abstract

A pandemic caused by the novel coronavirus, severe acute respiratory syndrome - coronavirus 2 (SARS-CoV-2), has caused high rates of mortality, predominantly in adults. Children are significantly less affected by SARS-CoV-2 with far lower rates of recorded infections in children compared to adults, milder symptoms in the majority of children and very low mortality rates. A suspected late manifestation of the disease, paediatric inflammatory multisystem syndrome - temporally associated with SARS-CoV-2 (PIMS-TS), has been seen in small numbers of children and has a more severe disease course than acute SARS-CoV-2. The pandemic has meant that children around the world have been kept off school, isolated from their extended family and friends and asked to stay inside. The UK has been declared as being in an economic recession and unemployment rates are increasing. These indirect effects of SARS-CoV-2 are likely to have a significant impact on many children for years to come. Consolidating the knowledge that has accumulated during the first wave of this pandemic is essential for recognising the clinical signs, symptoms and effective treatment strategies for children; identifying children who may be at increased risk of severe SARS-CoV-2 infection; planning the safe delivery of healthcare and non-health related services that are important for childrens' wellbeing; and engaging in, and developing, research to address the things that are not yet known. This article summarises the evidence that has emerged from the early phase of the pandemic and offers an overview for those looking after children or planning services.

Keywords acute respiratory distress syndrome; children; COVID-19; PIMS-TS; viral transmission

Introduction

Severe Acute Respiratory Syndrome - Coronavirus 2 (SARS-CoV-2) has, up to the 10th Aug, 2020, caused nearly 19.6 million infections and 727,000 deaths worldwide.[1] This impact has largely been on adults. But what of children? Although not the face of the COVID-19 pandemic, they have been an important part of the story. Now is the time to consider what was learnt during the first wave, to prepare for any future wave(s) and to ensure that children are prioritised in this "new normal" as soon and safely as possible. With this in mind, we aim to discuss evidence, dilemmas, and theories, around COVID-19 in children.

What is the SARS-CoV2 virus, and how does it cause infections?

SARS-CoV-2 is a novel coronavirus, first isolated from patients with pneumonia in Wuhan, China, in late 2019. Of hundreds of coronaviruses, only seven are known to cause disease in humans; four seasonal coronaviruses (NL63, HKU1, OC43 and E229), Severe Acute Respiratory Syndrome (SARS-CoV), Middle East Respiratory Syndrome (MERS), and SARS-CoV-2. SARS-CoV-2 is carried in the respiratory tract of infected people and spread during speech and coughing. In droplet form, the virus remains viable and infectious for several hours.[2] Transmission occurs through either aerosol inhalation or transfer from a contaminated surface to the mouth. In order to develop an infection, the infectious dose and the viral load are important — if we think of the infection as a bonfire, the infectious dose (the number of particles needed to start an infection) is the size of the spark needed to light the fire and the subsequent viral load (the amount of virus that someone is carrying) is how big the bonfire (or severe the infection) is.

Coronaviruses take their name from spikes covering their surface, which aid entry into host cells. Using these spike-proteins, SARS-CoV-2 are thought to interact with Angiotensin Converting Enzyme 2 receptors (ACE2-r), expressed on the outer membrane of host cells in various tissues, particularly alveolar epithelial cells, the endothelium and the intestinal epithelium.[3] It is unclear what role, if any, the levels of soluble ACE2 play in host susceptibility to coronaviruses, and if ACE2 represents the only cell receptor used by SARS-CoV2.

Why does COVID-19 affect children less than adults?

Worldwide, children constitute only 2% of recorded infections.[4,5] When children have had contact with people infected with COVID-19 they are probably less likely to contract the infection compared to adults.[6–8] Furthermore, they are far less likely to develop clinical symptoms, and severe illness is rare.[9,10] It is not yet clear why this is the case, particularly when viral respiratory illnesses typically affect children more commonly than healthy adults and Influenza virus is associated with a more severe course in young children.[11] The replication dynamics of SARS-CoV-2 are poorly described, but viral load in symptomatic patients is very high, and is higher in older patients,[12] which may in part account for the disease severity in the elderly. Children are also likely to have other viruses in their upper respiratory tract, and interactions and competition with SARS-CoV-2 may dampen its ability to cause infection.[13]

ACE2-r may hold some of the answers. Like SARS-CoV-2, SARS-CoV uses the ACE2-r to enter cells and it has been shown that undifferentiated cells (which express lower levels of the ACE2-r) are less likely to be infected with the virus.[14] Children have significantly lower levels of ACE2-r than adults in their nasal epithelium,[15] and this may make them less susceptible to infection.

The immune system varies with age,[16] both in its composition and response to viruses. It is likely that the immune systems of babies, older children, and adults differ in response to SARS-CoV-2. Some differences might reflect the ability to protect against the virus, whereas others might relate to the more harmful effects of the immune response to infection. Previous exposure to seasonal coronavirus may also provide a level of protection through cross-reactive T-cell epitopes against SARS-CoV-2.[17]

How do you test for COVID-19?

Testing for COVID-19 can assess for either acute or previous infection, to detect early and late manifestations of the disease. For acute infection, reverse transcriptase polymerase chain reaction (RT-PCR) is used, and is most accurate when performed on a nasopharyngeal sample. Factors that affect the accuracy of testing include the quality of sample, stage of disease, and viral load in

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the patient.[18] Overall, RT-PCR for SARS-CoV-2 has a high specificity of 95% but a lower sensitivity of approximately 70%.[18,19]

Detection of recent or previous infection is undertaken using serological testing for IgG and IgM. Depending on the type and timing of test, the sensitivity varies from 66% to 97.8%, and the specificity from 96.6% to 99.7%.[20]

Knowing whether someone is currently, or has recently been, infected by COVID-19 is useful, but it does not determine whether someone who tests positive is shedding live virus. Whilst viral replication stops 5–7 days after the onset of symptoms, patients can remain RNA-positive for up to a fortnight afterwards.[21] The results of the tests should therefore be taken within the context of the patient's presenting features and the community prevalence of COVID-19.

What are the clinical, laboratory and radiological features of acute COVID-19 in children?

The commonest acute presenting features in children with COVID-19 are fever, cough, lethargy, coryzal symptoms, and shortness of breath.[10] In the International Severe Acute Respiratory and emergency Infections Consortium WHO Clinical Characterisation Protocol UK (ISARIC WHO CCP-UK) a distinct cluster of muco-enteric symptoms (including abdominal pain, vomiting, diarrhoea, conjunctivitis and rash) was noted in the paediatric population.[10] Around 10% of hospitalized children with COVID-19 have an additional infective diagnosis such as urinary tract infection, appendicitis and sepsis.[22]

Laboratory features of acute COVID-19 are variable and a significant proportion of children have normal investigations. Lymphopaenia, elevated inflammatory markers including C Reactive Protein (CRP) and procalcitonin have been documented but are by no means universal.[23,24] Many Chinese children suspected of having COVID-19 underwent Computed Tomography (CT) of the thorax. The radiological findings of subpleural lesions were strongly associated with SARS-CoV-2 infection, along with more general findings consistent with viral infection,[25] but performing a CT did not alter the management of the majority of these children.

When chest radiography has been performed in children with COVID-19 no specific features have been found to be diagnostic and therefore the indications for chest X-ray remain as they were before the pandemic. Children with COVID-19 who have radiological evidence of pneumonia are significantly more likely to require ICU admission.[26]

How does COVID-19 affect neonates?

Very few neonates have been reported to have COVID-19. The majority who have been infected have not required intensive care unit (ICU) admission, although compared to all children, age under 1 month is a risk factor for ICU admission.[26] Limited evidence suggests vertical transmission to neonates, whether intrauterine or perinatal, is possible but rare[27] and it is thought that the majority of infected neonates contracted COVID-19 after birth. Current literature does not suggest that SARS-CoV-2 can be transmitted through breast milk as no replicable virus has been identified.[28] The World Health Organisation has concluded that mothers with suspected or confirmed COVID-19 should not be separated from their infants and that they should be encouraged to initiate and continue breastfeeding.[29]

Is COVID-19 worse in children with pre-existing medical conditions?

Over 10% of English children in hospital with COVID-19 were diagnosed whilst an inpatient.[22] This may reflect increased levels of testing in hospital which can result in a high rate of false positive tests during periods of low to moderate prevalence and can detect infection in asymptomatic and pauci-symptomatic children who are admitted for an unrelated reason. However, it may also highlight children's increased susceptibility to infection during a hospital stay and requires further investigation. A North American Observational study of 48 children with COVID-19 who were admitted to ICU found that 86% had pre-existing co-morbidities. These included being medically complex (40%), immunosuppressed (23%), obese (15%) and diabetic (8%). Thirty six percent of children in this series required mechanical ventilation and the association of respiratory support with co-morbidity is unclear.[30]

It is likely that families with children with certain co-morbidities such as cancer have been actively shielding from an early stage of the pandemic. Early studies do not suggest that there is increased susceptibility to infection in many groups who were origionally asked to shield[31] but ongoing data collection about the impact of co-morbidity on the rate and severity of COVID-19 is needed to better elucidate any associations.

Treatment options

Most children with COVID-19 require only supportive therapy, with less than a quarter of hospitalized children requiring oxygen and very small numbers requiring ventilatory support.[22,26,32] However, a small number of children do become severely unwell with COVID-19 and require specialist therapies. The therapeutic options have been assessed primarily in adult patients with severe COVID-19 as the numbers of children with severe COVID-19 are so small.

Adult literature currently shows that the most effective agent for reducing mortality in critically unwell adults with acute COVID-19 is dexamethasone.[33] This reduces 28 day mortality in adults requiring oxygen by 20% and in adults requiring ventilation by 33%. It shows no benefit in adults who have not required either of these therapies. Remdesivir, an anti-viral treatment, has been shown to reduce time to clinical improvement in adults and is available for use in children.[34]

How should respiratory failure from COVID-19 be managed?

As respiratory compromise is relatively unusual with COVID-19 in children, its presence should trigger consideration of its cause.

- COVID-19 pneumonia leads to patchy areas of consolidation, which reduce lung capacity.
- High levels of inflammation are damaging to lung parenchyma, this inflammation in the longer term could lead to

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lung fibrosis. The magnitude of this risk is currently uncertain. [35]

- COVID-19 infection is associated with anxiety.[36] This can lead to tachypnoea, which in itself can be damaging to lungs and causes fatigue of respiratory muscles.
- COVID-19 is a prothrombotic state,[37] and in a child with disproportionately high oxygen requirement, a pulmonary embolism (or microthrombotic events) should be considered.

What is PIMS-TS?

PIMS-TS (Paediatric Inflammatory Multisystem Syndrome - Temporally Associated with SARS-CoV-2) is an emerging phenotype of illness that has been described in observational series from the UK, USA, Italy, France and Spain. Although definitions vary by country, the consistent features are inflammation and organ dysfunction in the absence of another clear cause. Presentation can overlap with acute COVID-19 illness, or be a delayed response up to six weeks later.[4,7,9]

The presentation of PIMS-TS is varied: some children present acutely unwell with features of shock, others with features consistent with complete or incomplete Kawasaki Disease, and others with more non-specific features.[38] Definitions, whether from the UK or US, include the presence of persistent fever at presentation. Abdominal pain is present in over 50% of children, along with hand and foot swelling, mucous membrane changes, non-purulent conjunctivitis, rash and gastrointestinal disturbance.[38] A proposed list of investigations is presented in Table 1.[39]

Therapeutic options include intravenous immunoglobulin (IVIg), methylprednisolone and more targeted immune modulation including Anakinra, Tocilizumab and Infliximab.[39–42] In common with Kawasaki's disease a significant proportion of children may develop coronary artery aneurysms, making follow-up echocardiography essential.[39,43]

Investigations for patients with suspected PIMS-TS

Investigations	First line diagnostic tests to determine whether PIMS-TS is a possible diagnosis	Second line tests to differentiate PIMS-TS from other conditions and determine severity
Haematological	Full Blood Count	D-Dimer
Biochemical	C-Reactive Protein	Fibrinogen
	Liver function Tests	Lactate Dehydrogenase
	Urea, Creatinine and Electrolytes	Ferritin
		Troponin
		N-terminal pro-B-type natriuretic peptide
		Blood gas and lactate
Microbiological		SARS-CoV-2 RT-PCR and serology
		Septic and viral screen (lumbar puncture if specific indications)
Imaging and other		Chest Radiograph
		12 lead ECG
		Echocardiogram

Table 1

What do we know about COVID-19 in children in Low and Middle Income Countries?

Little is known about COVID-19 in Low and Middle Income Countries (LMICs) and issues with testing and reporting of cases has made tracking the spread and incidence of the disease difficult. At the time of writing, the African continent has reported 885,000 cases and 16,000 deaths with the majority of these in South Africa. India alone has reported 64,000 new cases in one day.[44]

The spread and severity of COVID-19 is expected be further exacerbated in LMICs by crowded living conditions, poor sanitation and difficult access to healthcare. The economic impact of enforced lockdown and social distancing has the potential to increase violence in areas already experiencing conflict, and violence against women and girls has been noted to increase since the beginning of the COVID-19 pandemic.[45] Food insecurity has been highlighted as a key area for concern by the World Bank.[46] It is extremely likely that the negative impact of COVID-19 on children in LMICs will be much greater than the impact of the virus itself.[47]

What is the impact of lockdown on children?

Lockdown causes deficiencies and inequity that may have a long-term effect on the wellbeing of children. It may particularly impact learning progress, socialising, friendship, play, romantic relationships and physical activity. In addition, children in lockdown experience an increase in both violence and addictive behaviours (e.g., junk food, alcohol, and other substances), and a decrease in positive factors related to health promotion (e.g., vaccination).[48,49] Concerns about the well-being of teenagers' mental health led to a review of child suicide rates during the pandemic. Whilst the numbers of deaths due to suicide were not statistically significantly increased compared to the previous year, themes around isolation and poor mental health were recognized as contributing factors for childhood suicide during the pandemic.[50]

Some have argued there may be potential benefits for certain groups of children, including more time to share with family and appreciation of the value of social responsibility for the protection of the most vulnerable. However, for many, and particularly the most vulnerable children in our society, the balance of harms and benefits of a lockdown, and particularly school closure, clearly points away from this being a positive experience for many children.

What COVID-19 research is happening in children?

There are several key differences in the way research studies have been organized and delivered regarding COVID-19 and paediatrics. In the UK, the National Institute of Health Research (NIHR) has produced a list of prioritized COVID-19 studies, to ensure that despite the reallocation of resources to support the clinical services that were most under stain from the first wave, there were clear research objectives.

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The prioritized studies that have been most relevant to the paediatric population have included the following:

- ISARIC-WHO: A tiered study that collects clinical and biological data on COVID-19 positive patients. Includes children and adults.
- BPSU study - Neonatal complications of coronavirus disease (COVID-19). A national surveillance study of babies born to mothers with COVID-19 and of neonates who develop COVID-19.
- DIAMONDS: A biomarker study examining both COVID-19 and other infectious/inflammatory illnesses. Includes children and adults.
- PRIEST (recruitment completed): An emergency department study collecting details of the presentation of suspected COVID-19 patients to improve triage.
- RECOVERY: An open label, multi-arm platform study, with randomisation to different treatment arms (or standard of care). It has evolved to include neonates and children, and now has a randomisation option for children with PIMS-TS which includes IVIg, steroids and supportive care in the first randomisation and Tocilizumab and standard care (which can include giving Anakinra or Infliximab) in the second randomisation.

The RECOVERY trial has been one of the most effective trials within the COVID-19 pandemic internationally. It has shown that hydroxychloroquine is ineffective[51] and that dexamethasone reduces mortality for individuals requiring oxygen, and particularly for ventilated patients.[33]

Enrolling children whenever possible into trials for both COVID-19 and PIMS-TS is essential. We have already seen with both ISARIC and the RECOVERY trial the impact that rapidly mobilized, actively recruited trials can have on the knowledge and treatment of a new condition. Adaptations to the RECOVERY trial now mean that children can be recruited to both phases, enabling high quality data collection within a trial whilst not removing the required multi-disciplinary team working that is essential for decision making about unwell children with severe acute COVID-19 and PIMS-TS.

Conclusion

The COVID-19 pandemic is predicted to come in waves and the well-being of children must be prioritized and protected. They have sacrificed their social and educational development during the first wave, and going forward the focus must be on safely but actively returning them to normality. As paediatricians, we must be alert to cases of PIMS-TS, and other unusual presentations, and enrol children into appropriate research studies. Last and not least, we have a duty to keep up to date with published literature so we can provide care that is as evidence-based as possible when we are presented with children who may have COVID-19. ◆

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