Review

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The impact of the COVID-19 pandemic on child health

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Abstract: Most Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infections in children are mild or asymptomatic. Severe Coronavirus Disease 2019 (COVID-19) in children is infrequent. An estimated 0.3–1.3% of children with SARS-CoV-2 infection were admitted to hospital, and of these 13–23% needed critical care. SARS-CoV-2 related deaths were very rare in children, estimated at 2 per million. The vast majority of admitted children had one of shortness of breath, fever, and cough, but atypical symptoms are more common in children. Cases of Multisystem Inflammatory Syndrome in Children (MIS-C) have been linked to SARS-CoV-2 infection. Cardinal symptoms include prolonged fever, clinical signs of inflammation, gastro-intestinal symptoms, and cardiac dysfunction. Twenty two to 80% of patients with MIS-C needed critical care; mortality of MIS-C is around 2%. Six to 24% of children with MIS-C had coronary artery dilatation or cardiac aneurysms. Equipose still exists between first-line treatment with immunoglobulins and steroids. Outcomes for children with MIS-C are generally very good in those recognised early and started on appropriate treatment. Vaccination schemes for children are rapidly expanding, with the benefits of preventing severe COVID-19 disease and MIS-C and reducing community transmission outweighing the risks of adverse events of, amongst others, myocarditis temporally related to COVID-19 vaccination in children and young adults. The imposed social distancing measures reduced the overall number of children with acute illness or injury presenting to urgent and emergency care facilities worldwide. No clear signal was seen that large numbers of

children had a delayed presentation to emergency care departments with a serious illness. The social distancing measures negatively impacted the mental health of children.

Keywords: child; child health; COVID-19; multisystem inflammatory syndrome in children (MIS-C); SARS-CoV-2; social distancing measures.

Introduction

Early data from China already signalled low numbers of children presenting to hospitals with severe respiratory illness during the initial Coronavirus Disease 2019 (COVID-19) outbreak [1]. Despite this, many health facilities dealing with acutely unwell children and young people prepared for potentially large numbers of unwell children infected with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Yet, this never materialised and quite the opposite was true with very few children presenting to urgent and emergency care facilities [2]. This review will cover topics related to SARS-CoV-2 infection in children and the wider impact of the COVID-19 pandemic on child health.

Children with COVID-19

The vast majority of SARS-CoV-2 infections in children are asymptomatic or mild [1, 3–6]. Testing strategies for SARS-CoV-2 varied between countries and in time [7], and hence it will be difficult to determine the true rate of children infected with SARS-CoV-2 developing more severe acute illness with the need of being admitted to hospital. A large-scale multinational cohort study, the CHARYBDIS study, using routinely collected data from the United States, Europe, and Asia found that 0.3–1.3% of children diagnosed with COVID-19 were admitted to hospital in the period between January and June 2020 [8]. Based on population seroprevalence studies from the United Kingdom (UK) this percentage might be as low as 100–400 per

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million children during the second phase of the COVID-19 pandemic [9–11].

Typical symptoms of fever (69%), cough (48%) and shortness of breath (23%) were present amongst hospitalised children 18 years and under who tested positive for SARS-CoV-2, according to data from the International Severe Acute Respiratory and emerging Infection Consortium (ISARIC), a prospective multinational observational study; with 85% of admitted children having at least one of these [12]. Atypical symptoms occurred more often in hospitalised children than adults. For example, children regularly present with gastro-intestinal features, including some serious conditions such as intussusception [13–19]. Additionally, studies reported up to 40% positive tests in children admitted without any COVID-19 disease related symptoms, mainly as a result of routine admission or pre-operative screening in the more recent stages of the pandemic [20–22]. In general, children and young people with severe neuro-disabilities, Down's Syndrome, underlying conditions resulting in immunosuppression, and children with learning disabilities were at higher risk for severe COVID-19 disease [4, 11].

In the UK data from the ISARIC cohort, 18% (116/632) of hospitalised children were admitted to critical care. This number was replicated in the study by the TBNet research group, with 13% (48/363) of hospitalised children needing critical care across European hospitals in early 2020 [3]. A study linking the UK National Child Mortality Database and Public Health England testing data identified children aged 18 years and under who died with a positive SARS-CoV-2 test between March 2020 and February 2021. In this study, a total of 3,105 childhood deaths were reported and, of these, 61 deaths (1.9%) tested positive for SARS-CoV-2; 25 of these were caused by SARS-CoV-2 with another three deaths related to Multisystem Inflammatory Syndrome in Children (MIS-C) temporally related to SARS-CoV-2 infection [23]. The 25 children who died of SARS-CoV-2 equate to a mortality rate of 2 per million children.

A recent increase in paediatric COVID-19 related hospital admissions in the United States (US) is believed to be related more to the high prevalence in the community of the SARS-CoV-2 Delta variant, and its increased ability for transmission, rather than an increase in severity [24, 25]. For example, in the COVID-NET study from the US that included data from over 250 acute-care US hospitals in 14 States, the median duration of admission of children was two days (IQR 1–4 days) for the period June 20th 2021 – July 31st 2021; and of these, 23.2% of admitted children needed critical care, and 1.8% died during hospitalisation [25]. There was no clear signal that admitted children during this period were more severely

unwell than the preceding period between March 1st 2020 and June 19th 2021.

MIS-C

Early in the COVID-19 pandemic, a new inflammatory condition was identified in children, occurring some 2–6 weeks after initial, often asymptomatic, SARS-CoV-2 infection, called the Multisystem Inflammatory Syndrome in Children (MIS-C) [26–32]. A year into the COVID-19 pandemic, cases of MIS-C have been described globally [33], and it is now believed that MIS-C is a true novel immunopathogenic illness [31, 34, 35]. Importantly, the incidence of MIS-C is rare: for example, between March 2020 and July 2020 there were a total of 449 cases of MIS-C in children aged <16 years in the UK [11]. Although children of all ages can be affected, it is more frequent in the adolescent age group [28]. Similarly, boys appear affected more often, as well as children from ethnic minorities and more deprived backgrounds, likely reflecting increased transmission and higher seroprevalence rates in these groups.

Case definitions of MIS-C were issued by the World Health Organisation (WHO), Center for Disease Control and Hygiene (CDC), and Royal College of Paediatrics and Child Health (RCPCH) in April – May 2020. These, although differing slightly (Table 1) [36–38], all included criteria of 1) persistent fever, 2) clinical signs and biochemical profiles reflecting ongoing inflammation, 3) multiorgan involvement including cardiac dysfunction, 4) the absence of other reasonable explanations of the acute illness, and 5) evidence of a preceding SARS-CoV-2 infection or exposure. Guidance was subsequently issued to support front-line clinicians in the early recognition and management of children at risk of MIS-C [39].

Typically, children with MIS-C present with prolonged fever, clinical signs of inflammation (e.g. conjunctivitis, rash, and oral mucosal changes), gastro-intestinal symptoms, and cardiac dysfunction [27, 28, 40]. Concerningly, 6–24% of children with MIS-C had coronary artery dilatation or cardiac aneurysms [33, 41–44]. MIS-C mimicking appendicitis [45] and other serious abdominal pathology [46] have been described, as well as children with neurological involvement [47].

Clinically, MIS-C can be difficult to differentiate from Kawasaki Disease, a childhood medium artery vasculitis, or Toxic Shock Syndrome [48, 49]. However, each of these diagnoses appear to have distinct biochemical patterns. Notably, children with MIS-C had higher white blood cell count, neutrophil count, ferritin and CRP, as well as more

Table 1: Three definitions of MIS-C.

	Population	Clinical signs and symptoms	Evidence of multiorgan involvement	Markers of inflammation	Evidence of other infections	Evidence of SARS-CoV-2 infection	Additional comments
World Health Organisation [38]	Children and adolescents 0–19 years	Fever > 3 days and two of the following: ^a – Rash or bilateral non-purulent conjunctivitis or muco-cutaneous inflammation signs (oral, hands or feet) – Hypotension or shock – Acute gastrointestinal problems (diarrhoea, vomiting, or abdominal pain)	Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities, including echocardiogram findings or elevated troponin/proBNP Evidence of coagulopathy (by PT, APTT, elevated d-dimers)	Elevated markers of inflammation such as ESR, CRP, or procalcitonin	No other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes	Evidence of COVID-19 (RT-PCR, antigen test or serology positive), or likely contact with patients with COVID-19	
Centre of Disease Control and Prevention (US) [37]	An individual under 21 years	Presenting with fever	Evidence of clinically severe illness requiring hospitalisation with multisystem (>2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological)	Evidence of inflammation could include but is not limited to an elevated CRP, ESR, fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase, or interleukin 6, elevated neutrophils, reduced lymphocytes and low albumin	No alternative plausible diagnoses	Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology or antigen test; or COVID-19 exposure within the four weeks prior to the onset of symptoms	Some individuals may fulfil full or partial criteria for Kawasaki disease but should be reported if they meet the case definition for MIS-C Consider MIS-C in any paediatric death with evidence of SARS-CoV-2 infection
Royal College of Paediatrics and Child Health (UK) [36]	Any child	Persistent fever	Evidence of single or multi-organ dysfunction (shock, cardiac, respiratory, renal, gastrointestinal or neurological disorder) with other additional clinical, laboratory or imaging and ECG features	Neutrophilia, elevated CRP and lymphopaenia.	Exclusion of any other microbial cause, including bacterial sepsis, staphylococcal or streptococcal shock syndromes, infections associated with myocarditis such as enterovirus	SARS-CoV-2 PCR testing positive or negative	Children fulfilling full or partial criteria for Kawasaki disease may be included

^aTwo of the following of clinical signs and symptoms, or evidence of multiorgan involvement. CRP, C-reactive protein; ECG, electrocardiogram; ESR, erythrocyte sedimentation rate; RT-PCR, reverse-transcriptase polymerase chain reaction; proBNP, pro B-type natriuretic peptide; PT, partial thromboplastin time; APTT, activated partial thromboplastin time.

profound lymphopaenia and thrombocytopaenia compared with Kawasaki Disease [31, 50, 51]. Increased levels of D-dimers, B-type natriuretic peptide, troponin, and pro-inflammatory interleukines have also been linked to MIS-C [35, 52, 53]. A novel point-of-care diagnostic test for diagnosing MIS-C using RNA sequencing, developed by the multinational DIAMONDS research consortium, is showing initial encouraging results [54–56].

Whereas using immunoglobulins as first line treatments in Kawasaki Disease and Toxic Shock Syndrome are well established [57, 58], equipoise still exists between immunoglobulins and steroids for the treatment of MIS-C [33, 42, 59]. Taking the costs and global scarcity of immunoglobulins into account, the option of using steroids as first line treatment for MIS-C would have important implications, in particular in low- and middle-income countries where immunoglobulins might not be readily available. In observational studies, both immunoglobulins and steroids were effective in switching off the inflammatory process in nearly all cases, with swift cessation of fever and marked reduction of inflammatory markers [33, 42, 59]. The RECOVERY trial, which has previously successfully evaluated treatments for adults with COVID-19, is expected to present the results of the first randomised treatment trial for immunoglobulins vs. steroids in children with MIS-C [60]. Immunomodulation with biologicals, such as inhibitors of IL-1, IL-6, and TNF, have also been suggested in MIS-C. Other treatment considerations in MIS-C include starting aspirin and heparins. Because of the overlap in clinical presentation with toxic shock syndrome, early administration of broad-spectrum antibiotics will be important. Cardiac dysfunction should be recognised promptly, with diagnostic roles for troponin and B-type natriuretic peptide levels in blood, electrocardiogram and echocardiogram, and early initiation of inotropic support should be considered in addition to careful fluid resuscitation.

In initial cohorts, 40–80% of children with MIS-C were admitted to critical care units [29–31, 42, 61]. Across studies, approximately 2% of patients with MIS-C died [29–31, 42, 61]. The Best Available Treatment Study, including cases from 34 countries between June 2020 and February 2021 reported fewer children needing critical care, with 22% (138/614) of children requiring organ support defined as inotropic support, mechanical ventilation or extracorporeal membrane oxygenation support [33]. This lower rate of admission to critical care units supports the observation that MIS-C has a wide clinical spectrum of severity. Possibly, it also reflects improved recognition and management over time. Outcomes for children with MIS-C appear good in those where the diagnosis was made early and appropriate treatment was started [62].

Vaccinating children

Different strategies have been deployed around the world to vaccinate children and young people against SARS-CoV-2 [63]. The European Union, UK, and the US currently advocate vaccinations for those aged 12 years and over [11, 64, 65], with roll out of vaccinations for younger children expected soon. As the risks of severe COVID-19 and MIS-C are very small in children and as vaccines are typically administered in healthy individuals, these risks need to be balanced against the benefits of being vaccinated against SARS-CoV-2 and the potential risks associated with such a vaccination. Cases of myocarditis in children and young adults following mRNA vaccines have caused concern, and although many of these cases appear mild and transient [66, 67], some have needed hospital admission, and even admission to intensive care and some deaths have been reported [66, 68–70]. Mostly, cases of myocarditis were temporally linked to the second vaccination, yet a causal relationship, although suspected, has not been proven [71]. Additionally, there is the important aspect of vaccines reducing household and community spread [72].

Long COVID

Until now, the prevalence of post-acute or long COVID syndrome has only played a minor role in the decision-making processes around mitigation measures against SARS-CoV-2. Post-viral infection syndromes have been described previously [73, 74]. Although believed to be less common than in adults, early studies observed persisting symptoms after SARS-CoV-2 infection in a high proportion of children [75–78]. Yet, available data in children largely lacked appropriate control groups amongst other design flaws. The prospective observational CLoCK study has thusfar provided most reliable evidence, matching children with and without positive SARS-CoV-2 polymerase chain reaction results and looking at their symptoms at time of test results and three months later [79]. Children with positive SARS-CoV-2 PCR test result more often had a single (35.4 vs. 8.3%) or 3+ symptoms (30.6 vs. 6.2%) at the time of testing than those with a negative result; somewhat surprising, at three months the presence of physical symptoms was higher for both children with a positive test as well as for children with a negative test: 66.5% (test positive) vs. 53.5% (test negative) for a single symptom, and 30.3% (test positive) vs. 16.2% (test negative) for 3+ symptoms. Symptoms of tiredness, headache, and shortness of breath persisted most often at three months. Scores

for mental health and well-being were the same between those testing positive and those testing negative. Those who tested positive were more likely to disclose issues with mobility, doing usual activities, and pain/discomfort on quality-of-life scores. In general, there appears to be a post-viral syndrome with persisting symptoms in children with a previous SARS-CoV-2 infection, considerably limiting daily functioning in a small group of children. However, similar symptoms are also seen in children without a prior SARS-CoV-2 infection, in whom symptoms were potentially related to another viral infection or explained by the impact of COVID-19 social distancing measures.

Social distancing measures and the impact on child health

Efforts to contain SARS-CoV-2 spread in the community have differed between countries, but, on the whole, high-income countries had some social distancing measures in place at one or more moments over the last year. Social distancing measures varied from advice on hand hygiene, hand washing and physical distancing, to full lockdown of entire societies and blanket ‘Stay at home’ orders. In many countries schools were closed for prolonged periods of time. These social distancing measures greatly reduced the number of children presenting to emergency departments for acute illness or injury [80–84]. For example, there was a notable reduction of respiratory tract infections over the winter of 2020–2021 [85]. Interestingly, with the relaxation of social distancing measures, and with children returning to schools, familiar childhood infections returned, resulting in out-of-season outbreaks of respiratory viruses such as respiratory syncytial virus [86–88].

Concerns were raised about more severe presentations to hospitals as a result of delays in healthcare seeking behaviour and changes in how to access healthcare [89–92]. In the UK this prompted the RCPCH to issue a national alert with information for parents on when and how to access urgent and emergency care during the first phase of the COVID-19 pandemic [93]. However, Roland et al. concluded that delays in presentation were infrequent, and that only a minority (six out of 51 (11.8%)) of children with a potential delay in presentation were subsequently admitted to one of seven hospitals [94]. Studies on delays in presentations for appendicitis [95, 96] and testicular torsion [97–100] reached contradictory conclusions. No increase in overall childhood mortality was noted over the first period of the COVID-19 pandemic in the UK [101].

The social distancing measures had significant effects on many aspects of child health. For example, increased ED presentations for child abuse and neglect were observed [102, 103], some of which might have reflected changes in healthcare pathways [104]. Similarly, although overall numbers of traumatic injuries reduced, there was an increase in non-accidental injuries [105] and injuries sustained at home [106]. Perhaps most alarming has been the large increase in mental health issues and eating disorders [107–110].

Finally, Unsworth et al. first detected an increase of new onset type 1 diabetes in children and a possible association with SARS-CoV-2 in the UK [111]. Similarly, Salmi et al. found an increase in children registered to the national diabetes database in Finland early in the COVID-19 pandemic [112]. By now, evidence is mounting to show the role of SARS-CoV-2 in the pathogenesis of new onset diabetes mellitus [113, 114]. Moreover, other viruses, such as the group of enteroviruses, have previously been linked to type 1 diabetes mellitus [115]. However, other studies did not find an increase in new onset diabetes in children and young people, nor a change in severity at time of first presentation [116, 117]. Future research will need to provide more definitive evidence of the association between SARS-CoV-2 and new onset diabetes.

Conclusions

As severe COVID-19 disease is rare in children, societies and governments have focussed on adult COVID-19 disease for the majority of the COVID-19 pandemic. The child’s voice has largely been unheard throughout most of the pandemic. However, many aspects of child health have been influenced by the COVID-19 pandemic and mitigation efforts. School closures and other social distancing measures affected vulnerable children from disadvantaged families the worst, and it worryingly impacted the mental health of children at a large scale. Overall, there was a marked decrease in acute illness and injuries in children owing to the social distancing measures, providing insights on how we can reduce the burden of childhood disease in future. Moreover, there has not been a clear signal that the COVID-19 pandemic resulted in changed health seeking behaviour leading to large numbers of children with delayed presentations of serious illness. Vaccination programmes for children are accelerating, contributing to reducing COVID-transmission in the community, as well as preventing cases of children with severe COVID-19, MIS-C, or long Covid. The controversies about the need to vaccinate

children and about the safe reopening of schools have, for now, put the children at the forefront of this COVID-19 pandemic.

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