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Review

Pediatric COVID-19: Immunopathogenesis, Transmission and Prevention

Geraldine Blanchard-Rohner [1,2,3,*], Arnaud Didierlaurent [2], Anne Tilmanne [4], Pierre Smeesters [4] and Arnaud Marchant [5]

1 Center of Vaccinology, Department of Pathology and Immunology, Faculty of Medicine, University of Geneva, 1205 Geneva, Switzerland
2 Pediatric Immunology and Vaccinology Unit, Division of General Pediatrics, Department of Pediatrics, Gynecology and Obstetrics, Geneva University Hospitals, University of Geneva, 1205 Geneva, Switzerland; arnaud.didierlaurent@unige.ch
3 Children's Hospital of Geneva, 6, Rue Willy-Donzé, 1211 Geneva, Switzerland
4 Children's Hospital Queen Fabiola, Université libre de Bruxelles, 1020 Brussels, Belgium; anne.tilmanne@huderf.be (A.T.); pierre.smeesters@huderf.be (P.S.)
5 Institute for Medical Immunology, Université libre de Bruxelles, 1050 Charleroi, Belgium; Arnaud.Marchant@ulb.be
* Correspondence: Geraldine.blanchardrohner@hcuge.ch

Abstract: Children are unique in the context of the COVID-19 pandemic. Overall, SARS-CoV-2 has a lower medical impact in children as compared to adults. A higher proportion of children than adults remain asymptomatic following SARS-CoV-2 infection and severe disease and death are also less common. This relative resistance contrasts with the high susceptibility of children to other respiratory tract infections. The mechanisms involved remain incompletely understood but could include the rapid development of a robust innate immune response. On the other hand, children develop a unique and severe complication, named multisystem inflammatory syndrome in children, several weeks after the onset of symptoms. Although children play an important role in the transmission of many pathogens, their contribution to the transmission of SARS-CoV-2 appears lower than that of adults. These unique aspects of COVID-19 in children must be considered in the benefit–risk analysis of vaccination. Several COVID-19 vaccines have been authorized for emergency use in adolescents and clinical studies are ongoing in children. As the vaccination of adolescents is rolled out in several countries, we shall learn about the impact of this strategy on the health of children and on transmission within communities.

Keywords: COVID-19; SARS-CoV-2; pediatric; multisystem inflammatory syndrome in children (MIS-C); immunopathogenesis

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1. Introduction

Since the beginning of the coronavirus disease 2019 (COVID-19) pandemic, children are underrepresented in terms of frequency and severity, accounting for less than 2% of diagnosed cases [1–3]. This under-representation is partly explained by the fact that children are less often diagnosed with a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, as they are less symptomatic than adults and because they appear less susceptible to the infection.

It is estimated that up to 70% of children infected with SARS-CoV-2 remain asymptomatic [4–6]. In symptomatic children, clinical presentation is usually unspecific and indistinguishable from other respiratory virus infections, as the most frequent symptoms are fever and coughing, and up to 15% of children also present gastrointestinal symptoms, while anosmia is present in less than 1% of the cases [7].

If COVID-19 is a benign disease in most children, a very small proportion of pediatric patients develop severe disease and require hospitalization, accounting for only 1.5% of all

COVID-19 hospital admissions [8]. Although it has been difficult to identify risk factors for severe disease in children, toddlers and adolescents are more likely to be hospitalized than young infants, and children with chronic pulmonary disease, congenital cardiac disease or neurological disease are more likely to be admitted to intensive care units [8]. The mortality associated with COVID-19 in children is very low, as pediatric deaths represent only 0.08% of all deaths associated with COVID-19 [9]. In the spring of 2020, clusters of children in Europe and America developed a severe hyperinflammatory syndrome resembling Kawasaki disease (KD) or toxic shock syndrome [10–13] several weeks after diagnosis of SARS-CoV-2 infection. The syndrome was named multisystem inflammatory syndrome in children (MIS-C) by the US Centers for Disease Control and the WHO, or paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) by the UK Royal College of Paediatrics and Child Health (RCPCH).

It remains unclear why children are less susceptible to COVID-19 and why some develop MIS-C. Regarding the lower susceptibility, several hypotheses have been proposed, including cross-reactive immunity against seasonal coronaviruses to which children have been exposed and a lower expression of the angiotensin-converting enzyme 2 (ACE2) receptor, required for virus entry into human cells through interaction with the protein S, but data supporting these possibilities remain inconclusive. Data are emerging which suggest that children may develop a more rapid and more regulated immune response to SARS-CoV-2, allowing viral control with limited inflammation. This peculiar immune response profile could involve training of innate immunity by exposure to vaccines and pathogens in childhood [14]. Although children are less affected by COVID-19, they are infected and contribute to the transmission of SARS-CoV-2 [8]. Characterizing the immune response to SARS-CoV-2 in children who present with uncomplicated COVID-19 is required to understand the mechanisms underlying MIS-C and to define the immunological mechanisms controlling viral excretion and transmission that can be targeted by vaccination.

2. Immune Response to SARS-CoV-2 Infection in Children

Understanding why children are generally less prone to develop severe COVID-19 and associated symptoms could help to define immune mechanisms of protection against SARS-CoV-2 infection in the general population. The way children respond to SARS-CoV-2 is somewhat unusual, since the severity of infections with many other respiratory viruses, such as respiratory syncytial virus or influenza, is generally higher in children. This difference cannot be explained by a reduced viral load, as children have similar and sometimes higher viral copies in the first days of infection as compared to adults, but this viral load does not correlate with the severity of symptoms [15–18]. There is also no clear evidence that an age-dependent variation in the ACE2 expression level correlates with reduced disease severity. The gene expression of ACE2 in the nasal cavity and lungs was initially shown to be lower in young infants and to increase with age [17,19,20], but in later studies it was found to be similar in infected adults and children [21].

Because infection with common cold human coronaviruses (HCoVs)—HCoV-229E, -HKU1, -NL63 and -OC43—is frequent in children, it has been hypothesized that the presence of antibodies or cross-reactive T cells induced by HCoVs infection could provide protection in young individuals [22,23]. However, if children have high frequencies of class-switched B cells against SARS-CoV-2 and related coronaviruses, the level of HCoVs-specific antibodies is lower in children than in adults and was not associated with the risk of SARS-CoV-2 infection or MIS-C [21,24–28]. On the other hand, antibodies to HCoVs cross-react primarily with the S2 portion of the spike protein and, therefore, have limited capacity to neutralize SARS-CoV-2 [29]. It is possible that non-neutralizing HCoVs-specific antibodies could also contribute to viral control through Fc-dependent mechanisms and promote deleterious inflammatory responses, although evidence for a pathogenic role of antibodies in SARS-CoV-2 infection remains inconclusive [30–33]. Overall, the role of pre-existing and potentially cross-reactive HCoVs-specific antibodies in age-dependent susceptibility to SARS-CoV-2, or in disease severity, remains uncertain [34].

Early control of SARS-CoV-2 replication during primary infection is mainly mediated by the innate immune system [35]. Severe disease is associated with a lower initial interferon (IFN) response, followed by uncontrolled and persistent inflammation [36]. A key question is, therefore, whether children mount a less intense inflammatory response resulting in fewer and milder symptoms, or whether they have a more potent innate immune response, controlling viral replication more efficiently. Baseline cytokine levels are generally lower in children [37] and lower levels of inflammatory cytokines are detected in the lungs of children suffering from acute respiratory distress syndrome than in adults [38]. Studies initially reported that clinical parameters of inflammation were either undetectable or low in children with COVID-19 [14,39–41]. However, similar or higher systemic levels of cytokine were observed in later studies of hospitalized children and adults [21]. On the other hand, high levels of inflammatory cytokines were observed in severe cases of pediatric COVID-19 [42–44] and also in children with mild disease [28]. A pivotal study by Pierce et al. showed that children have a more intense nasal innate immune response, including higher levels of IFN-gamma and IFN-alpha, as compared to adults, suggesting that they may develop higher anti-viral responses at the mucosal level early on during infection [21]. A potent and efficient IFN response may, therefore, contribute to protection of children against COVID-19-associated symptoms [45]. A potential role for trained innate immunity, due to previous vaccinations or common infections, in the control of SARS-CoV-2 infection in children has been proposed [46] but currently lacks experimental evidence.

Analyses of peripheral blood immune cells in the first days after onset of symptoms revealed similar profiles in children and adults, including activation of monocytes and dendritic cells (DC) and transiently reduced numbers of lymphocytes, monocytes, DCs and NK cells [28,47]. Neutrophils appear to be less activated in pediatric, as compared to adult, COVID-19 cases, and this could mitigate tissue inflammation and damage [48]. On the other hand, children have higher numbers of circulating lymphocytes, which may contribute to better disease control [49–51]. As circulating T, B and NK cells decrease post-infection, they could be recruited at the site of infection earlier and in higher numbers in children than they are in adults.

Does a more efficient innate immune response result in a different adaptive immune response to SARS-CoV-2 in children, as compared to adults? It is now well established that children can mount a robust neutralizing antibody response to SARS-CoV-2 [17,52–54]. Initial reports from small pediatric cohort studies showed lower serum neutralizing activity, as compared to adults [21,55], and a reduced breadth of the antibody response to the spike protein [55]. A pre-print report indicates that the level of SARS-CoV-2 antibodies is reduced in children (N = 122) as compared to adults (N = 36), independently of disease severity, with a relatively higher proportion of antibodies targeting non-structural proteins, such as ORF3b and NSP1, than the nucleocapsid (N) or spike (S) proteins [56]. In contrast, other studies described similar levels of SARS-CoV-2 antibodies in both age groups, including those specific to the N protein [17,26,28,57,58]. Systems serology analyses, involving multiparametric assessment of antibody responses, showed a similar functional antibody profile, including phagocyte and complement-activating IgG, in children and adults with mild COVID-19 [33,54]. We recently conducted a longitudinal study of household contacts of COVID-19 cases and observed a similar magnitude and breadth of SARS-CoV-2-specific antibody response in children and adults with mild disease [28]. This study also indicated a more rapid onset of antibody response to the receptor-binding domain (RBD) and a more rapid appearance of peripheral blood B cell transcriptomic signature in children than in adults. A more rapid B cell response to SARS-CoV-2 in children could also contribute to a better control of the virus and to reduced symptoms. Indeed, levels of neutralizing antibodies and antibody-secreting B cells seven days after the onset of symptoms inversely correlated with viral load in children [59]. In addition, higher levels of somatic mutations in memory B cells and a more sustained antibody response were associated with a faster recovery from symptomatic COVID-19 in adults [60]. Limited data are available regarding the persistence of antibody responses in children. In a small cohort of children, anti-SARS-

CoV-2 IgG declined six months after infection with lower levels than their infected parents at the same time point [61]. In a recent larger cohort study, children and adolescents showed high and durable antibody responses to SARS-CoV-2, following mild or asymptomatic infection [62]. Regarding cell-mediated immunity, only a few reports describe a lower or similar magnitude of SARS-CoV-2-specific T cells in children [21,57,63]. As the magnitude of the adaptive immune response to SARS-CoV-2 is related to severity of symptoms, it is essential that studies compare adults and children with similar clinical presentations.

3. Multisystem Inflammatory Syndrome in Children (MIS-C)

In contrast to children with acute COVID-19, children with MIS-C have no clinical features of active SARS-CoV-2 infection but have a history of COVID-19 or of contact with a person with COVID-19 around 4 weeks before the development of MIS-C symptoms [13]. Furthermore, MIS-C cases were typically observed 3–6 weeks following the peak incidence of COVID-19 in the general population [13,64]. Initially, MIS-C was reported as an atypical form of Kawasaki disease (KD) in regions of the world most affected by COVID-19, in Europe and in North and Latin America [11,12,65]. The exact incidence of MIS-C is uncertain. According to a study in New York, MIS-C occurs in two out of every 100,000 infected children [66]. Some ethnic groups were overrepresented, at least at the beginning of the pandemic, such as the African and Hispanic communities [10,11]. This could be explained by population-based genetic susceptibility; viral factors, as new variants of the virus might be more prone to induce immunopathological responses (for instance, due to epitopes with superantigen activity); or social determinants, as some ethnic minorities might have been more exposed to SARS-CoV-2 infection [67]. Children with MIS-C are older than children with KD, with a median age of 8–9 years, as compared to 3 years in KD [11,64].

Clinically, children with MIS-C present more heterogeneous symptoms than classical KD, as most children present with persistent fever, systemic inflammation, shock and multiple organ involvement [68]. Gastrointestinal manifestations are observed in 50–80% of MIS-C cases, sometimes with features of acute abdominal pain. They also frequently present with cutaneous rash and neurological symptoms, with features of meningitis and encephalitis [11,13,64,65,69,70]. Further, they very often present with cardiac dysfunction, with the occurrence of coronary artery dilation in 4–20% of children [11,64,71]. Patients often present with shock or hemodynamic instability; 60–80% require hospitalization in an intensive care unit; and 50% need inotropes and/or fluid resuscitation [11,64,72]. This syndrome usually resolves rapidly with corticosteroids and intravenous immunoglobulins (IVIG) [11,64,73–75]. The fatality rate is estimated to be 1–2% [66]. Inflammatory response in children with MIS-C is characterized by an increase in levels of C-reactive protein (CRP), procalcitonin, troponins, brain natriuretic peptide (BNP), ferritin and cytokines, such as IL-1, IL-6, IL-8, IL-10, IL-17, IL-18, IFN-γ and TNF, associated with profound lymphopenia and neutrophilia [10,11,13,74,76,77].

The physiopathology of MIS-C has been studied, but there is still no clear explanation as to why a small proportion of infected children develop MIS-C. It has been reported that the various symptoms of MIS-C reflect local vasculitis and inflammation of the affected organs. Similarly to KD, MIS-C is triggered by a previous infection and is likely an autoimmune syndrome. The inflammatory markers, such as CRP, ESR, procalcitonin and cytokines, appear more elevated in MIS-C as compared to other pediatric COVID-19 cases [13]. However, the inflammatory response is more intense in MIS-C compared to children with KD, and the cytokine profile is different; in KD, there is a robust IL17A increase, which is not observed in MIS-C. In contrast, MIS-C is associated with elevated levels of IL-1, which could be induced by endothelial cells damaged by autoantibodies and complement [78]. Autoantibodies of multiple specificities, including endothelial, gastrointestinal and immune cells, have indeed been observed in MIS-C [77,78]. These autoantibodies may form immune complexes and trigger immune damage to host tissues [77]. The production of autoantibodies may be due to cross-reactivity between SARS-CoV-2 and self-antigens. Although observed after infection, the production of autoantibodies has not been reported

following COVID-19 vaccination (mainly targeting the spike antigen), suggesting that tissue damage due to SARS-CoV-2 infection involves other viral antigens than the S antigen. SARS-CoV-2 infection in the gastrointestinal tract may particularly favor the production of autoantibodies in MIS-C patients, and, in line with this hypothesis, many MIS-C cases have mesenteric adenitis and ileitis [11,65,79]. There are also possible roles played by direct virus dissemination and by a direct effect of the virus in the pathogenesis of MIS-C, as various autopsy reports have identified SARS-CoV-2 RNA on post-mortem tissues, in the extracellular compartment and within several cell types (cardiomyocytes, heart and brain endothelial cells, mesenchymal cells, macrophages and neutrophils) [80,81]. Therefore, the hyperinflammatory process and local vasculitis, combined with a direct, cytopathic effect of the virus in affected organs, could favor the onset of MIS-C. Another possibility is the occurrence of antibody-dependent enhancement (ADE) of coronavirus entry. Indeed, it has been suggested that SARS-CoV-2 antibodies bound to Fc receptors on macrophages and mast cells could favor virus entry and contribute to immune dysregulation [82,83]. The development of MIS-C may also involve a suppression of type I and type III interferon responses, which could first lead to an uncontrolled local viral replication with increased secretions of various cytokines, and then to an exaggerated adaptive immune response, involving B and T cells cross-reacting with self-antigens and triggering autoimmunity [78,84–86]. One hypothesis is that a unique part of the SARS-CoV-2 S protein could act as a superantigen, inducing oligoclonal activation of T cells [87]. This is supported by a recent report by Moreews et al., who observed an expansion of activated T cells expressing the Vbeta 21.3 T cell receptor beta-chain variable region in both CD4 and CD8 subsets in the majority of MIS-C patients, and not in control patients [88].

The humoral immune response in MIS-C patients appears to be different to that in children with uncomplicated COVID-19, although available data are limited. MIS-C patients produce neutralizing antibodies and have lower levels of IgM and higher levels of IgA and anti-spike IgG, as compared to other pediatric cases [89]. Another study reported that children with MIS-C had higher titers of SARS-CoV-2 spike RBD-specific IgG, as compared to children with uncomplicated COVID-19 [90]. All MIS-C children also had RBD IgM antibodies, suggesting recent SARS-CoV-2 infection. RBD IgG titers correlated with parameters of disease severity, such as erythrocyte sedimentation rate and duration of hospitalization and ICU stay [90]. These observations suggest that moderate levels of antibody protect against infection, while, above a certain threshold, higher levels of antibody may promote hyperinflammation.

It has been hypothesized that patients with MIS-C could have an unknown primary immunodeficiency [91]. Inborn defects of type I interferon responses are associated with severe COVID-19, with poor control of viral replication and excessive pulmonary and systemic inflammation [36,92,93]. Various immune defects have been associated with virus-triggered hyperinflammatory disease, such as herpes viruses and hemophagocytic lymphohistiocytosis (HLH). Several genes have been identified for HLH (such as PRF1, UNC13D, STX11 and STXBP2) that encode molecules involved in the cytotoxicity of CD8-T cells and NK cells [94]. In this case, CD8-T cells and NK cells cannot lyse infected cells and this results in excessive immune stimulation (43). Another example is XIAP or NLRC4 deficiencies, which are associated with an overstimulation of the inflammasome [95]. However, monogenic or oligogenic defects associated with MIS-C have not been identified yet.

4. SARS-CoV-2 Transmission by Children in Household Studies

Clinical clusters studies are a good way to understand the transmission of a disease. Many SARS-CoV-2 clusters have been reported and often include children, but rarely as the primary cases. The general consensus is that children are less frequently secondary cases than adults [96–103], or even that there is a similar attack rate across all age categories [104]. There are limited data about the infectivity of children showing a lower infectivity than adults. A Swiss study found that children were the first to develop SARS-CoV-2 symptoms in family clusters only in 8% (3/39) of the cases [105]. In 637 households in Israel, the

infectivity of children was estimated to be 63% (95% CI: [37%, 88%]), relative to that of adults [106]. In South Korea, among 107 pediatric COVID-19 index cases and their 248 household members, the median age of pediatric COVID-19 index cases was 15 years (IQR 10–17 years), and the secondary attack rate was only 0.5% (95% CI 0.0–2.6%) [107].

Infectivity may vary with the age of children. A follow-up study of 5706 index cases in South Korea showed 11.8% (1248/10,592) and 1.9% (921/48,481) RT-PCR confirmed infection rates among household contacts and non-household contacts, respectively. The number of secondary cases was significantly different according to the age of the index case. For 0–9-year-old index cases, 5.3% of household contacts and 1.1% of non-household contacts were positive, whereas for 10–19-year-old index cases, 18.6% of household contacts and 0.9% of non-household contacts were positive, suggesting higher infectivity of older children [108]. These age-dependent transmission patterns, with higher secondary attack from adults (28.3%; 95% CI 20.2–37.1%) than from children (16.8%; 95% CI 12.3–21.7%; $p < 0.001$), have also been found in systematic reviews [109]. Outside the context of household transmission, data are scarce but confirm that children are rarely the primary source of secondary transmission in childcare and school settings and are more likely to be infected by an adult household member [110].

Clinical studies analyzing clusters of transmission, however, have several limitations, especially considering SARS-CoV-2 peculiarities. Children are often underrepresented as index cases, potentially because they are often asymptomatic [6,111]. However, the "index case" is often considered as the one infecting the rest of the family [112]. On the other hand, wide circulation of the virus among asymptomatic children has not been demonstrated [113]. It is, therefore, unlikely that children are the asymptomatic transmitters responsible for the infection of their relatives in the majority of familial clusters.

Important data were reported by Laxminarayan et al. [114]. Their tracing analysis of 84,965 confirmed cases and 575,071 contacts in two Indian provinces showed the highest probability of transmission within case–contact pairs of similar age. This enhanced transmission risk in similar age pairs seems strongest among children aged 0–14 years and among adults aged $\geq$65 years, although the greatest proportion of test-positive contacts within most age groups were exposed to index cases aged 20–44 years. An increased transmission risk within similar age pairs could be explained by different type and duration of contacts according to age, leading to a different risk of contamination. Such phenomena could contribute to the discrepancies seen in secondary attack rates across the studies, where attention is given to index cases or secondary infected people, but rarely to the transmitter–infected pair. However, cautions must be taken comparing epidemiological data over time, as shown by a study in the UK demonstrating differences between the two epidemiological waves. In contrast to the first COVID-19 wave, data suggested an increased risk of reported SARS-CoV-2 infection and COVID-19 among adults living with children during the second wave [115]. This difference could be explained by the different context in which the majority of children lived between the first and second waves—fewer contacts, due to fear of the virus and the closing of schools, during the first wave; and an increase in contacts, due to psycho-social necessity, less virus-related anxiety in the younger population and open schools, during the second wave.

Seroprevalence studies can also be used to estimate the incidence of SARS-CoV-2 infection. In Switzerland, a serosurvey showed a significantly lower seroprevalence among children aged 5–9 years (0.8%) and a lower risk of seropositivity compared to individuals aged 20–49 years (RR 0.32) [116], therefore confirming the studies on attack rate. Only few studies have been published on this topic, and it will also be important to assess the durability of antibodies following SARS-CoV-2 infection in children for the interpretation of seroprevalence studies [61,62].

5. Vaccination of Children

COVID-19 vaccination of children is the subject of several debates, and different approaches are currently being followed by countries where COVID-19 vaccines are suf-

ficiently available to immunize this population. Clinical trials of mRNA and inactivated vaccines have been conducted in adolescents and have demonstrated a favorable safety profile and a similar immunogenicity to that observed in young adults [117,118]. Although sample size was relatively limited, as compared to adult studies, high efficacy of the BNT162b2 mRNA vaccine was shown in 12–15-year-old adolescents [117]. Immunogenicity and safety studies of mRNA vaccines are currently being conducted in younger children. Recent results showed immunogenicity of the Coronavac inactivated vaccine in children 3–11 years old [118]. Non-human primate studies showed potent and durable antibody and T cell responses to mRNA vaccines in infant animals [119]. Based on these studies, mRNA and inactivated COVID-19 vaccines have been approved for emergency use in adolescents by the regulatory authorities of several countries, including the US, Israel, the UK and China, and by the European Medicine Agency; vaccination of this population is being rolled out in an increasing number of countries. Notably, the UK recently decided to restrict vaccination to adolescents who are at risk of severe COVID-19 and to those who are household contacts of immunosuppressed patients (https://www.gov.uk/government/news/jcvi-issues-advice-on-COVID-19-vaccination-of-children-and-young-people, accessed on 31 July 2021) As for any vaccine in any target population, the decision to recommend and implement COVID-19 vaccination of adolescents and younger children is based on benefit–risk analyses [120–123]. Although most children remain asymptomatic, 6% of children are hospitalized; 13% of those hospitalized meet the criteria for severe disease with a fatality rate of 1%, while others suffer from prolonged symptoms (long COVID) and could, therefore, benefit from vaccination [124]. This benefit is stronger for vulnerable children who are at risk of severe COVID-19. On the other hand, although children are not predominant contributors to SARS-CoV-2 transmission, preventing infection by vaccination would indirectly reduce the risk of infection and disease for their contacts. This would be particularly important if those contacts were vulnerable and responded poorly to vaccination because of immunosuppression. Compulsory COVID-19 vaccination of children has been proposed to achieve high vaccination coverage, at the level of the population, and herd immunity [125–127]. However, as vaccine hesitancy in adults remains high in many countries, the prospect of reaching herd immunity, especially for variants of concern, appears more distant, and the argument of targeting children for compulsory vaccination has become weaker. Children would also benefit from COVID-19 vaccination if this would allow them to relax control measures, resulting in increased and diversified social contacts and reduced psychological impact of being a potential vector of the disease in the household [121]. Thus, several benefits of COVID-19 vaccination can be identified for healthy children, although globally they appear less marked than for adults. Although clinical trials have shown favorable safety profiles of mRNA and inactivated COVID-19 vaccines, the sample size of these studies is relatively limited, and long-term follow-up is still lacking. More safety data are being collected by countries where adolescent vaccination is being rolled out. This surveillance has allowed the identification of several cases of perimyocarditis following immunization of young adults and adolescents with the BNT162b2 or the mRNA-1273 vaccine, particularly in young male adults and adolescents [128–130]. These cases were rare, with an estimate of between 1/10,000 and 1/100,000 vaccinees, and were mild and self-limited. Therefore, it was concluded that the benefit of COVID-19 vaccination of adolescents, including the prevention of COVID-19 hospitalization, intensive care unit admission and death, outweighed the risk of perimyocarditis associated with mRNA vaccination [129]. As vaccine coverage of adults further increases, the proportion of COVID-19 cases in children will increase. With accumulating evidence of favorable safety profiles, COVID-19 vaccination of children is likely to be further promoted in the coming months and years.

6. Concluding Remarks

In contrast to respiratory tract infections caused by other viruses, SARS-CoV-2 has a lower impact on the health of children as compared to adults. However, severe disease,

including MIS-C, has been observed and COVID-19 can be fatal in previously healthy children. Several hypotheses have been proposed to explain the favorable outcome of SARS-CoV-2 infection in children. Studies suggest that a robust, early innate immune response could play an important role. On the other hand, risk factors of severe COVID-19 and MIS-C remain poorly understood. Children at risk of severe COVID-19 because of underlying medical conditions can be offered vaccination. Identifying children at risk of MIS-C would help to extend this strategy. Based on their immunogenicity and safety profiles, several COVID-19 vaccines have been proposed to adolescents in an increasing number of countries. The lessons learned and experience gained from the COVID-19 pandemic will be very important for the prevention and the care of other infections affecting children and for the pathogens that will cause future pandemics.

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