

Forum

The impact of COVID-19 on children and lessons for pandemic preparedness

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Children and adults experienced the COVID-19 pandemic differently. While the impact on children was significant, it was different from what had originally been expected. Here, we outline key developments and learnings from the COVID-19 pandemic's effects on children and draw lessons for pandemic preparedness.

Introduction

In December of 2019, a cluster of adults in China's Hubei Province were reported to have experienced a syndrome of atypical pneumonia-like illness of unknown cause and did not respond to standard treatments. In early January 2020, the causative agent of the outbreak was identified as a novel coronavirus, subsequently named SARS-CoV-2. Although the earliest reported cases were in adults, physicians, scientists, and health care systems that care for and study viral respiratory tract infections in children began to prepare for a pandemic that many felt may disproportionately affect infants and children. The concern about the pediatric age group largely stemmed from the fact that children often have the highest attack rates in the population for viral respiratory tract infections and that these viruses, including influenza and respiratory syncytial virus (RSV), typically demonstrate risk for severe disease clustered at the extremes of age. However, as the pandemic evolved, it became apparent that many features of the disease known as COVID-19 were different in children than had been expected and that the biggest impacts on the pediatric age group were those that had not been anticipated. Here, we discuss some of the key learnings from the COVID-19 pandemic's effects on children and consider implications for pandemic preparedness.

Epidemiology and risk for severe disease in children

Prior to the emergence of SARS-CoV-2, the most important viral respiratory tract infections of childhood were influenza

and RSV, both of which are known to have young children as a risk group for severe disease. A 2019 global systematic review of influenza found that the highest rates of hospital admission were reported for children <5 years old.¹ A 2023 systematic review of RSV-associated hospitalization found that in high-income countries, the highest rate of RSV hospitalization was in infants <1 year old across all case definitions.² In Canada, it is estimated that 1%–2% of infants are admitted to hospital because of RSV infection. Risk factors for severe influenza and RSV disease in children are well described and, in addition to young age, include prematurity, chronic lung diseases, congenital heart disease, immunocompromise and suppression, neurologic disorders, and other comorbidities. In the early days of the pandemic, out of an abundance of caution, many young children and those with underlying comorbidities were admitted to the hospital for observation and supportive care. However, as the pandemic unfolded, and while serious outcomes in children occurred rarely, it became increasingly clear that COVID-19 in children was, in general, a milder disease than influenza or RSV.

In Canada, as in other countries, existing infectious disease surveillance infrastructures rapidly pivoted to collecting data on children hospitalized with COVID-19. A series of serosurveys conducted between January 2021 and August 2022 in British Columbia found that infection-induced antibodies were highest in those <20 years old, illustrating the rapid spread of the virus through child and adolescent populations.³

A national study using data collected by the Canadian Pediatric Surveillance Program (CPSP) from the beginning of the pandemic to mid-2021, prior to the emergence of the Omicron variant and immunization in children, found that nearly 4 out of 10 children admitted with SARS-CoV-2 infection did not have COVID-19-related disease but rather had incidental infection or were admitted for infection control or social reasons.⁴ In contrast to what was expected, hospitalized children <1 year old had a significantly lower risk of severe disease, while the risk was highest for children aged 2–5 and 16 to <18 years.

SARS-CoV-2 variants and immunity have changed over time due to both infection with new variants and vaccination, and ongoing study of which children are at highest risk remains important. A Canadian study by CPSP and the Immunization Monitoring Program Active (IMPACT) surveillance network found that children were admitted to the hospital most often during the Omicron wave and that most were primary infections in unvaccinated age groups, illustrative of a pattern seen in other countries.⁵ The presence of certain underlying comorbidities, and, in particular, multiple comorbidities, increases the risk for severe disease. A US-population-based study of hospitalized children >6 months of age from October 2022 to April 2024 found that few children (<5%) were up to date with COVID-19 vaccination as per the recommendations at the time, and there was a shift in the age of those hospitalized toward younger ages, likely reflecting increasing immunity in older children.⁶ While 40% of children had no comorbidity, more than half had an underlying medical



condition, and a third had multiple comorbidities, with this percentage increasing in older age groups.⁶ A global systematic review and meta-analysis of risk factors found that cardiovascular and neurological disorders, chronic pulmonary conditions other than asthma, obesity, diabetes, and immunocompromise were all consistently associated with severe disease.⁷ Better understanding of risk groups for severe outcomes in children now allow risk stratification and admission and treatment strategies for COVID-19 in children are now more tailored to at-risk groups.

While numerous studies have now described the overall lower severity of COVID-19 in children compared to adults, and these findings have remained consistent through the emergence of new variants, the underlying reasons and why this differs from other viral respiratory tract infections remain poorly understood. Some proposed reasons include differences in ACE2 receptor expression and children exhibiting a more robust innate immune activation, particularly in the upper respiratory tract, less T cell exhaustion, lower systemic levels of pro-inflammatory cytokines, higher levels of secretory IgA in the nasal mucosa, and frequent exposure to seasonal coronaviruses, which may lead to partial protection.

Unexpected clinical outcomes

An important lesson from the COVID-19 pandemic is the importance and challenge of monitoring novel or unexpected outcomes following infection. First identified in April 2020, multisystem inflammatory syndrome in children (MIS-C) is a rare but serious post-infectious complication of SARS-CoV-2 infection in children that is an example of such an unexpected outcome. The syndrome shares features with Kawasaki disease and toxic shock syndrome but is distinct in its pathophysiology and age distribution. It typically appears 2–6 weeks after infection and often follows asymptomatic or mild SARS-CoV-2 infection. MIS-C is believed to be a post-infectious hyperinflammatory response triggered by SARS-CoV-2 that involves dysregulated immune activation, including T cell and macrophage activation, cytokine storm, and autoantibody production. Genetic predisposition and host immune factors likely contribute, but the mechanisms remain under investigation. In the early days of MIS-C, ICU admission

for multisystem organ dysfunction and hemodynamic instability was common, and treatment strategies rapidly evolved. Current treatment regimens include aggressive supportive care and first-line therapy with corticosteroids and intravenous immunoglobulin, and for cases refractory to first-line treatments, additional immune-modulating therapies, including IL-1 receptor antagonist, IL-6 inhibitor, and anti-TNF drugs, are considered. As was seen with acute COVID-19, there were important population disparities in MIS-C incidence, with higher incidence in Black, Hispanic, and South Asian children documented in multiple countries. The peak incidence of MIS-C occurred during the Alpha and Delta variant waves (2020–2021), and it has decreased sharply globally since mid 2022, particularly in countries with high pediatric COVID-19 vaccination rates. The global experience with MIS-C highlighted the need for rapid development of harmonized case definitions of new conditions, the importance of pediatric-specific clinical guidelines, and the value of rapid data sharing across institutions and between countries.

COVID vaccines in children, including adverse events following immunization

Vaccination proved central to achieving control of the COVID-19 pandemic and facilitating the transition of COVID-19 to an endemic disease. Vaccine clinical trials for adults proceeded rapidly, followed by trials first for adolescents 12 years and older with BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna), then for children 5–11 years, and finally those 6 months to 5 years.⁸ Trials of COVID-19 mRNA vaccines in children and adolescents demonstrated over 90% efficacy in all age groups and no safety signals. Protein subunit vaccines were authorized in adolescents and are recommended for booster doses as an alternative to mRNA vaccines. Inactivated and viral-vector COVID-19 vaccines were also studied in children, primarily in China, and shown to have moderate to high efficacy.⁸ Due to the emergence of the rare but potentially fatal vaccine-induced thrombosis with thrombocytopenia syndrome, adenoviral vector vaccines were not authorized for children.

The BNT162b2 COVID-19 mRNA vaccine was the first to be given emergency

authorization for children 12–15 years in April/May 2021. In Canada, the US, and several other countries, vaccination of adolescents was strongly recommended to reduce the risk of transmission, severe COVID-19 disease, and MIS-C. COVID-19 mRNA vaccines were authorized for children 5–11 years of age in November 2021 (US and Canada), shortly before the first Omicron wave. Because children had a lower risk of severe COVID-19 overall, universal vaccination in this age group was not strongly recommended in all countries. For younger children, vaccines were even more delayed and were only approved in mid-2022 after many children had been infected with the Omicron variant. Vaccine uptake among children younger than 12 years was much lower overall than for adolescents. Early post-implementation data showed that COVID-19 mRNA vaccination was associated with significant reductions in the risk of hospitalization with COVID-19 and MIS-C in children and adolescents.⁹ Earlier access to COVID-19 vaccination for young children may have reduced the burden of pediatric hospitalizations during the Omicron wave.

As BNT162b2 was authorized and being implemented for adolescents, the first reports of myocarditis and pericarditis following COVID-19 mRNA vaccination were emerging in young adults, primarily males, in Israel and the US. Analysis of surveillance and epidemiologic data from the US, UK, Canada, and Europe confirmed the association. An increased risk was found in males 12–17 years of age in approximately 10 per 100,000 vaccinees.¹⁰ Among adults, the risk appeared to be higher with the mRNA-1273 100 µg-dose vaccine product than with BNT162b2 (30 µg mRNA), which eventually led to a preferential recommendation for BNT162b2 in adolescents and young adults.¹⁰ Prospective surveillance continues to show that the clinical course and outcomes of post-vaccination myocarditis were less severe than in patients with MIS-C-related or non-vaccine-associated myocarditis; however, a subset of patients have ongoing symptoms and/or persistent changes on cardiac MRIs, underscoring the need for long-term follow-up.¹¹

Myocarditis and pericarditis were confirmed to be associated with only COVID-19 mRNA vaccines, though surveillance data suggested a possible link

with protein subunit vaccines. The latter were only approved for adolescents 12 years and older in 2023 and have been used primarily as booster doses.⁹ Reassuringly, myocarditis was not seen in association with vaccination in children younger than 5 years and was very rarely seen in boys 5–11 years after dose 2, at a lower rate than adolescents.¹⁰

Research to identify the mechanisms underlying post-vaccination myocarditis is ongoing to inform future vaccine development.^{12–14} Studies have reported increased innate immune activation, a distinct steroid hormone profile (elevated DHEAS, DHEA, and cortisone levels lasting months), and persistence of full-length spike protein in affected patients.^{12,13} In contrast, autoantibodies were not detected in either of these studies. With COVID-19 mRNA vaccines continuing to be recommended for high-risk children and adolescents, and with the development of mRNA vaccines against other pathogens, understanding the mechanism through which COVID-19 mRNA vaccines trigger myocarditis is critical to optimizing the safety of these vaccines.

Secondary impacts of the pandemic on child health

Though the direct impact of COVID-19 was less for children than for other age groups, the non-pharmacologic interventions (NPIs) put in place to curb community spread of SARS-CoV-2 disrupted systems worldwide, including the delivery of routine immunizations and education.

Canada is an illustrative example of how a high-resourced country's immunization programs can be disrupted. Prior to the pandemic, Canada delivered immunization through a combination of primary care providers, school-based programs, and public health clinics. Many public health units and primary care clinics suspended routine immunization services, particularly during the first and second waves of the pandemic. School-based immunization programs were delayed or canceled due to school closures, affecting vaccines such as those for HPV, meningococcal, and hepatitis B. Staff were redeployed to COVID-19 testing, contact tracing, and vaccination efforts, which strained the capacity to deliver routine immunizations. Additionally, some families faced challenges such as fear of COVID-19 exposure, transportation barriers, childcare responsibilities, or job

loss, which further hindered access to immunization services. Globally, countries with weaker health systems pre-pandemic experienced even more significant disruptions to routine immunization. One of the most concerning outcomes of the pandemic was the increase in the amount of “zero-dose” children—those who did not receive even a single dose of any vaccine and who are disproportionately located in remote, fragile, conflict-affected, and vulnerable settings.

Following the global decrease in routine immunization, as well as decreased natural exposure to other infectious diseases, it was not surprising that when NPIs were relaxed, there was a surge in infections in children, most notably from respiratory viruses including influenza and RSV. This resulted in a surge in pediatric hospitalizations and health-system demand that, in many locations, exceeded the peak of the pandemic. Many regions, including in Canada, have also seen an increase in the number of severe bacterial infections including invasive pneumococcal disease, group A streptococcus, and *Mycoplasma pneumoniae* as well as rates of measles infection not seen in decades.

School closures were one of the earliest NPIs implemented to curb the spread of COVID-19. In Canada, provinces like Ontario and Quebec experienced some of the longest school closures in North America. However, the evidence on the effectiveness of school closures is mixed, and questions have been raised about the balance between benefit and risk of school closures given their broader societal costs including academic disruption, remote learning challenges, and impacts on student and educator mental health, many of which were exacerbated in vulnerable populations.¹⁵

With SARS-CoV-2 now an endemic infection, renewed focus is needed on routine immunization catch-up campaigns and on strengthening health systems, including immunization delivery and infrastructure, to ensure resilience during future disruptive events. Furthermore, vaccine hesitancy increased around the world during the pandemic. Renewed efforts to rebuild trust in immunization programs, including improved communication and a focus on equity and community engagement, especially in historically marginalized populations, are needed.

Importance of child research platforms and networks for pandemic preparedness

When the COVID-19 pandemic began, there was an immediate need to rapidly generate and disseminate evidence about this new disease, a need that became even more urgent with the emergence of MIS-C. Existing pediatric research and surveillance networks such as the Paediatric Active Enhanced Disease Surveillance (PAEDS) network in Australia, Respiratory Virus Hospitalization Surveillance Network (RESP-NET) in the United States (renamed COVID-NET), Pediatric European Network for Treatment of AIDS and Infectious Diseases (Penta-ID), Canadian Paediatric Surveillance Program, and IMPACT pivoted to conducting research on COVID-19, MIS-C, and, later, the impact of vaccination in children.^{4,5} Early data generated by these networks were critical to informing public health measures and vaccination policy in children.

Vaccine safety surveillance programs and networks also proved critical in providing continuous monitoring of the largest vaccine roll-out in history. Programs such as the Canadian National Vaccine Safety Network (<https://canvas-network.ca/>), a participant-based active reporting system, were scaled up (from ~40,000 participants/year to 1.3 million registrants), and international vaccine safety consortia such as the Brighton Collaboration (<https://brightoncollaboration.org>) and Global Vaccine Data Network (<https://www.globalvaccinedatanetwork.org/>) expanded activities with new funding.

The pandemic also mobilized funding for new networks, including long-term studies of vaccine-associated myocarditis, the International Network of Special Immunization Services (INSIS) to investigate mechanisms of rare adverse events following immunization, and the Improving Outcomes of Pediatric COVID-19 Research Network (POPCORN; <https://www.popcornpediatrics.ca>) in Canada, which brought together pediatric emergency, hospitalist, critical care, and infectious disease research networks to establish a platform for pediatric observational and interventional studies, and study of indirect consequences of SARS-CoV-2.^{11,14} However, launching new networks during the pandemic proved challenging because of the rapidly changing COVID-19 landscape and the lengthy processes

needed to establish these networks and prepare sites for enrollment. Ongoing funding is needed to support these networks to maintain readiness for the next pandemic.

Gaps in pediatric research networks became clear with the arrival of the pandemic. For example, lack of clinical trial networks for children hampered studies into treatments for COVID-19 and MIS-C, leading pediatric guidelines to extrapolate from adult data or to rely on small observational studies and expert opinion. Lack of coordination also led researchers to form their own ad hoc networks, leading to duplications. Another gap was the lack of funding and infrastructure to collect bio-samples from pediatric patients. Some sites were able to collect samples on an ad hoc basis, and efforts are underway to combine these cohorts.^{13,14} However, coordinated multicenter prospective studies with sample collection may have accelerated research into biomarkers for severe COVID-19 outcomes and adverse events following immunization.

Conclusion and recommendations

The pandemic was experienced differently by children compared to adults, and important knowledge gaps remain. Improved understanding of the pathophysiology of COVID-19 and MIS-C in children and how they differ from adults is needed to better predict the risk posed by new SARS-CoV-2 variants. Such insight also could inform the response to future novel betacoronaviruses. Further studies are needed to uncover the biological mechanism(s) through which COVID-19 mRNA vaccines trigger myocarditis and pericarditis, including the role of genetic factors, spike protein, and the mRNA-lipid nanoparticle platform. This is important for informing COVID-19 vaccine recommendations for high-risk children and youth as well as the development of mRNA vaccines.

The experience of the COVID-19 pandemic underscores the need for standing national and international networks for pediatric research that can respond to emerging threats. Multidisciplinary networks are needed to study the epidemiology of acute infection; monitor for novel post-infectious clinical entities; identify risk factors for severe disease; evaluate treatments and preventive measures, including vaccine safety and effectiveness; and assess the impacts of public health in-

terventions on child well-being beyond infectious disease. Further research is needed to develop and evaluate strategies to better combat misinformation and rebuild trust in public health. Pandemic preparedness planning should also incorporate strategies to minimize disruptions to routine public health systems, including immunization, and to develop a school closure policy that is data driven, equitable, and supports learners, educators, and families. In summary, greater consideration of children's unique health needs in pandemic preparedness research and planning is important to inform public policy and improve children's health.

DECLARATION OF INTERESTS

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