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REVIEW

Effect of the COVID-19 pandemic on the pediatric infectious disease landscape

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Abstract

This narrative review aims to present an overview of the COVID-19 pandemic's effects on the landscape of pediatric infectious diseases. While COVID-19 generally results in mild symptoms and a favorable prognosis in children, the pandemic brought forth significant consequences. These included persistent symptoms among infected children ("long COVID"), a profound transformation in healthcare utilization (notably through the widespread adoption of telemedicine), and the implementation of optimization strategies within healthcare settings. Furthermore, the pandemic resulted in alterations in the circulation patterns of respiratory pathogens, including influenza, RSV, and *Streptococcus pneumoniae*. The possible reasons for those changes are discussed in this review. COVID-19 effect was not limited to respiratory infectious diseases, as other diseases, including urinary tract and gastrointestinal infections, have displayed decreased transmission rates, likely attributable to heightened hygiene measures and shifts in care-seeking behaviors. Finally, the disruption of routine childhood vaccination programs has resulted in reduced immunization coverage and an upsurge in vaccine hesitancy. In addition, the pandemic was associated with issues of antibiotic misuse and over-prescription.

Conclusion: In conclusion, the COVID-19 pandemic has left a profound and multifaceted impact on the landscape of pediatric infectious diseases, ranging from the emergence of "long COVID" in children to significant changes in healthcare delivery, altered circulation patterns of various pathogens, and concerning disruptions in vaccination programs and antibiotic usage.

What is Known:
- *COVID-19 usually presents with mild symptoms in children, although severe and late manifestations are possible.*
- *The pandemic resulted in a dramatically increased use of health care services, as well as alterations in the circulation patterns of respiratory pathogens, decreased rates of other, non-respiratory, infections, disruption of routine childhood vaccination programs, and antibiotic misuse.*

What is New:
- *Possible strategies to tackle future outbreaks are presented, including changes in health care services utilization, implementation of updated vaccine programs and antibiotic stewardship protocols.*
- *The decline in RSV and influenza circulation during COVID-19 was probably not primarily related to NPI measures, and rather related to other, non-NPI measures implementation, including specific pathogen-host interactions on the level of the biological niche (the nasopharynx).*

Keywords COVID-19 · Pediatric infectious diseases · SARS-CoV-2 · Healthcare services · Vaccines · Antibiotic stewardship

Abbreviations

COVID-19	Coronavirus disease 2019
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
MIS-C	Multisystem inflammatory syndrome in children
HPV	Human papillomavirus
LMIC	Low-middle-income countries
AMR	Antimicrobial resistance

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Introduction

In May 2023, the World Health Organization declared the end of the coronavirus disease 2019 (COVID-19) pandemic, marking a significant milestone in the global fight against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. The pandemic caused a massive global health crisis, which led to a large-scale change in the practice of pediatric medicine, affecting various social, medical, scientific, and behavioral aspects [2]. Scientists and public health officials around the globe were promoted to enhance our understanding of this devastating illness quickly. As a result, 3 years after the outbreak, we have more insight into the pandemic management and control and have witnessed the emergence of new countermeasures. In this article, we will present an overview of our current knowledge of the pandemic effects on the landscape of pediatric infectious diseases. Significant changes will be highlighted and notable breakthroughs, some surprising and others expected, will be presented, while pointing out knowledge gaps which require further exploration.

Direct impact of COVID-19 on children

Acute COVID-19 in children

Children with COVID-19 usually present with mild symptoms and are at lower risk of hospitalization and life-threatening complications, compared with adults [3]. Numerous surveillance studies on a national level confirmed that disease outcomes in children were mild, with fewer hospitalizations and mortality rates than in adults [4–8]. Even in hospitalized cases, only a third presented with a significant respiratory involvement [4, 9–12] Furthermore, severe manifestations of COVID-19, including the multisystem inflammatory syndrome in children (MIS-C), are rare. Although morbidity can be severe, the prognosis of MIS-C and other COVID-19 severe presentations are usually favorable with suitable treatment [13, 14]. The excellent outcomes of young febrile infants with COVID-19 closely resembled other respiratory viral etiologies of fever in this age group, with a low number of fatalities [15].

Long COVID-19

COVID-19 long-term complications were a source of major concern among healthcare providers. There is a variability in reports from different countries regarding the scope of this phenomenon, and the specific symptomology it can present in children affected [16, 17]. An elaborate discussion on this subject will be presented by Töpfer et al.

Burden on healthcare services

Despite the benign course of the disease in the pediatric population, the COVID-19 pandemic significantly impacted healthcare service utilization [18–20]. The lack of understanding of the COVID-19 pathophysiology and the prognosis in children led to a massive investment in resources during the pandemic. The immense burden of the pandemic on healthcare systems and the long-term sequelae of COVID-19 are significant considerations in attempting to create the most effective response at different levels of treatment [21]. In primary care, the COVID-19 pandemic has illustrated how a global health crisis can profoundly alter healthcare delivery within communities, evident by shifts in patient consultation methods [22]. In the realm of secondary and tertiary healthcare systems, the pandemic has shed light on emerging imperatives such as safeguarding the health of healthcare professionals, creating new protocols and collaborative teamwork, and addressing logistical concerns, including the need for the future design of hospitals to enable effective isolation measures [23]. In addition, it is important to highlight the neglect of children with chronic conditions during the pandemic. These patients might have suffered from a lack of diagnosis, treatment, or additional symptomology during the pandemic period.[24]

All of the above should alert healthcare policymakers regarding the need to tackle future outbreaks with various tools, including (but not limited to) telemedicine, cohorts of patients, healthcare professionals training, and maximizing personnel usage [25, 26]. In addition, due to the long but unknown effect of COVID-19, follow-up on patients might be required and taken into consideration by the physician [25, 27].

COVID-19 impact on other viruses/bacteria

Decline in the rates of respiratory infections

During the pandemic, the patterns of some prevalent pediatric infectious diseases changed dramatically [28]. At the peak of COVID-19, a decrease was noted in other respiratory infectious diseases, such as influenza, respiratory syncytial virus (RSV), and other vaccine-preventable diseases [29, 30]. Before 2020, the seasonal peaks of RSV and non-pandemic influenza viruses typically occurred during the winter season in the northern and the southern hemispheres, excluding tropical regions [31, 32]. However, the emergence of the COVID-19 pandemic disrupted these patterns [29, 30] resulting in the absence of regular virus circulation in many areas for over a year, which resurged unexpectedly in various ways [28]. Surprisingly, other respiratory viruses, such as

rhinovirus and enterovirus (RV/EV), as well as adenovirus, have experienced only minor changes in their circulation and remained near pre-pandemic seasonal levels [33]. The decreased infection rate was not limited to viral infections, as the rates of overall and bacteremic pneumonia, along with other pneumococcal diseases, have also decreased [34]. The cause of this substantial reduction is presently unclear and could be attributed to a variety of factors.

Reasons for changes in other respiratory pathogen circulation

Several researchers have attributed these changes to non-pharmaceutical interventions (NPIs) and mitigation measures used in many countries, such as reduced social interactions (social distancing), increased use of personal protective measures, and changes in healthcare-seeking behaviors [35–38]. According to these researchers, non-pharmaceutical interventions during the COVID-19 pandemic altered not only the spread of SARS-CoV-2, but also the predictable seasonal circulation patterns of many endemic viral illnesses in children [39].

In contrast, some researchers were reluctant to accept the argument that NPI campaigns affected the circulation patterns of endemic viral infections. As was mentioned above, the circulation patterns of several respiratory viruses, like rhinovirus, enterovirus (RV/EV), and adenovirus, were not affected as RSV and influenza circulation patterns were [33]. Furthermore, the COVID-19 infection rate, the goal of the NPI campaign, was not necessarily affected by social distancing [40]. Only a successful vaccination campaign was effective in reducing morbidity and mortality rates of the disease caused by SARS-CoV-2 [41, 42].

Evidently, other explanations are needed for the noted changes in RSV and Influenza circulation patterns [43]. Several studies suggested that the phenomenon of reduced RSV and influenza circulation was a result of the competition of viruses with COVID-19 on the biological niche of the nasopharynx, as it resembles the gate point of respiratory infection [28, 44]. Researchers suggested a variety of theories to explain these dynamics. During the peak of the pandemic, this competition was determined by the benefit of numbers and, therefore, to the wide spread of COVID-19 and the near elimination of other viruses' circulation. Indeed, as COVID-19 numbers declined, some reports suggested that several respiratory viruses, such as RSV and influenza, returned to their typical, pre-pandemic circulation pattern [45, 46]. This was driven by natural immunity to SARS-CoV-2 and the increased vaccination rates that led to the development of mucosal immunity [47–49].

The competition between different respiratory viruses (i.e., the changing circulation patterns) was a result of the COVID-19 effect on the biological niche of the nasopharynx itself. SARS-CoV-2 binds to specific receptors on the surface of epithelial cells of the respiratory tract and therefore affects the pathogen-host interaction of viruses with different viral characteristics [50]. One prominent example of this concept was the finding of the differential impact of the pandemic on enveloped vs. non-enveloped viruses. In the case of enveloped viruses, such as influenza, COVID-19 resulted in the near-complete interruption of transmission of those viruses, as opposed to the impact on non-enveloped viruses, like rhinovirus, which were almost not affected [51].

Non-pharmaceutical interventions probably did not affect the pneumococcal transmission, as studies from Israel and France presented steady pneumococcal carriage and density rates in children during the pandemic [34, 52, 53]. Despite this fact, invasive pneumococcal disease (IPD), and other pneumococcal diseases (e.g., pneumonia) rates declined substantially [34]. Therefore, it is more likely to assume that the decline in IPD and pneumonia rates was not affected by NPI's unmeasured effect on carriage rate, but rather by the disruption of co-infection of viral agents, such as RSV, needed to generate the disease [54].

Notably, there were reports of resurgence of RSV and other respiratory pathogens post-COVID-19 pandemic [43, 55]. It was suggested that this recuperation can be a result of genetic bottlenecking brought on by case reduction during the COVID-19 pandemic, now leading to a rise in viral genetic diversity [43, 56]. The Pediatric Infectious Disease Group, in an attempt to elucidate the unanticipated upsurge in respiratory infections occurring between seasons on a global scale, introduced the concept of "immunity debt" [57]. According to this hypothesis, extended periods of limited viral exposure might have led to an increased pool of immunologically susceptible individuals, notably among children. Consequently, the re-emergence of viruses could result in more severe disease outcomes. Supporting this evidence is the resurgence of RSV cases during the winter of 2021–2022 in Italy [58], increased incidence of IPD in England [59], and other reports of hand-foot-mouth epidemic in Egypt [60]. Yet, this phenomenon is not yet fully explained [43, 56].

Future implications

The potentially modified effect of RSV and influenza on IPD suggests that interventions targeting respiratory viruses, such as passive immunization like monoclonal antibodies or active vaccines for RSV and influenza, could prevent a large proportion of pediatric IPD and pneumonia cases in the future [52, 53, 61, 62]. When preparing for the next pandemic, it is crucial to understand the possibility of displacement of viral transmission and seasonality and tackle this by vaccination against RSV and flu according to age and not necessarily according to seasonality.

Reduction in other, non-respiratory, infectious agents

COVID-19 pandemic effects were noted to be wider than just on infectious respiratory disease, as reduced rates of other prevalent diseases in children, such as urinary tract and gastrointestinal infections, were noted, during the pandemic [63]. A study examining data on 375,000 children from Massachusetts pediatric primary care network reported a decline in 12 common childhood infections, including skin and soft tissue infections (−35%) [64]. In Denmark, acute gastroenteritis in children decreased significantly during COVID-19 restrictions [65]. Similarly, there was a decrease in the incidence of urinary tract infections in Finnish children, with the most prominent decrease observed in daycare-aged children [66]. Probably none of the prevalent infectious mentioned above is presumed to be directly affected by SARS-CoV-2. Still, all those infections presented a notable decline in their incidence. This phenomenon can be explained in several manners [39, 66]. First, improved hygiene measures and social restrictions may have influenced the transmission of pathogens. Second, changes in care-seeking behaviors can play a role as individuals opt out of seeking medical care for such ailments. This argument can also explain why children referring to the emergency department, in case of febrile urinary tract infections, were more severely ill than in the previous two years, probably due to a delayed access, caused by the fear of potential hospital-acquired SARS-CoV-2 infection [67]. In addition, the decline could be a result of a lack of laboratory services and other public health resources invested differently [39, 68].

As for the post-pandemic period, a growing body of knowledge is collected to understand the effect of COVID-19 on the behavior of non-respiratory infectious agents. For example, the severity and number of group A streptococcus cases in Spain and France in children increased significantly in 2022, compared to the pre-pandemic COVID-19 period [69, 70]. Possible explanations might be "immune debt" [57] or genetic changes of the pathogen itself that are not fully understood [71].

Future implications

Understanding the effect of the pandemic on the landscape of non-respiratory agents is crucial for our efforts to protect children from severe illness. Health system resources should be invested fluidly, according to recorded data, in order to detect and treat the current map of infectious diseases. Special campaigns should be considered to encourage parents to seek treatment earlier to reduce severe disease sequelae. In addition, investing in effective tools, like improving hygiene measures, can help reduce the transmission of pathogens and prevent disease.

Research (drugs, vaccines, publications)

COVID-19 has had a profound impact on global pediatric research. The pandemic has witnessed an unprecedented surge in research publications dedicated to this disease, encompassing efforts to find solutions and explore various applied or related aspects [72–74]. A significant decline in non-COVID-19 research alongside an exponential rise in COVID-19-related publications was observed [75]. Additionally, a displacement of clinical trial publications (−24%) and a redirection of research grants away from fields less closely tied to COVID-19 were noted [76]. This rapid influx of COVID-19 publications, driven in part by editorial policy, may have influenced the overall quality of research output, leading to a neglect of COVID-19-unrelated publications. On the other hand, the worldwide scientific adaptation to COVID-19 has led to unprecedented international collaboration that was considered impossible before [76, 77].

Vaccines

The rapid development of vaccines during the COVID-19 pandemic has been a major achievement in the history of modern medicine [78]. The development timeline of the COVID-19 vaccine is nothing short of remarkable, with the first SARS-CoV-2 sequences published to phase 1 trials completed in just 6 months. Additionally, in an effort to promote vaccination in particular vulnerable cohorts, such as pregnant and breastfeeding women, children, and immunocompromised patients, these populations were included in vaccine trial very early in the course of the trials, when the benefit-risk profile of these vaccines was still limited [79]. This timeline starkly contrasts the typical vaccine development timeline of 3 to 9 years [80]. Several factors have contributed to the accelerated development of COVID-19 vaccines. Firstly, there was a prior understanding of the spike protein significance in coronavirus pathogenesis and the importance of neutralizing antibodies against it for immunity [81]. Secondly, nucleic acid vaccine technology platforms have evolved, allowing for the rapid creation and manufacture of thousands of doses once the genetic sequence is known. Lastly, development activities can be conducted in parallel without increasing risks to study participants, further accelerating vaccine development. With the demonstrated clinical efficacy of the mRNA-based vaccines, the usage of such technology to prevent and control future epidemics and pandemics looks promising [82]. This technology is also promising in other, non-infectious disease prevention. Indeed, some early studies suggested a potential benefit from mRNA-based vaccines in preventing and treating specific cancers [83–85].

Other issues neglected (e.g., decline in vaccine uptake, burden on the health system, society trust in vaccines/anti-vaccine movement)

Impact on routine vaccination programs

The COVID-19 pandemic has disrupted routine childhood vaccination programs in many countries. Immunization coverage was lower in COVID-19-affected children than in unaffected children, ranging from as low as 2% lower for BCG and hepatitis B, 0 to 9% for diphtheria, tetanus, and pertussis vaccines, followed by a 10% reduction for polio [86]. Coverage reduction was more remarkable in vaccine doses given in later age groups as at least a 28% decrease was noted in human papillomavirus (HPV) vaccination in England in the year 2020 [87]. It is important to recognize that among population subgroups, COVID-19 affected those from rural areas and low middle-income countries (LMIC), who experienced the highest reduction in vaccine coverage [86, 88]. Lockdowns, travel restrictions, and reduced access to healthcare facilities have resulted in missed or delayed vaccinations for many children. For example, the pandemic limitations have directly affected HPV vaccination rates which in some countries is administered at schools [87]. Another reason that cannot be ignored is the anti-vaccine activists around the world, which led to a break of trust and promoted vaccine hesitancy among many parents worldwide [89–91]. This has raised concerns about potential outbreaks of vaccine-preventable diseases, such as measles and pertussis, as well as decreased immunity in the pediatric population, which may have long-term consequences on overall public health [92, 93].

Lastly, health systems themselves attributed the decline in vaccination rate, as they decided to redirect resources, to focus on the SARS-CoV-2 vaccination campaign. For instance, Israel officials decided to suspend its yearly influenza vaccination campaign during the pandemic, to improve public complaints about the new SARS-CoV-2 vaccines (personal communication).

Nations must prioritize adequate vaccination to safeguard against potential pandemics caused by vaccine-preventable diseases including mapping populations who suffered from reduced vaccination rates during the pandemic and filling these gaps for the future, while investing in restoring public trust in vaccination campaigns like influenza that were neglected during COVID-19. For example, expanding vaccine programs to a wider range of age groups could help to increase the coverage rates of HPV. It is advised to streamline the vaccination process by reducing waiting times at health centers, addressing parental concerns and anxieties, improving vaccine availability, and expanding access to remote regions. Ensuring comprehensive catch-up programs is crucial, particularly in LMIC, to prevent any gaps in vaccine coverage.

COVID-19 effect on antibiotic use, stewardship programs, and antibiotic resistance

The COVID-19 pandemic intensified the misuse of drugs, including antibiotics, with no evidence of effectiveness in treating SARS-CoV-2 infection [94]. Several studies attributed the misuse of antibiotics to physicians' fear of co-infection between SARS-CoV-2 and drug-resistant bacteria or fungi in adults [95]. Others explain that pneumonia from SARS-CoV-2 is challenging to distinguish from other viral and bacterial etiologies. Increased prescriptions in adults may also be associated with a higher prevalence of comorbidities and risk of adverse outcomes. Even though antibiotic prescription at COVID-19-related visits was substantially lower for children and adolescents than adults, the phenomenon has increased the prevalence of antibiotics in medical centers and communities [96–98]. The gratuitous use of antibiotics for COVID-19 treatment and the lack of a coherent treatment strategy raise concerns about the emergence of antimicrobial resistance (AMR) [99]. Broad-spectrum antimicrobials are frequently prescribed to patients hospitalized with COVID-19, which potentially catalyzes the development of AMR. In a systematic review and meta-analysis during the first 18 months of the pandemic, AMR prevalence was high in COVID-19 patients and varied by hospital and geography, although substantial heterogeneity existed [100].

Physicians and public health professionals should prepare for the next outbreak. Health systems should encourage antimicrobial stewardship as a priority while dealing with a viral pandemic. In addition, antibiotic stewardship guidelines should be enforced to avoid antibiotic misuse and contain the emergence of antimicrobial resistance. Vaccine development should focus on desirable pathogens associated with drug resistance that emerge during a viral pandemic. Immunization programs, including maternal vaccination, should be developed to offer circumventing defense in case of a new global health crisis.

Conclusion

In this article, we attempted to present an overview of our current knowledge of the pandemic's tremendous effects on the landscape of pediatric infectious diseases, in discrepancy to its mild clinical outcomes. We raised our concerns about persistent symptoms among infected children and necessitated substantial adaptations in healthcare utilization, especially the prompting of the

implementation of telemedicine and optimization strategies for healthcare personnel.

We presented the alterations in the circulation patterns of respiratory pathogens, including influenza and RSV, and described their relation to the pandemic with possible explanations for the changes recorded, in comparison to other viral and pneumococcal agents. COVID-19 effect was not limited only to respiratory infectious diseases, as other non-respiratory infectious agents, such as urinary tract and gastrointestinal pathogens, have displayed decreased transmission rates, likely attributable to heightened hygiene measures and shifts in care-seeking behaviors.

Notably, the disruption of routine childhood vaccination programs has resulted in reduced immunization coverage and an upsurge in vaccine hesitancy. In addition, when combating antimicrobial resistance, it is important to address the issues of antibiotic misuse and over-prescription. In preparation for future outbreaks, comprehensive vaccination programs must be prioritized, warranting concerted efforts from physicians and public health professionals.

Authors' contributions Moshe Shmueli, Idan Lender, and Shalom Ben-Shimol have all contributed equally to the conception and design of the review, drafted and revised the manuscript and approve its publication.

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Declarations

Conflict of interest Shalom Ben-Shimol has received within the last 35 months grants by Pfizer. He serves as scientific consultant and on the review board of Pfizer and MSD, and belongs to the speaker bureau of Pfizer, MSD, and GSK. The other authors do not report any conflict of interest.

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