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Munblit, Daniel; Greenhawt, Matthew; Brough, Helen A; Pushkareva, Anna; Karimova, Diana; Demidova, Anastasia; Warner, John O; Kalayci, Omer; Sediva, Anna; Untersmayr, Eva; Rodriguez Del Rio, Pablo; Vazquez-Ortiz, Marta; Arasi, Stefania; Alvaro-Lozano, & Montserrat [and 4 more]










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Allergic diseases and immunodeficiencies in children, lessons learnt from COVID-19 pandemic by 2022: A statement from the EAACI-section on pediatrics

Daniel Munblit¹  | Matthew Greenhawt²  | Helen A. Brough^{3,4} | Anna Pushkareva⁵ | Diana Karimova⁵ | Anastasia Demidova⁵ | John O. Warner¹  | Omer Kalayci⁶  | Anna Sediva⁷ | Eva Untersmayr⁸ | Pablo Rodriguez del Rio⁹ | Marta Vazquez-Ortiz¹ | Stefania Arasi¹⁰  | Montserrat Alvaro-Lozano¹¹ | Sophia Tsabouri¹²  | Elena Galli¹³  | Burcin Beken¹⁴  | Philippe A. Eigenmann¹⁵ 

¹Inflammation, Repair and Development Section, Faculty of Medicine, National Heart and Lung Institute, Imperial College London, London, UK

²Section of Allergy and Clinical Immunology, Children's Hospital Colorado, University of Colorado School of Medicine, Aurora, Colorado, USA

³Children's Allergy Service, Evelina Children's Hospital, Guy's and St. Thomas' Hospital, London, UK

⁴Paediatric Allergy Group, Department of Women and Children's Health, School of Life Course Sciences, King's College London, London, UK

⁵European Academy of Allergy and Clinical Immunology (EAACI), Zurich, Switzerland

⁶Pediatric Allergy and Asthma, School of Medicine, Hacettepe University, Ankara, Turkey

⁷Department of Immunology, 2nd Medical Faculty, Charles University and Motol University Hospital, Prague, Czech Republic

⁸Institute of Pathophysiology and Allergy Research, Center of Pathophysiology, Infectiology and Immunology, Medical University of Vienna, Vienna, Austria

⁹Allergy Department, Hospital Infantil Universitario Niño Jesus, Madrid, Spain

¹⁰Translational Research in Pediatric Specialities Area, Division of Allergy, IRCCS, Bambino Gesù Children's Hospital, Rome, Italy

¹¹Allergology and Clinical Immunology Department, Institut de Recerca Sant Joan de Déu, Hospital Sant Joan de Déu, Universitat de Barcelona, Barcelona, Spain

¹²Child Health Department, University of Ioannina School of Medicine, Ioannina, Greece

¹³Pediatric Allergology Unit, Department of Pediatric Medicine, S.Pietro Hospital Fatebenefratelli, Rome, Italy

¹⁴Department of Pediatric Allergy and Immunology, Acibadem University School of Medicine, Istanbul, Turkey

¹⁵Pediatric Allergy Unit, Department of Woman, Child and Adolescent, University Hospitals of Geneva, Geneva, Switzerland

Correspondence

Daniel Munblit, Inflammation, Repair and Development Section, National Heart and Lung Institute, Faculty of Medicine, Imperial College London, London, UK.
Email: daniel.munblit08@imperial.ac.uk

Editor: Jon Genuneit

Abstract

By the April 12, 2022, the COVID-19 pandemic had resulted in over half a billion people being infected worldwide. There have been 6.1 million deaths directly due to the infection, but the pandemic has had many more short- and long-term pervasive effects on the physical and mental health of the population. Allergic diseases are among the most prevalent noncommunicable chronic diseases in the pediatric population, and health-care professionals and researchers were seeking answers since the beginning of pandemic. Children are at lower risk of developing severe COVID-19 or dying from infection. Allergic diseases are not associated with a higher COVID-19 severity and mortality, apart from severe/poorly controlled asthma. The pandemic

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disrupted routine health care, but many mitigation strategies, including but not limited to telemedicine, were successfully implemented to continue delivery of high-standard care. Although children faced a multitude of pandemic-related issues, allergic conditions were effectively treated remotely while reduction in air pollution and lack of contact with outdoor allergens resulted in improvement, particularly respiratory allergies. There is no evidence to recommend substantial changes to usual management modalities of allergic conditions in children, including allergen immunotherapy and use of biologicals. Allergic children are not at greater risk of multisystem inflammatory syndrome development, but some associations with Long COVID were reported, although the data are limited, and further research is needed. This statement of the EAACI Section on Pediatrics provides recommendations based on the lessons learnt from the pandemic, as available evidence.

KEYWORDS

allergic diseases, allergy, asthma, care, children, COVID-19, eczema, food allergy, immunodeficiencies, lockdown, long covid, MIS-C, pandemic, post-covid-19 condition, SARS-CoV-2, vaccination

1 | INTRODUCTION

The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has placed a significant burden on public health worldwide. As of April 2022, the number of confirmed coronavirus disease 2019 (COVID-19) cases globally is reaching half a billion individuals.¹ The acute presentation, clinical characteristics, risk factors, and outcomes of COVID-19 have now been widely investigated² in different populations and age groups.³⁻⁵ It has become evident that a subset of patients suffering from COVID-19 subsequently experience consequences of SARS-CoV-2 infection, such as Long COVID/post-COVID condition or multisystem inflammatory syndrome weeks to months after the acute phase^{6,7} bringing new challenges to health-care professionals, researchers, patients and their families.

European Academy of Allergy and Immunology (EAACI) section on pediatrics published a statement regarding the management of childhood allergies and immunodeficiencies during respiratory virus epidemics in the first months of COVID-19 pandemic.⁸ Since then, hundreds of studies investigated specifics of the pandemic, SARS-CoV-2 infection and associated factors in children with allergic diseases and primary immune deficiencies. We acknowledge that the views presented in this manuscript are based on expert opinion, but an extensive electronic search of MEDLINE and EMBASE databases via OVID was performed on December 27, 2021, using both free text and MESH terms, to inform the statement development process. The search strategies are provided in [Supplementary material](#).

Although the COVID-19 pandemic is now under a relatively good control, at least in some parts of the world, thanks to wide implementation of vaccination programs, information, and advice presented in this manuscript are based on extensive experience gained throughout the pandemic and may be helpful for the future respiratory virus epidemics.

Key Message

This statement from the EAACI-section on pediatrics provides recommendations regarding allergic diseases and immunodeficiencies in children based on the lessons learnt from the COVID-19 pandemic as per current best evidence.

2 | COVID-19 IN CHILDREN

Although COVID-19 predominantly affected adult populations,⁹ approximately two in ten laboratory-confirmed COVID-19 cases in the United States were children and young people.¹⁰ Children often experience different symptoms when compared with adults,¹¹ with a wide range of clinical features present at the time of hospital admission.^{3,12,13} COVID-19-associated hospitalization rates among children aged <18 years accounts for 8.0 per 100,000 with the highest rate among children aged <2 years (24.8%).¹⁴ Although most children experience mild COVID-19, severe disease and sequelae may still occur. Among hospitalized children, up to a third of patients require intensive care unit (ICU) admission,¹⁴ some experience single or multi-organ failure, and many require respiratory support.

Overall, however, COVID-19 is associated with a favorable prognosis in children. United Nations Children's Fund (UNICEF) data, as of January 2022, suggests that less than half percent of all COVID-19 deaths occurred in children and young people, with 58% of this number being adolescents aged 10–19 and 42% children aged between 0 and 9 years.¹⁵ Similarly, nationwide data from the United States showed that children ranged from 1.5% to 4.6% of total cumulated hospitalisations, and from 0.1% to 1.5% of all child COVID-19 cases resulted in hospitalization with <0.01% of all child COVID-19 cases resulting in death.¹⁶

There is no single explanation of why children are less susceptible to severe COVID-19, but a few hypotheses were proposed. Children have lower expression of ACE2 receptors in their nasal and lower airways epithelium when compared with adults¹⁷ and are more likely to have acquired immunity to common coronaviruses due to common exposure to a wide variety of pathogens.¹⁸ These viruses may be potentially associated with the downregulation of ACE2 expression in respiratory epithelial cells and antibodies that potentially cross-react to SARS-CoV-2¹⁸ as well as more robust interferon (IFN) response upon the entry of the virus.¹⁹ Children are also less likely to have chronic premorbidities that may contribute to milder COVID-19 and more favorable outcomes.

2.1 | Are there known risks of allergic children contracting SARS-CoV-2 infection?

Earlier studies suggested that there was no difference between allergic and nonallergic children in clinical, laboratory and immunological findings and allergy does not seem to be a risk factor for either development or severity of SARS-CoV-2 infection.²⁰⁻²⁸ However, data from large national incident cohort studies from Europe and the United States demonstrated that individuals with asthma may be at higher risk of hospital admission with COVID-19,²⁹⁻³¹ particularly school-aged children with previous recent hospital admission or two or more courses of oral corticosteroids.³⁰ One of the potential explanations behind this phenomenon may be related to the ACE2 expression within bronchial epithelium with some evidence suggesting that ACE2 expression is linked to upregulation of viral response genes in a subset of type 2-low patients with asthma.³² It was also suggested that co-infections with rhinovirus and SARS-CoV-2 may pose significant risks of patients with asthma, due to potential role of rhinovirus in ACE2 overexpression in patients with asthma.³³ However, comorbid asthma or other allergic diseases have not proven thus far to pose a risk of severe COVID-19 outcomes or severe disease.³⁴ Indeed, a systematic review suggested preexisting asthma reduced risks³⁵ and increasing levels of allergy in children with asthma was associated with lower ACE2 expression in nasal epithelium harvested from brush-biopsies.³⁶

3 | PANDEMIC IMPACT ON PATIENT CARE AND MITIGATION STRATEGIES

COVID-19 pandemic resulted in restrictive measures implementation, which inevitably affected delivery of health-care services. The problem was at its' peak in the first months of the pandemic, but some restrictions are still in place. Findings of a recent World Health Organization Global survey conducted from November to December 2021 demonstrated disruptions in all health-care settings worldwide.³⁷ The pandemic overloaded emergency departments but also had a detrimental effect on noncommunicable disease resources and services.³⁸ Similar patterns were observed in allergy and clinical

immunology care with a reduction in face-to-face,³⁹ immunotherapy services,⁴⁰ allergy testing, and hospital procedures, such as oral food challenges, immunoglobulin and biologicals administration⁴¹ as well as staffing problems.⁴² Some concerns were raised with regard to accessibility of "safe" foods and food allergy-related health services among food-allergic children and their carers.^{43,44} While the pandemic impacted the entire population, certain groups were found to be more vulnerable, which merits further consideration with regard to potential mitigation strategies. COVID-19 resulted in greater parent-reported resource losses and greater reductions in health-care access for Black, indigenous or other ethnic minority groups.⁴⁵ This effect was particularly substantial in families of children with asthma.

3.1 | Is it safe to perform routine clinical procedures in home settings?

A wide range of mitigation strategies, both regarding allergy diagnosis and management, was used throughout the time of pandemic, leading to some innovative approaches otherwise unlikely to be tested. A study in the United Kingdom (UK) attempted home allergy testing, sending kits for blood collection via finger prick sampling to the families. This approach was found particularly helpful in those residing far from the hospital and keen to avoid unnecessary travel during the pandemic and provided an opportunity to confirm or exclude allergy.⁴⁶ Another study from the UK showed that telehealth team medicine approach in severely asthmatic children with home spirometry resulted in reduced admissions, fewer missed visits, and no increase in steroid or antibiotic prescriptions. The virtual approach was felt to be successful in maintaining asthma control.⁴⁷

Following the closure of allergy services in many countries, routine oral food challenges (OFC) and drug challenges were canceled. Some centers adopted strategies to mitigate delays in the service provision. OFC were safely performed in an adapted field hospital⁴⁸ and empty COVID stepdown facility⁴⁹ through cross-hospital multidisciplinary collaboration, and anaphylaxis events were successfully managed in both settings^{48,49} with a large number of OFC performed on a daily basis.

A study in Japan followed over a thousand parents initiating home-based oral immunotherapy (OIT)⁵⁰ in their children and found that one of two children continued the home-based OIT well during pandemic.⁵¹ Association between parental anxiety about the disruption of the medical care system and lack of OIT progress was found, which highlights a need for additional family support which may result in a higher success rate of the treatment.

Although advancements were made at the time of pandemic, and mitigation strategies tested may provide us with useful tips regarding approaches to patient needs in the postpandemic era, they should not be expedited in routine clinical practice without additional rigorous validation. Many studies had limited sample size and were performed in a single center which does not allow for extrapolation of the results at an international scale. Specifically, oral food challenges for IgE-mediated food allergy and unsupervised home introduction

of possible allergenic foods should not be encouraged at home in the absence of established protocols and training.

3.2 | Are there any known benefits and harms of lockdown measures for allergic children?

Although there were detrimental effects on children and young people's physical and mental well-being during the pandemic, some studies reported improvements in seasonal respiratory allergy symptom control, particularly during lockdown measures.^{52,53} Nonpharmaceutical interventions, such as handwashing, masks, and social/physical distancing, reduction in the concentrations of traffic-related air pollutants^{54,55} and decline in other respiratory infections incidence, may have contributed to reduced impact on allergic disease^{56,57} particularly respiratory,^{58–63} number of exacerbations^{59,62,64–71} and the odds of emergency room visit and/or hospital admissions.^{59,66,72–78} Improvements were normally associated with time spent at home, and stronger effects were found in some studies among individuals with severe disease.⁵² Despite strong associations of lockdown measures and improvements in allergic children, anxiety levels and perceptions of elevated health risk were increased among carers,⁷⁹ regardless of the actual health state of the child.⁶¹ Although increased levels of anxiety at the time of pandemic were described in the general population, particularly fuelled by the infodemic,^{80,81} some studies reported higher anxiety and poor health-related quality of life in mothers of allergic children.⁸²

At the same time, lockdown measures resulted in children spending more time indoors, and several studies reported those allergic to house dust mite having significantly worse nasal symptoms⁸³ and increased need for medications when compared with the same period in the pre-pandemic year.⁸⁴ Preliminary data from the CORAL birth cohort showed higher rates of egg sensitization and eczema in children born during the first pandemic lockdown when compared with a national historic data.⁸⁵ Some protective measures, such as more intensive hand hygiene, were reported to be associated with rapid development of hand eczema among a high proportion of young children⁸⁶ and adults.⁸⁷ It is also worth noting that some sources reported increased number of children with adenovirus, rhinovirus, respiratory syncytial virus (RSV), human metapneumovirus, influenza, and parainfluenza visiting hospitals after lockdown.⁸⁸

3.3 | Can telemedicine substitute face-to-face clinics?

Routine health-care services disruption resulted in an increased use of telemedicine^{89,90} for the management of all allergic conditions, particularly respiratory allergies,³⁹ eczemas,⁹¹ urticaria and food allergy^{92–94} as well as home introduction food services.⁹⁵ Wearable sensors were used in some countries to continuously track personal location and physical activity and assess compliance with the

lockdown measures in children with asthma.⁹⁶ Data from many studies suggest that it is possible to achieve a good control of allergic diseases⁶⁶ in most children using follow-up telemedical care and mobile applications,^{39,97,98} and that it may transform existing models of allergy care.^{99–101} Overall, similar patient satisfaction with in-person, video, and telephone consultations during the COVID-19 pandemic was reported.¹⁰² A plethora of different support models focused on remote care provision (e.g., home food introduction protocols, educational and supportive videos, written guidelines, online chats and 24-h hotlines). Stratification against level of risk in a particular individual was developed at the time of pandemic and may become permanent.¹⁰³

Less personal consultations, "lack of physical touch," inability of dermatological conditions proper assessment and feeling of consultation and diagnostic procedures being more disjointed were named among the main disadvantages of telemedicine,^{100,104} and the majority would still prefer for their children to be seen in a face-to-face clinic.¹⁰⁵ Telemedicine has many advantages, but it is important to note that even for telemedical consultations, children still need to be accompanied by their parents/carers and potential additional costs, ethical and legal aspects as well as sociocultural specifics merit further investigations before telemedicine is implemented widely.¹⁰⁶

4 | MANAGEMENT OF ALLERGIC DISEASES DURING PANDEMIC

Multiple statements and position papers outlined recommendations regarding management of allergic conditions at the time of pandemic.^{8,107–110} Overall, there is no evidence suggesting that allergic individuals merit special consideration and that substantial changes should be made to routine practice, beyond issues stemming from masking/social distancing and local governance of aerosolising office-based procedures. Similar approaches apply to children with allergic conditions, and they should remain on their usual medications during the time of pandemic.⁶⁴ Topical medications widely used in treatment of allergic diseases, such as antihistamines and corticosteroids, can be safely continued even in patients at risk of COVID-19.¹¹¹ Indeed, although there is conflicting evidence, they may have protective effects.

4.1 | Are there any precautionary measures related to treatment of allergic diseases to be aware of?

Routine clinical practice can be delivered in a regular fashion, accounting for local regulatory measures depending on COVID-19 spread and vaccination rates. It is highly recommended, however, to avoid/minimize use of nebulized medication or other aerosol-generating procedures where possible, to reduce the risk of spreading virus to health professionals and other patients/family members.¹¹⁰

4.2 | Should allergen immunotherapy be continued at the time of pandemic?

Allergen immunotherapy (AIT) is usually safe, and a widely used treatment method with demonstrated effectiveness in allergic rhino-conjunctivitis and asthma management,¹¹² but is normally administered in clinical settings in light of potential systemic reactions. Some real-life and modeling studies at the time of pandemic demonstrated that home immunotherapy self-administration can be a safe and cost-effective option if patients are carefully preselected.¹¹³ On average, one in three patients managed with subcutaneous immunotherapy (SCIT) discontinued the treatment during the COVID-19 pandemic^{92,114} with being infected with COVID-19 and thinking that the AIT practice stopped because of pandemic were among the most common reasons for cessation. An international survey of physicians carried out by EAACI reported no concerns regarding reduced tolerability of AIT under real-life circumstances.¹¹⁵ Overall, SCIT and sublingual immunotherapy (SLIT) can be safely continued in any individual not infected with SARS-CoV-2 infection.¹⁰⁷ "In symptomatic patients with exposure to or contact with SARS-CoV-2-positive individuals, or patients with positive test results (RT-PCR)" AIT should be discontinued.¹⁰⁷ It is desirable to recommend SLIT over SCIT at the time of pandemic as the latter is associated with multiple hospital visits, putting an individual at unnecessary risk of contracting COVID-19.

4.3 | Is it safe to use biological therapy at the time of pandemic?

Use of biological therapy in adolescents with moderate-to-severe atopic dermatitis was under debate during the first wave of pandemic.¹¹⁶ Later research studies demonstrated that dupilumab use even among individuals infected with COVID-19¹¹⁷ was not associated with severe outcomes and may potentially reduce COVID-19-related severity,¹¹⁸ and can be safely used during pandemic.¹¹⁹ Although biological therapy is normally delivered in clinical settings, home administration in severe chronic urticaria¹²⁰ and asthmatic children, supported by video calls and home spirometry, was shown to be feasible, safe and is positively perceived by children and their carers.¹²¹ There is no reason to suggest that noninfected individuals using biological therapy (at least omalizumab and dupilumab) for the management of allergic diseases should not continue using it.¹⁰⁸

5 | ACUTE COVID-19 IN PATIENTS WITH PRIMARY IMMUNE DEFICIENCY

Children with primary immune deficiency (PID) were the main focus of concern since the very beginning of the pandemic, particularly in the absence of SARS-CoV-2 vaccines. Although PID is among main

preexisting conditions associated with COVID-19 in children,¹²² patients with antibody or phagocytic defects and those with combined PID who have already been transplanted are more likely to get asymptomatic or mild COVID-19.¹²³

Data regarding mortality risk in patients with immune deficiency are conflicting with some studies showing no increase in patients with PID,¹²⁴⁻¹²⁷ others reported immunodeficiency to be associated with a greater risk of death than that in the general population.¹²⁸⁻¹³¹ Severity was more often associated with preexisting comorbidities and age rather than type of PID¹²⁹ and high level of awareness, extra-precautions, and self-isolation were named among potential protective factors.¹²⁵ Recently published data, however, suggested that combined immune deficiency and immune dysregulation were among the most vulnerable inborn errors of immunity subgroups, associated with higher mortality risk of COVID-19 infection.¹³² Special molecular defects associated with deficiency of the IL-1 receptor (DIRA deficiency), STK4 deficiency (combined immunodeficiency), and RAB27A deficiency (diseases of immune dysregulation) were also associated with a higher mortality from COVID-19,¹³³ but these results require further confirmation due to the rarity of these defects. Children with APS1, immune dysregulation due to an error in central tolerance seem to be in an increased danger due to their blocking of IFN response by preexisting antibodies to IFN type I.¹³⁴

5.1 | Is there a need for practice change in patients with primary immune deficiency?

There is a need for the development of specific therapies for patients with inborn errors of immunity, particularly subtypes more prone to infection development and associated with unfavorable prognosis. Patients with primary immune deficiency are among the most vulnerable population and must be vaccinated to reduce the risks of severe COVID-19 illness and death. As immune response to SARS-CoV-2 vaccines may differ in people with primary immune deficiency, individual approach is required and specific guidance has been developed by major organizations, such as Centers for Disease Control and Prevention (CDC).¹³⁵ It is important to note that parental anxiety about the need to come to the hospital for IVIG therapy¹³⁶ and running out of medications¹³⁷ was reported at the time of pandemic, which requires attention and patient reassurance. Transition from clinic-based to home-based immune globulin treatment in selected patients was shown to be made successfully, and home-based IVIG or subcutaneous immune globulin (SCIG) may represent a safe alternative for high-risk patients to decrease potential exposures at the time of pandemic.¹³⁸ It is well established that most children admitted to the hospital with severe COVID-19 have not been fully vaccinated or were not eligible for vaccination. In the absence of reliable treatments, mitigating progression to severe COVID-19 vaccination is the primary prevention strategy.

6 | MULTISYSTEM INFLAMMATORY SYNDROME (MIS-C)

Although children normally face a less severe clinical course with acute COVID-19 infection,¹³⁹ it is difficult to estimate long-term impact of acute infection, as well as cumulative influence of the infection with the pandemic restrictions on their health. It may well continue for years, affecting different areas of their life, such as education, emotional state, financial well-being and potential direct and indirect effects on physical and mental health.¹⁴⁰ The United Nations (UN) warned of “unprecedented risks to the rights and safety and development of the world's children.”¹⁴¹

In May 2020, a case series in London described children presenting with hyperinflammatory shock showing features similar to atypical Kawasaki disease, Kawasaki disease shock syndrome or toxic shock syndrome.¹⁴² This was the first report of previously unknown consequence of COVID-19 infection, which has now been described in several countries worldwide¹⁴²⁻¹⁴⁴ and defined as a multisystem inflammatory syndrome in children (MIS-C)¹⁴⁵ or pediatric inflammatory multisystem syndrome temporally associated with COVID-19 (PIMS-TS).

Systems-level analyses of blood immunological markers demonstrated that the inflammatory response in MIS-C features differ from the cytokine storm during severe acute COVID-19, while sharing several features with Kawasaki disease, differing with regards to T-cell subsets, interleukin (IL)-17A, and biomarkers associated with arterial damage.¹⁴⁶ Recent research demonstrated association of MIS-C with the combination of HLA A*02, B*35 and C*04 alleles suggesting potential genetic susceptibility.¹⁴⁷

MIS-C is fortunately a very rare consequence of COVID-19 with reported incidence of 316 (95% CI, 278–357) per 1,000,000 SARS-CoV-2 infections.⁷ Common approaches to the management of children with MIS-C manifestations include intravenous immune globulin (IVIG), corticosteroids or biologic agents in various combinations, depending on clinical settings.¹⁴⁸ The best available treatment modality is still under consideration with outcomes of two large observational studies bringing conflicting results regarding the efficacy of management with IVIG, glucocorticoids or a combination of both.^{149,150}

6.1 | Are children with allergic conditions at risk of MIS-C development?

Data regarding potential risk factors are still emerging, and available evidence is limited. Risk factors associated with MIS-C development included male sex, Black/African American and Hispanic or Latino ethnic group, younger age, obesity and not having a pediatric complex chronic condition.^{7,143,151} There are so far no data suggesting that children with allergic diseases are at higher risk of MIS-C development, episode severity or mortality. There are also no specific recommendations regarding the management of allergic children with MIS-C as there is no evidence available to suggest that any alterations to usual approaches are necessary.

7 | LONG COVID/POST-COVID-19 CONDITION

Although most people recover from COVID-19, many report a wide range of persistent signs and symptoms months and even years after initial SARS-CoV-2 infection.¹⁵² Many terms are used to describe COVID-19 consequences condition, including “post-COVID syndrome,” “post-acute sequelae of SARS-CoV-2 infection (PASC),” but Long COVID remains the most widely used term, which is highly preferred by people with lived experience.^{153,154} In early 2021, the World Health Organization (WHO) set up a technical working groups to provide clinical definition for Long COVID and suggested using the term “post COVID-19 condition”,¹⁵⁵ with an International Classification of Diseases (ICD) code U09.9 that became effective on October 2021. Later, a clinical case definition of post-COVID-19 condition was developed by the WHO as a result of an international Delphi consensus¹⁵⁶ and research definition for children and young people was proposed.¹⁵⁷

Although health authorities quickly recognized the importance of Long COVID,² children remained largely neglected at the time of pandemic, with most research being focused on previously hospitalized adults.⁶ As children have been much less likely to be admitted to hospital, pediatric Long COVID has been largely overlooked, and concerns have been raised about the lack of pediatric services and studies in children postacute COVID-19.^{158,159} Although data regarding incidence/prevalence of Long COVID in children and risk factors associated with the development of this condition are lacking, recent research provide some preliminary information. Consequences of COVID-19 in children and young people are similar to those reported in the adult population and often include fatigue, weakness, cognitive problems, skin rashes, and many more,¹⁶⁰⁻¹⁶² but it is hard to estimate the real prevalence due to the small number of controlled studies¹⁶⁰ and difficulties with appropriate control group selection. Overall, cohort studies suggest lower prevalence in children when compared with adults, with 20% of previously hospitalized children having post-COVID-19 condition 6 months and 11% 1 year after discharge.¹⁶³

7.1 | Are children with allergic conditions at greater risk of Long COVID development?

Multiple factors were associated with higher risk of Long COVID development in adults. Among them female sex, severity of acute SARS-CoV-2 infection, older age, and preexisting comorbidities, particularly chronic lung conditions, including asthma.^{152,164-167} Risk factors associated with Long COVID development in children remain largely unknown with some limited evidence naming female sex,^{162,168,169} older age,^{161,169} poorer physical and mental health before COVID-19¹⁶² and history of neurological and allergic diseases^{161,163} among risk factors. However, the certainty of evidence is low, and findings should be interpreted with caution due to the small number of studies, the small samples size, and their high risk

of bias.¹⁷⁰ Further research is needed to investigate the role of eosinophils and/or Th-2 responses in COVID-19 and its sequelae.^{171,172}

Although it is premature to make any statements regarding links between allergic diseases and risks of Long COVID development, importance of the condition recognition remains relevant for any medical field, including allergy. Often, worse achievement or absenteeism at school are incorrectly attributed to other causes, with Long COVID being missed which results in under-referral of cases to dedicated clinics, multidisciplinary teams, and rehabilitation services.¹⁷⁰

Although no treatment is currently recommended for Long COVID treatment, limited evidence suggests that vaccination may be associated with a lower risk of Long COVID development¹⁷³ and antihistamines may lead to clinical improvement.¹⁷⁴ It is highly advised to encourage people to follow local government guidance for vaccination to reduce the risk of a further acute infection, regardless of its effect on ongoing symptomatic COVID-19 or Long COVID-19.¹⁷⁰

8 | SARS-COV-2 VACCINATION

There are multiple efficacious COVID-19 vaccines¹⁷⁵ available for children as young as 5 years and older worldwide, with FDA authorizing Moderna and Pfizer-BioNTech COVID-19 vaccines for children down to 6 months of age recently.^{176,177} While the vaccines are safe, there has been concern for associated adverse events following immunization (AEFI), most notably myocarditis in children, and allergic reactions in adults and children of all ages.¹⁷⁸ Since December 2020, multiple reports of immediate, potentially severe allergic reactions attributable mainly to COVID-19 vaccines have been published.¹⁷⁹ The mRNA vaccine reactions have been theorized as attributable to the vaccine excipients polyethylene glycol (PEG) in the mRNA vaccines and polysorbate 80 (PS) in the viral vector vaccines, given these are the most relevant excipients in these vaccines with literature supporting these as rare but recognized allergic drug allergy triggers.¹⁸⁰ In response, most international health authorities recommended restricting persons allergic to a vaccine excipient from receiving a vaccine containing that excipient, and restricting persons reacting to an initial dose of the vaccine from receiving any additional doses. Theoretical concern for potential for cross-reactivity between PEG and PS further limited vaccination options for persons.¹⁷⁹ While initial restrictions in some countries also extended to persons with a history of allergic reaction of any severity to other unrelated medications or vaccines, these have gradually lessened. In most countries, current restrictions only pertain to persons with severe reactions to the vaccine or vaccine excipients, and no longer contraindicate a PEG allergic person from receiving a PS-containing vaccine, and vice versa. There are no countries that currently recommend restricting any COVID-19 vaccine based on a history of unrelated medication or food allergy, and it is important to emphasize that neither vaccine platform contains foods as excipients.¹⁷⁹

To date, there are sparse data regarding allergic reactions in children to either mRNA or adenovirus-vector COVID-19 vaccines. The majority of the data pertaining to COVID-19 vaccine allergic reactions are from adult patients, and thus, we can only extrapolate these findings to children under age 16.

8.1 | What is the risk of an initial reaction to a COVID-19 vaccine?

While initial publications suggested that the rate of immediate allergic reactions to the vaccines may be high, the rate of reactivity has decreased significantly over the first year of the vaccines being available. A 2021 meta-analysis of adjudicated large data reporting sources (>20,000 patients in clinical trials, >500,000 from governmental databases) showed that the incidence rate of immediate severe allergic reactions to an initial dose of any COVID-19 vaccine is 7.91 per million doses.¹⁷⁹ Although this rate includes trials and datasets that excluded vaccination in persons with known vaccine excipient allergic individuals or persons younger than age 16, there has been limited published pediatric experience in vaccinating PEG-asparaginase allergic children. Three published reports from academic medical centers observed no severe allergic reactions to date among a total of 82 persons with PEG-asparaginase allergy.¹⁸¹⁻¹⁸³

8.2 | In persons with immediate reactions to a first dose, what is the risk of reaction upon revaccination?

Among adults with an immediate allergic reaction to their first mRNA COVID-19 vaccine, very few appear to react if revaccinated with a second dose of the same vaccine. A recent meta-analysis noted that across 22 studies inclusive of 1366 patients, the risk of a repeat immediate vaccine allergic reaction is 0.16% (95% CI 0.01%–2.94%), and for adults experiencing a severe first-dose reaction who were revaccinated to a 2nd dose of the same mRNA agent, the risk of repeat anaphylaxis is 4.94% (95% CI, 0.93%–22.28%). Overall, the risk of nonsevere immediate allergic symptoms among this population is 13.6% (95% CI 7.76%–22.9%). However, none of these studies included children younger than age 16.¹⁸⁴ Even in highly allergic adults and those with a reaction to the first dose, the vaccine can be safely administered in a tertiary allergy service.

8.3 | What allergens are attributable to these reactions, and what data are known regarding skin testing to these agents?

Despite speculation as such, PEG and PS have not been definitively identified as allergic triggers of COVID-19 vaccine allergic reactions. The low meta-analyzed rate of repeat reactions suggests

against PEG and PS as IgE-mediated triggers, in particular when these data were drawn from a population where 100% of persons were presumed to have reacted to some component of the vaccine.¹⁸⁴ There also appears to be very little utility in performing skin testing to PEG, PS, or the mRNA agent itself. In a nested meta-analysis of 16 studies within the second-dose reactions analysis, where persons with first-dose reactions were both skin tested to any combination of PEG, PS, or the mRNA vaccine and then re-administered the provoking vaccine agent, pooled skin test sensitivity was extremely poor. Skin testing sensitivity to either mRNA vaccine was 0.19 (95%CrI 0.02–0.52) and specificity 0.96 (95%CrI 0.85–1). Polyethylene glycol (any molecular weight PEG) test sensitivity was 0.02 (95%CrI 0.00–0.07) and specificity 0.99 (95%CrI 0.95–1). Polysorbate (any polyoxyethylene group number) test sensitivity was 0.03 (95%CrI 0.00–0.11) and specificity 0.98 (95%CrI 0.91–1). Combined for any agent, test sensitivity was 0.03 (95%CrI 0.00–0.09) and specificity was 0.98 (95%CrI 0.95–1.00) (Greenhawt et al manuscript submitted for publication).

8.4 | How should the allergist approach COVID-19 vaccination?

While no specific pediatric data are available, extrapolated data from adult populations suggest that immediate allergic reactions to both initial and subsequent mRNA-COVID-19 vaccines are very rare. In mid-2021, an international multidisciplinary expert panel developed 11 GRADE recommendations regarding the assessment and management of immediate allergic reactions to mRNA COVID-19 vaccines.¹⁷⁹ This was recently updated in 2022, with seven additional recommendations (Greenhawt et al manuscript submitted for publication). The GRADE guidance strongly recommends vaccinating individuals despite preexisting excipient allergy, and re-vaccinating individuals despite a first-dose reaction. Furthermore, the guidance strongly recommends against either preemptive skin testing to the vaccine or vaccine excipients prior to administering the initial dose or as part of the evaluation for revaccinating someone after a first-dose reaction. Lastly, the guidance strongly recommends that vaccination of persons with a history of allergic reactions to one of the COVID-19 vaccines, PEG, or PS should not be administered in a general medical setting, and only under the supervision of a trained allergy specialist, in a setting where severe allergic reactions can be managed. The guidance is more preference-sensitive with respect to premedicating individuals before initial or subsequent vaccination and the necessity of using a graded-dosing approach. While this GRADE guidance is limited by lack of pediatric data beyond very limited case series experience with safely vaccinating PEG-asparaginase allergic children to PEG-containing mRNA COVID-19 vaccines, these are the most representative data available and can be extrapolated to children (Greenhawt et al manuscript submitted for publication).

TABLE 1 A summary of lessons learned from COVID-19 pandemic with regard to allergic diseases in children

Acute Covid-19

Allergic children

- Usually, allergic children do not significantly differ from general population in specific clinical, laboratory, and immunological findings during acute COVID-19 infection episode
- Allergy does not seem to be a risk factor for either development or severity of SARS-CoV-2 infection
- Although allergic diseases are not normally associated with a higher risk of COVID-19 mortality, school-aged asthmatic children with previous recent hospital admission or two or more courses of oral corticosteroids merit attention due to higher risks of hospital admission

Primary immune deficiency

- Combined immune deficiency and immune dysregulation are associated with a higher risk of mortality from COVID-19
- Home-based IVIG and SCIG use as well as appropriate vaccination may reduce the risks in individuals with primary immune deficiency

COVID-19 consequences

Multisystem inflammatory syndrome (MIS-C)

- There are so far no data suggesting that children with allergic diseases are at greater risk of MIS-C development, episode severity, or morality. Usual approaches to MIS-C treatment should be applied

Long COVID/post-COVID-19 condition

- Risk factors associated with Long COVID development in children remain poorly investigated with some limited evidence suggesting female sex, older age, poorer physical and mental health before COVID-19, and history of neurological and allergic diseases are among potential risk factors
- Although treatment for Long COVID is currently unavailable, some preliminary data suggest a positive effect of antihistamines, while appropriate vaccination may reduce the risk of Long COVID development

SARS-CoV-2 vaccination

- Vaccination is required to any individual, regardless of preexisting excipient allergy, and revaccination is needed for individuals despite a first-dose reaction
- Vaccination of individuals with a known history of allergic reactions to one of the COVID-19 vaccines, PEG, or PS should not be administered in a general medical setting, but only under the supervision of a trained allergy specialist, in a setting with all necessary equipment for the management of severe allergic reactions available

Specifics of management of allergic diseases during COVID-19 pandemic

- Routine clinical practice can be delivered in a regular fashion, accounting for local regulatory measures depending on COVID-19 spread and vaccination rates
- Children should remain on their usual medications during the time of pandemic
- Biologicals (at least omalizumab and dupilumab) were safely used during the pandemic and their use, even among individuals infected with COVID-19, was not associated with severe outcomes
- SCIT and SLIT can be safely continued in any individual not infected with COVID-19
- SCIT and SLIT should be discontinued in symptomatic patients with exposure to or contact with SARS-CoV-2-positive individuals, or PCR-positive individuals
- Use of nebulized medication or other aerosol-generating procedures should be avoided

TABLE 1 (Continued)

Overall impact of COVID-19 pandemic
<ul style="list-style-type: none"> • Pandemic was associated with reduced incidence of allergic disease, number of exacerbations, and/or emergency room visits/hospital admissions • Significantly worse nasal symptoms in children allergic to house dust mite and increased incidence of hand eczema among a high proportion of young children • Increased levels of anxiety in children and caregivers was reported
Potential mitigation strategies
<ul style="list-style-type: none"> • Many diagnostic measures (e.g., SPT, OFC, and spirometry) were successfully and safely performed at home, providing an opportunity for those unable to visit hospital, but much data are required for use in routine clinical practice to be recommended • Telemedicine and use of mobile applications became a major part of the routine clinical practice with data from multiple studies showing that good control can be achieved in most children

9 | CONCLUSION

COVID-19 pandemic resulted in a dramatic increase in morbidity and mortality, detrimental consequences to human well-being and society, and disruption of national and international health-care services. Although pandemic seems to be well-controlled, COVID-19 remains a challenge, with consequences of SARS-CoV-2 infection already observable in many individuals while long-term effect is yet to be established. The lessons of the pandemic (Table 1), however, should not be forgotten, and future generations may benefit from experience gained throughout the past 2 years, and build upon it if other respiratory virus epidemic occur.

CONFLICT OF INTEREST

DM reports receipt of grants from the British Embassy in Moscow, UK National Institute for Health Research (NIHR), and Russian Foundation for Basic Research for COVID-19 and Long COVID research. He is also a cochair of International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) Global Pediatric Long COVID Working Group, member of ISARIC working group on long-term follow-up in adults, co-lead of the Post-COVID Condition Core Outcomes (PC-COS) project, chair of the Core Outcome Measures for Food Allergy (COMFA) consortium. MG is a consultant for Aquestive; is a member of physician/medical advisory boards for DBV Technologies, Sanofi/Regeneron, Nutricia, Novartis, Aquestive, Allergy Therapeutics, AstraZeneca, ALK-Abello, and Protal, with all activity unrelated to vaccines/vaccine development or COVID-19 treatment; is an unpaid member of the scientific advisory council for the National Peanut Board and medical advisory board of the International Food Protein Induced Enterocolitis Syndrome Association; is a member of the Brighton Collaboration Criteria Vaccine Anaphylaxis 2.0 working group; is the senior associate editor for the *Annals of Allergy, Asthma, and Immunology*, and is member of the Joint Taskforce on Allergy Practice Parameters. He has received honorarium for lectures from ImSci, MedLearningGroup,

RMEI Medical Education, and multiple state/local allergy societies. He received past research support ending in 2020 from the Agency for Healthcare Quality and Research (K08-HS024599). HB reports speaker honoraria from Sanofi, DBV Technologies, and GSK. PRR reports consulting fees from Miravo, FAES. Payment or honoraria for lectures from Aimmune Therapeutics, GSK, FAES, Novartis, ALK-Abello, LETI Pharma, Sanofi, Stallergenes, and Miravo. SA reports honoraria for lectures from Ulrich. EU reports receipt of a research grant from Desentum Oy. JOW reports funding from Danone/Nutricia, Friesland-Campina, and Airsonett. He also serves an Anaphylaxis Campaign clinical and scientific panel chairman and acknowledges travel expenses as a speaker covered by the World Allergy Organization. MAL received research funding from the Spanish Pediatric Society of Clinical Immunology, Allergy and Asthma (SEICAP), the Catalan Society of Allergy and Clinical Immunology (SCAIC); reports honoraria for consultancy and/or advisory board and/or lectures from ALK-Abello, FAES Pharma, LETI Pharma, Merck, Aimmune, DBV Technologies, Allergy Therapeutics, Stallergenes, Diater, Novartis, Uriach, Nestle, and Sanofi Genzyme. SA has participated as an advisory board member and/or consultant, and/or speaker for Novartis, and Ulrich outside the submitted work.

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ORCID

Daniel Munblit  <https://orcid.org/0000-0001-9652-6856>

Matthew Greenhawt  <https://orcid.org/0000-0002-2365-9372>

John O. Warner  <https://orcid.org/0000-0001-7123-6369>

Omer Kalayci  <https://orcid.org/0000-0001-8715-5694>

Stefania Arasi  <https://orcid.org/0000-0002-8135-0568>

Sophia Tsabouri  <https://orcid.org/0000-0001-7584-5401>

Elena Galli  <https://orcid.org/0000-0001-6692-9101>

Burcin Beken  <https://orcid.org/0000-0001-7677-7690>

Philippe A. Eigenmann  <https://orcid.org/0000-0003-1738-1826>

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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