**Title:** Impact of COVID-19 on pediatric asthma: practice adjustments and disease burden.

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**Abstract**

**Background:** It is unclear whether asthma may affect susceptibility or severity of the Coronavirus Disease 2019 (COVID-19) in children and how pediatric asthma services worldwide have responded to the pandemic.

**Objective:** To describe the impact of the COVID-19 pandemic on pediatric asthma services and on disease burden in their patients.

**Methods:** An online survey was sent to members of the Pediatric Asthma in Real Life (PeARL) think-tank and the World Allergy Organization Pediatric Asthma Committee. It included questions on service provision, disease burden and on the clinical course of confirmed cases of COVID-19 infection among children with asthma.

**Results:** Ninety-one respondents, caring for an estimated population of >133,000 children with asthma, completed the survey. COVID-19 significantly impacted pediatric asthma services: 39% ceased physical appointments, 47% stopped accepting new patients, 75% limited patients visits. Consultations were almost halved to a median of 20 (IQR: 10-25) patients per week. Virtual clinics and helplines were launched in most centers.

Better than expected disease control was reported in 20% (10-40%) of patients, while control was negatively affected in only 10% (7.5-12.5%). Adherence also appeared to increase. Only 15 confirmed cases of COVID-19 were reported among the population; the estimated incidence is not apparently different from the reports of general pediatric cohorts.

**Conclusion:** Children with asthma do not appear to be disproportionately affected by COVID-19. Outcomes may even have improved, possibly through increased adherence and/or reduced exposures. Clinical services have rapidly responded to the pandemic by limiting and replacing physical appointments with virtual encounters.

**Key words:** asthma, child, virus, adherence, COVID-19, SARS-CoV2, control

**Abbreviations:**

99% CI: 99% Confidence intervals

ACE2: Angiotensin converting enzyme 2

ACQ: Asthma Control Questionnaire

ACT: Asthma Control Test

COVID-19: Coronavirus Disease 2010

FeNO: Fractional Exhaled Nitric Oxide

IQR: Interquartile range

PeARL: Pediatric Asthma in Real Life

PEFR: Peak expiratory flow rate

REG: Respiratory Effectiveness Group

RR: Relative risk

SARS-CoV2: Severe Acute Respiratory Syndrome Coronavirus 2WAO: World Allergy Organization

**Highlights box**

**What is already known about this topic?**

COVID-19 has a mild disease course in children and adolescents. Chronic respiratory conditions, including asthma, have been suggested as risk factors, however, asthma in children is highly variable in both triggers and severity.

**What does this article add to our knowledge?**

During the pandemic, pediatric asthma services limited consultations and established virtual clinics. However, respondents perceived their patients’ asthma control to be retained or even improved, while treatment adherence was considered increased. Children with asthma were not disproportionately affected by COVID-19.

**How does this study impact current management guidelines?**

Trigger avoidance and treatment adherence can rapidly improve asthma control in children, even under lockdown pressure. Children/adolescents with asthma do not appear to need additional prophylactic measures from COVID-19 when asthma is well-treated.

**Introduction**

The ongoing Coronavirus Disease 2019 (COVID-19) pandemic, induced by severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), is driving an unprecedented international research and clinical mobilization, to understand and contain the disease[[1]](#endnote-1). COVID-19 has less direct impact in children and adolescents than in adults, although all ages are affected[[2]](#endnote-2). In children, as in adults, pre-existing chronic conditions appear to increase the risk for severe or fatal disease[[3]](#endnote-3),[[4]](#endnote-4). Despite initial clinical reports that did not identify asthma to be overrepresented among COVID-19 patients[[5]](#endnote-5), it has been suggested that asthma, particularly when uncontrolled, may be included among the underlying conditions imposing a risk for severe COVID-19 disease3. Further evaluation is urgently required, since children with wheezing illness/asthma constitute a significant proportion throughout the pediatric age span and is the most frequent chronic condition managed by pediatricians[[6]](#endnote-6),[[7]](#endnote-7).

In order to rationalize management and instruct the public healthcare system, it is crucial to understand whether asthma, allergy, or their treatments add risk, protect or have no discernible effects on the health of children with asthma [[8]](#endnote-8),[[9]](#endnote-9).

Symptoms of COVID-19 in children usually include dry cough and often fever. In contrast with infected adults, most infected children appear to have a milder clinical course[[10]](#endnote-10). Dyspnea may be present; however, wheeze has not been reported as part of the clinical presentation2,[[11]](#endnote-11),[[12]](#endnote-12). There is currently no published information about the clinical course or other characteristics of COVID-2019 in children with asthma. In parallel, COVID-19 pandemic introduced a need to change clinical practice, including minimizing face to face contact and limiting the use of aerosolising procedures. A need for guidelines in the context has been expressed[[13]](#endnote-13), however this is challenged by the lack of evidence.

In this context, pediatric asthma services around the world are being reorganized in order to face the new, uncertain, reality. Pediatric Asthma in Real Life (PeARL), a think-tank initiated by the Respiratory Effectiveness Group (REG), comprising of pediatric asthma experts from all around the world, aims to develop recommendations that will improve patient care[[14]](#endnote-14). In order to identify and share best practices, and in collaboration with the World Allergy Organisation (WAO) Pediatric Asthma Committee, we assessed the impact of COVID-2019 on pediatric asthma services and their patients through a survey addressed to large pediatric asthma clinics worldwide.

**Methods**

An online questionnaire was constructed with input from the PeARL steering group. It included questions about the operation of pediatric asthma clinics during the COVID-19 pandemic, changes in the methods used to communicate with and assess patients, estimates of overall disease activity and patient attitudes, as well as known cases of COVID-19 infection, within the respondents’ pediatric asthma cohorts. The survey questionnaire can be found in the online supplement. Sixty-two members of the participating groups, actively involved in the assessment and management of children with asthma, as assessed by a previous survey14, and representing clinical services in different healthcare systems were invited to complete the survey on April 09, 2020. The recipients were allowed to further forward the survey to additional clinical practices in their country. Due to the extraordinary circumstances and urgency, the allowed response time was ten days; no reminders were sent.

Responses are presented descriptively, as proportions or median (interquartile range) for numeric variables. We report pertinent differences in the responses across different responder groups:

1. Participants from countries with different COVID burden: (i) less than 10 deaths per million population [limited burden], (ii) between 10-100 deaths per million population [intermediate burden], (iii) more than 100 deaths per million population [high burden], as of April 19, 2020, the last day of the survey.
2. Participants from different continents. Adequate responses were collected from the Americas, Asia and Europe, which allowed meaningful comparisons.
3. Participants from countries with different economies. Countries with high versus low and middle income, according to the World Bank classification.
4. Participants from different practice settings, namely, primary care/private clinics, secondary care and tertiary/university hospitals.

We used Fisher exact test for comparing dichotomous data, given the relatively limited number of participants in each group. Kruskal-Wallis test was used for comparing continuous data, assuming a non-normal distribution. Between-group differences were formally tested only for findings around asthma control and treatment adherence, to avoid multiple comparisons and the risk of type 1 and/or type 2 statistical error. In an exploratory analysis, we extrapolated the estimates of respondents about asthma control, treatment changes and treatment adherence in their actual case numbers during the preceding month and we present the risk ratios of patients with favourable versus unfavourable outcomes. Given the limitations of this analysis, we chose to use the 99% confidence intervals.

While completion of questions was optional, each question was answered by >75% of the eligible participants for that question. Missing responses data were disregarded when evaluating the findings.

**Results**

Survey responses and patient population represented

All invited responded to the survey; response from additional centres, invited by the participants, led to an overall response rate of 146% over the original invitations. Ninety-one experts, each representing a different clinical practice from different care settings, economies and countries, including the whole spectrum of COVID-19 disease burden, completed the survey. Respondents were from 27 countries and five continents (Africa, Asia, Americas, Europe and Oceania), consulting a median of 20 (IQR: 10-25) children with asthma per week, corresponding to 89,804 annual visits in the 61 centres reporting this question, or an estimated 133,969 visits in the complete cohort. Characteristics of the respondent’s practices are summarised in Tables 1-2, E1-E3.

Effect of the COVID-19 pandemic on pediatric asthma practices worldwide

Over the recent time period, pediatric asthma clinics across the world have markedly changed their practice because of the COVID-19 pandemic (Table 1). Almost half of the participants (47%) reported their clinics did not accept/receive new patients during the epidemic, with responders from Asia being a notable exception, as 78% received new patients. Among the participating practices, 39% have ceased physical appointments; this proportion exceeded 60% in the more heavily burdened countries. Among centres that continued to run physically, 75% reported a decrease in the number of evaluated cases during the pandemic period. During the month preceding the completion of the survey, participants reviewed a median of 35 cases (IQR: 20-60), approximately half their normal rate, in parallel to the escalating measures to avoid patient contact.

In pediatric asthma clinics that continued accepting physical appointments, several practice changes were implemented to minimize these encounters. Further to the reduction of evaluated cases, the majority (62%) of clinics limited the frequency of planned monitoring encounters, with 28% reviewing only children with severe asthma, while 8% accepting only patients receiving biologics. Access to asthma medications was an issue in 30% of the participating centres, predominantly in Asia (44%).

Importantly, over 90% of participating centres have launched virtual online or telephone consultations to substitute or complement clinical visits, while 73% have used a help line to address the needs of their patients. About half of the participants considered virtual visits a suboptimal clinical encounter, only viable in the short term. Nevertheless, a considerable proportion (42%), found them acceptable, or, occasionally, as good as face-to-face visits. Several tools were used by all respondents to facilitate better distal monitoring of asthma control. Validated tools for evaluating asthma control, such as the asthma control test (ACT) or the asthma control questionnaire (ACQ), were used by 72% of the participants. Peak expiratory flow readings (31%) or portable spirometer readings (8.5%) were less often used, while treatment adherence was formally monitored in 42% of practices. Symptom recording apps or telemedicine platforms were used in 27% of centres.

There were some between-group differences in monitoring. Firstly, validated asthma control questionnaires were less favoured in private/primary care practices (33%), compared to proportions exceeding 80% in secondary, tertiary and university hospitals. On the contrary, 67% of the private practices opted for telemedicine platforms, in contrast to only 28% of the clinics in secondary care and 13% of the university/tertiary care hospitals. PEFR was more often used in less affluent countries (42% in low-/middle- versus 27% in high-income countries), while portable spirometers were solely available in high-income countries. Treatment adherence was more extensively evaluated in Asia (78%), than Europe (44%), or the Americas (16%).

Pediatric asthma burden during the COVID-19 pandemic

Evaluation on pediatric asthma burden during the pandemic was queried as proportions improving, remaining stable or worsening within each individual clinic, for a number of clinically relevant aspects (Table 2). Within each practice, a median of 70% (IQR: 60-80%) of evaluated patients were well controlled, 20% (IQR: 10-30%) partially controlled and 10% (IQR: 0-10%) uncontrolled. In subjectively evaluating their patient’s asthma control status, participants considered that while in 85% (IQR:70-100%) of cases this was in line with their previous symptom trajectories (as expected), in 20% (IQR: 10-40%) this exceeded their expectations, while control had deteriorated in only 10% (IQR: 7.5-12.5%). The risk ratio of the children with better than expected versus worse than expected asthma control was 2.69 (99% CI: 2.17-3.34), while all subgroup analyses yielded consistent findings. Apart from the prespecified subgroup analyses (by the countries’ COVID-19 burden, countries’ economy, continent and clinical setting), we also evaluated separately centres using or not using a validated questionnaire for evaluating asthma control and centres formally evaluating treatment adherence or not. In line with this impression of the clinical status, no treatment changes were required for 80% of patients (IQR: 60-90%), while similar proportion of patients (~10%) required treatment escalation or de-escalation. Treatment adherence was estimated to be unchanged in 80% (IQR: 60-100%) of patients, while it improved in 20% (IQR: 10-40%) of children with asthma, especially in the Americas (IQR: 20-63%). Reduced adherence was reported in only up to 10% of patients (IQR: 0-10%). Increased treatment adherence was consistently observed both in the overall study population (RR: 1.97, 99% CI: 1.66-2.33) and all the subgroup analyses.

Countries that were less severely hit by the COVID-19 epidemic, reported a higher proportion of well-controlled patients. However, there were no between-group differences in the expected symptom trajectories.

COVID-19 infection among children with asthma within the participating centres.

Suspected cases of COVID-19 in asthmatic children were reported in only 13/91 participating centres (14%). There were 100 such cases (a median of 3 suspected cases in each of these centres, IQR: 2-10). Of these, only 15 (15%) were confirmed, ten in one centre in Italy, 2 in Portugal and the remaining in two French centres. The most frequent presenting symptoms of the confirmed cases included nasal discharge or blockage and cough, while breathlessness, fever and wheeze were less often reported (details in table E4). Half of the reported cases also experienced non-respiratory symptoms, such as myalgia and fatigue. Eleven of these children (73%) experienced a mild clinical syndrome, three (20%) a moderate illness, and only one case (6.7%) required hospitalization. None required an admission to the intensive care unit or ventilation, and all made a complete recovery.

**Discussion**

There is no doubt that pediatric asthma clinics are among healthcare services significantly affected by the COVID-19 pandemic. The number of new patients evaluated is restricted, while there is also a reduction in the frequency and/or the total number of patients monitored. Additionally, use of several diagnostic modalities, including lung function testing, fractional exhaled nitric oxide (FeNO) or methacholine tests is limited, along with therapeutic interventions, such as nebulized treatments[[15]](#endnote-15). However, many services have actively responded to these challenges, most often by ‘virtual’ clinics or other telehealth appliances, that flourished in all medical specialties during the COVID-19 epidemic[[16]](#endnote-16). Clinicians consider such clinics suboptimal, nonetheless adequate for the, hopefully, short time period under lockdown. Standard tools such as the ACT or ACQ questionnaires were used, while objective measures, such as spirometry or PEFR, were less often feasible. The observed approaches are consistent with recent ad-hoc recommendations[[17]](#endnote-17).

Despite the above challenges, there was no apparent deterioration of asthma in the large majority of patients. In fact, based on the perceptions of the participants, improvement exceeded expectations in 20% of subjects. This was accompanied, and possibly partially mediated, by increased adherence to treatment plans – normally a major challenge in pediatric asthma management. Contrasting and very often unproven information has been circulated through the media in regard to maintenance medications and management. Among others, inhaled and/or systemic corticosteroids have been of particular interest, as both a potential COVID-19 treatment and as an increased susceptibility factor[[18]](#endnote-18). Our findings suggest that parents of children with asthma monitored in specialist clinics, have responded to messages on the need for treatment continuation, rather than unfounded fears about potentially detrimental effects of inhaled steroids. Furthermore, social distancing, sheltering at home and reduced school days reduced exposure to the main triggers of acute asthma events, most notably rhinovirus and other airway infections, outdoor allergens, physical exercise and air pollution[[19]](#endnote-19),[[20]](#endnote-20), may have well contributed to sustained, or even improved, outcomes during this period. Nevertheless, a small proportion of children (~10%) have deteriorated; confinement in children sensitized to indoor allergens and/or psychological factors may have contributed to this.

Despite the differences between countries regarding COVID-19 infection and policies, the number of pediatric asthma patients with suspected and, even more, confirmed COVID-19 was small, coming mostly from one tertiary center in Italy. It is noteworthy that even in these cases, the clinical course was benign, and wheezing, the hallmark of asthma, was observed in only 40%, while the simultaneous presence of other viruses was not assessed.

Our data cannot provide a concrete estimate of the clinically relevant COVID-19 infection incidence among children with asthma. However, taking into account (i) the reported COVID-19 incidence in the more severely affected countries (USA, Spain, Italy, France, UK; 2.2-4.8 cases per thousand population[[21]](#endnote-21)); and (ii) data suggesting that COVID-19 infection, severe enough to lead to seeking medical advice and thus diagnosed, is about 12.8 times less frequent in children than in adults3; 17-38 such cases per 100,000 of a non-selected pediatric population can be assumed. This is consistent with recent data on the burden of COVID-19 disease in children in China, South Korea and the USA, where it is uniformly very low3,[[22]](#endnote-22),[[23]](#endnote-23). In our survey, the estimated population of pediatric asthma patients represented within these countries was 20,000-40,000 i.e. the expected range of potential COVID-19 patients would be 3-15, suggesting that COVID-19 infection is not associated with severe asthma exacerbations.

It is possible that SARS-CoV2 does not induce bronchial hyperreactivity and asthma-like pathophysiology; nevertheless, this does not exclude the possibility of children with asthma, particularly uncontrolled asthma, developing more severe COVID-19 disease, as we have previously reported for influenza[[24]](#endnote-24). Furthermore, the impact of atopy on SARS-CoV2 susceptibility needs to be further evaluated, in light of recent findings suggesting that allergic sensitization and allergen exposure may reduce the SARS-Co2 receptor, ACE2[[25]](#endnote-25). However, only one case requiring hospitalization was identified through this survey, drawing information from a large number of children with asthma, including a large proportion with severe asthma, given the large proportion of respondents from tertiary centres. Further evaluation of children with asthma, poor symptom control and high severity in regards to the individual response to SARS-CoV-2 will be needed to draw a firm conclusion.

There are several limitations to this survey. Most importantly, the clinical data that are described are not based on direct evaluation of patients, but on the subjective evaluation of the respondents and therefore, there is a risk of recall bias. In addition, respondents might have been unaware of some of the acute presentations of their patients to alternative clinical sites. However, clinicians are well aware of this issue that is not specific to the COVID-19 era. There is a chance that changes in clinical practice due to COVID-19 may have led more patients to seek medical advice from alternative sources, however all participating centers offered either physical, virtual appointments or helplines for patients with acute symptoms.

In parallel, children with asthma tend to have less controlled disease at the time of the initial referral to the expect clinic. Therefore, the significant decrease in new referrals may partially account for the respondents’ perception that asthma control has improved during the pandemic. However, clinicians were specifically asked to compare their perceptions about disease control among patients during monitoring visits, during versus before the epidemic. As a result of these limitations, all findings described about the clinical burden of COVID-19 on children with asthma should be considered exploratory and further studies directly evaluating the clinical course of children with asthma are needed.

Moreover, responders are clinicians with high expertise and interest in the domain, therefore may not be representative of all pediatric asthma services. Nevertheless, our findings of limited COVID-19 burden within the included cohorts that are potentially selective for children with more severe or uncontrolled asthma, including patients treated with biologics, further supports our conclusions. Moreover, expertise and increased interest, as confirmed by the rapid response of the totality of invited, may also be considered a strong point. Input came from a wide geographical spread; unfortunately, Africa and Oceania were minimally represented. Similarly, the responses do not include many low-income countries, in which health services, underlying susceptibility to illness and disease impact may be different.

In conclusion, children with asthma do not appear to be disproportionately affected by COVID-19; relevant high-end services have rapidly responded, medication adherence has not been negatively affected and outcomes are promising. Ongoing epidemiological studies, including one initiated by this group, will be able to quantify any added and long-term risk of COVID-19 on children with asthma.

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