

The effect of the COVID-19 pandemic on pediatric intensive care admissions for severe acute asthma

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Abstract

Background – The incidence of pediatric asthma exacerbations during the COVID-19 pandemic has been evaluated; however, the incidence of severe acute asthma (SAA) requiring a Pediatric Intensive Care Unit (PICU) admission is unknown. Furthermore, we examined several factors which might influence this incidence, such as environmental triggers or changes in COVID-19 lockdown regulations. *Methods* – In this single-center, retrospective cohort study running from 2018 to 2021, all PICU admissions for SAA of children above two years of age at a tertiary hospital in the Netherlands were included. Information on potential asthma triggers during the pandemic, including viral infections, concentrations of ambient fine particulate matter (PM2.5) and pollen index were evaluated. *Results* – In total, 168 children were included in this study. While we observed a decrease in PICU admissions for SAA during lockdown periods, there was an increase in the admission rates in the periods without a lockdown, with the highest peak from August to November of 2021. This peak in the fall of 2021 did not align with pollen or ambient PM2.5 concentrations ($r_s = -0.04$ for pollen and $r_s = 0.23$ for PM2.5). *Discussion* – COVID-19 lockdowns influenced the admission rates for SAA at the PICU both during and after the lockdowns in the Netherlands. We hypothesize that an increase in viral infections after lockdown periods was the reason for the altered incidence of SAA at the PICU in late 2021, rather than air pollution and pollen concentrations.

Introduction

Pediatric asthma is the most common chronic lung disease in children worldwide and may cause serious morbidity and mortality¹. The main focus of optimal asthma management is symptom control and prevention of exacerbations of the disease. However, 5% of children suffer from uncontrolled asthma despite maximal therapy, substantially contributing to asthma burden in this patient group^{2,3}. Asthma exacerbations, defined as an acute deterioration requiring a prompt change in treatment, can be so severe that they require an emergency department (ED) visit, a hospital admission or even a pediatric intensive care unit (PICU) admission^{4,5}. Severe acute asthma (SAA) is characterized by unresponsiveness to conventional therapy and requires PICU admission for intravenous therapy and sometimes even intubation⁶.

Usually, an asthma exacerbation is triggered by a viral infection, mediated through increased T2 inflammation⁷. However, external/environmental features such as pollen or air pollution are also common triggers^{4,8}, influencing not only the occurrence of exacerbations but also, potentially, its pathobiology^{9,10}. The Coronavirus Disease 2019 (COVID-19) pandemic is another example of an external factor influencing the risk for asthma exacerbations, especially during periods of major daily disruptions, such as lockdowns¹¹.

It has been suggested that the societal changes during the COVID-19 pandemic, in terms of the environment, medical practice and medication usage, have significantly influenced asthma management and outcomes¹². While the incidence of asthma exacerbations in children during the COVID-19 pandemic has been evaluated^{11,13-15}, the incidence of SAA requiring PICU admission and treatment during the pandemic is, to our knowledge, not known. Therefore, the aim of this study was to examine the trend of admissions for SAA at the PICU before and during the COVID-19 pandemic and to evaluate whether this could be linked to the COVID-19 restrictions or other external factors including environmental triggers.

Methods

Study design and subjects – This study is a single-center, retrospective cohort study conducted at the Amsterdam University Medical Center (UMC), a tertiary medical center. The PICU has a 12-bed facility providing intensive care treatment for the northwestern parts of the Netherlands. The demographic, social, and clinical data were extracted from the electronic hospital records of all children admitted to the PICU of the Amsterdam UMC between 2018 and 2021 with a diagnosis of SAA. The diagnosis of SAA was made by a pediatrician and based on the following definition: “Severe aggravation of bronchial obstruction due to asthma that does not improve after a few doses of a bronchodilator by inhalation”. Wheezing children aged less than two years were excluded as these children will more likely present with bronchiolitis, and differentiation between bronchiolitis and asthma is extremely difficult. Additionally, the total number of children admitted to the PICU of the Amsterdam UMC was also extracted from the electronic patient file database.

Institutional Review Board approval – The study design was reviewed by the ethical committee of the Amsterdam UMC. Owing to the retrospective and anonymous nature of the current study it was deemed that informed consent was not necessary.

Data collection – The exact dates and levels of governmental COVID-19 restrictions in the Netherlands were obtained from the Oxford COVID response tracker¹⁶. The key stringency criteria examined within the current study were the complete closure of schools, a complete working from home order, or both being in effect. Environmental exposures were defined as the amount of ambient air pollution and pollen exposure in the Netherlands. Ambient air pollution was represented by particulate material with an aerodynamic diameter of less than 2.5 microns (PM_{2.5}) which has previously been associated with respiratory (and other) diseases¹⁷. Also, high concentrations of PM_{2.5} have been associated with an increase in asthma exacerbations, and children with asthma were at a higher risk of requiring an ED visit for an exacerbation¹⁸. Hourly concentrations of ambient PM_{2.5} were measured at the official monitoring stations of the Dutch National Institute for Public Health and the Environment (RIVM) (in concentrations of $\mu\text{g}/\text{m}^3$)¹⁹. As the residential information of the patients was not available, the “Stadhouderskade” station, which was the closest measuring station to the Amsterdam UMC (with a distance of 11 km) was considered the proxy for exposures in the area. The daily amount of total pollen in the Netherlands (pollen index) was obtained from the pollen monitoring station of the Leiden University Medical Center²⁰, located approximately 35 km. from the Amsterdam UMC. Pollen grains were collected at the roof-top level (approx. 20 m. above ground level) and counted following the requirements of the European Aerobiology Society²¹. The total daily values of all pollen types (in pollen/ m^3) were summed to give the pollen index used in this study, and then collapsed to monthly and annual averages.

Analysis – Statistical analysis was conducted using IBM SPSS Statistics for Windows version 28.0.1.1 (SPSS, Chicago IL, USA). Because of the small study population, only descriptive analyses were executed. Subgroups, based on period of time/years, were described by the means with standard deviation (for variables with a normal distribution) or median with 25th-75th percentiles (for variables not normally distributed) or by frequency with percentages for quantitative variables. Spearman correlations were calculated to evaluate the relationship between admission numbers and PM_{2.5} as well as pollen concentrations. Graphical representations of the collected data were generated using R version 4.2.2²².

Results

The number of PICU admissions for SAA

Between January 2018 and December 2021, 168 children were admitted to the PICU of the Amsterdam UMC for SAA. In the pre-pandemic years, admissions tended to peak in April; however, this was not observed for the pandemic years of 2020 or 2021. In 2021, a peak in admissions in the months August to November was observed instead (Figure 1). When comparing the trend of PICU admissions for SAA to the total PICU admission numbers of 2018-2021 in the Amsterdam UMC, it was observed that the peak of admissions for SAA in the fall of 2021 did not correspond to an increased overall admission rate at the PICU (Figure S1). The ratio of PICU admissions due to SAA relative to the total number of PICU admissions for the August to November peak (13% in August, 14% in September, 16% in October and 15% in November) was higher than that typically observed, as well as the peak month of April in the pre-pandemic years (10% in 2018 and 11% in 2019). Moreover, the annual relative percentage of PICU admissions due to SAA of the total PICU admissions was highest in 2021 (8%), followed by 2019 (6%), and 2020 and 2018 followed after (both with 5%) (Table S1).

Description of the study population

In the total study population, the mean age of the participants was 7.4 years and a minority were girls (38.7%) (Table 1). Regarding the socio-demographic status, 15.0% were living with a single parent with a divorce rate of 29.2%. These two variables were the lowest in 2020 and the highest in 2018 (2.8% and 22.2% vs. 25% and 37.5%, respectively). Additionally, 31.5% of our study population was exposed to tobacco smoke, while the year 2021 had the lowest percentage of exposure (25%). The majority of patients (70.2%) had a clinically diagnosed viral infection. This percentage was the highest in 2018 (87.5%), followed by 2021 (72.9%), 2020 (69.4%), and 2019 (53.7%). However, not all of these clinical diagnoses were confirmed by a nasal or throat swab with the highest load of testing being taken in 2020 and 2021. Regarding missing data, there were no missing variables for age and sex, and for the remaining variables the percentage of missing data did not exceed 8.9%, except for secondhand smoke exposure, which was missing for 24.7%.

Effects of external factors on admission rates

A relationship between lockdown measures during the pandemic (a complete working from home obligation and/or school closures) and admission numbers is observed and illustrated in Figure 2. It was found that when lockdown measures were most strict and schools were closed, the number of PICU admissions for SAA was the lowest, indicating an association between the two. After lockdown restrictions were lifted, the admission rate tended to increase. Most children (70.2%) showed signs of an airway infection as trigger for their SAA, and in 60.1% a viral test was taken (Table 1). Most often, the clinical diagnosis of a viral infection was not confirmed by a positive viral test, resulting in 38.7% of children being infected with an unknown virus. If confirmed, Rhinovirus (23.8%) was the most commonly detected virus, followed by Bocavirus (5.4%), and Enterovirus (4.2%) (Table S2). Finally, regarding environmental triggers, no relationship was found between the peak in the fall of 2021, and pollen or ambient PM2.5 concentrations (Fig S2). Moreover, no correlations were observed between the monthly PICU admission numbers and pollen or PM2.5 concentrations ($r_s = -0.04$ for pollen and $r_s = 0.23$ for PM2.5).

Discussion

This study demonstrates that the incidence of SAA at the PICU of the Amsterdam UMC was lower in the first year of the COVID-19 pandemic, which may be a result of lockdown measures protecting children from several asthma exacerbation triggers. Additionally, we observed a high-peak incidence in the fall of 2021 after all governmental restrictions had been lifted, which could be due to an increase in infection rate by viruses other than SARS-CoV-2.

A similar study conducted in Italy showed a decrease in incidence of children with asthma exacerbations visiting the ED during the first and second wave of the COVID-19 pandemic in 2020. They found that this was due to the closing of day care and schools, less air pollution because of reduced travel and fear of visiting hospitals during the peak of the pandemic that in turn led to avoidance or delay in seeking medical

care. They also attributed this observation to reduced exposure to viruses; however, they did not evaluate viral triggers in their study¹³. We found that during the peak period in 2021, respiratory viruses were the most frequent trigger for SAA. It is well known that viral respiratory tract infections are a major trigger for SAA, which typically induces a chemokine-mediated neutrophil pattern⁴. Due to the COVID-19-related restrictions, including increased hygienic measures, wearing face masks and social distancing, the spread of infectious agents was reduced and thereby asthma attacks diminished^{11,14}. We hypothesize that when restrictions were lifted, children were exposed to these viruses again, explaining the high rate in the peak of 2021. Another reason this peak could be attributed to the “Hygiene Theory”, introduced by Strachan in 1989. This theory states that the trend of allergic diseases may be associated with infectious diseases and unhygienic contact in early childhood could prevent allergic disorders²³.

Furthermore, increased hygienic measures during the pandemic may have decreased children’s immune training, which made them more susceptible to infection²⁴. Immunity debt implies the lack of protective immunity caused by prolonged low exposure to a specific pathogen. This makes children susceptible to viral disease, which is particularly of concern for viruses whose transient immunity is acquired through virus contact. For example, respiratory syncytial virus (RSV) maternal antibodies diminish soon after birth and without seasonal exposure immunity declines and susceptibility to subsequent (and possibly more severe) infection increases²⁵. There is also evidence that inducting trained immunity leads to enhanced potency of the immune system against viral infection²⁶. Therefore, we hypothesize that staying at home during the lockdown periods of the pandemic may reduce exposure to a wider range of infectious agents, resulting in a more vulnerable immune system against viral infection as well as an increased risk on asthma exacerbations, which may have contributed to the increase in SAA admissions observed in late 2021. However, as this observation is based on a single hospital, an evaluation of the immunological aspect of asthma exacerbations during the COVID pandemic is required.

Additionally, the COVID-19 pandemic also led to an increased rate of viral testing at the PICU, as the updated infection control measures required an active SARS-CoV-2 infection to be confirmed or ruled out by a rapid test before admission. Nevertheless, more extensive viral testing for respiratory viruses was limited because of decreased laboratory capacity during the pandemic. Thus, even though there was an increased frequency of viral tests taken during the pandemic years, it was usually still unknown what viral agent had caused the respiratory symptoms as our cases were not tested for all agents. Among the detected viral agents, Rhinovirus was the most commonly detected which was also observed in a similar study in Hong Kong from 2015 to 2020²⁷.

In a study conducted by Ulrich et al. in the U.S.A., a drastic decline in the number of ED visits due to asthma exacerbations was reported in 2020. This decline was proportionately larger than the decrease in the total number of ED visits. The authors attributed better air quality due to reduced travel as the reason for this decrease in asthma exacerbation rate¹⁵. In another study by Papadopoulos et al., it was found that the rate of asthma exacerbations in children was decreased during the pandemic in comparison with 2019. They proposed that this might be the effect of decreased exposure to asthma triggers and increased treatment adherence²⁸. Chauhan et al. found a decrease of ambient PM2.5 concentrations of up to 159% in certain areas during lockdowns, depending on factors such as local meteorological conditions and intensity of lockdown rules²⁹. While there is evidence supporting the association between pollen, PM2.5 concentration and asthma exacerbations^{18,30}, in this study no clear association was found. However, as this observation was based on a single monitoring site, a wider sampling would be required before drawing definite conclusions. This discrepancy might be explained by the more prominent role of a viral infection as a trigger for SAA rather than other triggers such as air pollution and pollen.

Strengths and limitations

This study utilized a well-defined population with detailed observations and personal histories covering a wide range of variables at clearly defined time points. However, by being restricted to a single center the findings are not as applicable in a wider context. Moreover, as we did not have information on the residential addresses of the participants, we used data from one air quality monitoring station as a proxy for personal

exposure to PM_{2.5}. Furthermore, confirmed viral test was not available for all participants. Also, diagnosing asthma in young children is challenging as it is difficult to instruct this patient group to do a spirometry test. Finally, given the retrospective nature of this study, we had limited information regarding some details of specific variables. For example, we were not able to obtain detailed information on smoking status, e.g. whether the parents of the children smoke on a daily basis or occasionally.

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None, all contributing researches met the criteria for authorship.

Impact statement

Severe acute asthma (SAA) is a severe asthma exacerbation usually requiring admission to a pediatric intensive care unit (PICU) and causes serious morbidity and mortality; moreover, over the past few decades the number of PICU admissions for SAA has shown a significant increase. The Coronavirus Disease 19 (COVID-19) pandemic has influenced the medical health care system as a whole including asthma and its exacerbation pattern. Over the past few years, changes to the number of asthma exacerbations and lockdown regulations or environmental triggers during the COVID-19 pandemic have been evaluated; however, SAA requiring PICU admission have not. In this study, the relationship between number of PICU admissions for SAA and the COVID-19 pandemic lockdown regulations. Additionally, changes to possible environmental factors triggering severe exacerbations, including air pollution and pollen index, are explored. This study took place in a tertiary hospital in Amsterdam, The Netherlands, and included all children over two years of age admitted for SAA to the PICU between 2018 and 2021. It was found that when COVID-19 restrictions were strict and lockdown was in place, number of SAA admissions at the PICU drastically decreased. After most restrictions had lifted, especially from August to November of 2021, a large peak in admissions was observed. It is hypothesized that outbreak of viral infections other than COVID-19 might have been the cause for this association, as spread of viruses was decreased during regulations. Finally, no association between air pollution and pollen index and SAA admissions was observed. In the future, it must be known that large societal changes may have an impact on SAA patterns and physicians must be aware of an increase in number of children coming to the ED with symptoms.

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Tables

Table 1 . Characteristics of the study population and potential SAA triggers.

Demographic characteristics

Time of admission (year)

Number of admissions

Girls

Age in years, mean \pm SD

Divorced parents

Living with a single parent

Environmental characteristics

Tobacco smoke exposure (TSE)

Ambient PM2.5 concentration (micrograms per cubic meter of air), median (25th-75th percentiles)

Pollen (grains per cubic meter of air), median (25th-75th percentiles)

Clinical characteristics

Clinical diagnosis of viral infection+

Conducting virology laboratory tests++

Allergy history

Previously diagnosed with asthma

Days between symptom onset and admission, median (25th-75th percentiles)

Duration of hospitalization in days, median (25th-75th percentiles)

Severe acute asthma triggers*⁵

URTI

Pneumonia

Allergens (e.g. pollen, dust mite, chemicals)

Dogs/cats

(Tobacco) smoke
Cold and/ or dry air
Physical exercise
Gastroesophageal reflux
No trigger

Abbreviations: PM_{2.5} = fine particulate matter; URTI = upper respiratory tract infection. Footnotes: + As per physician

Figures

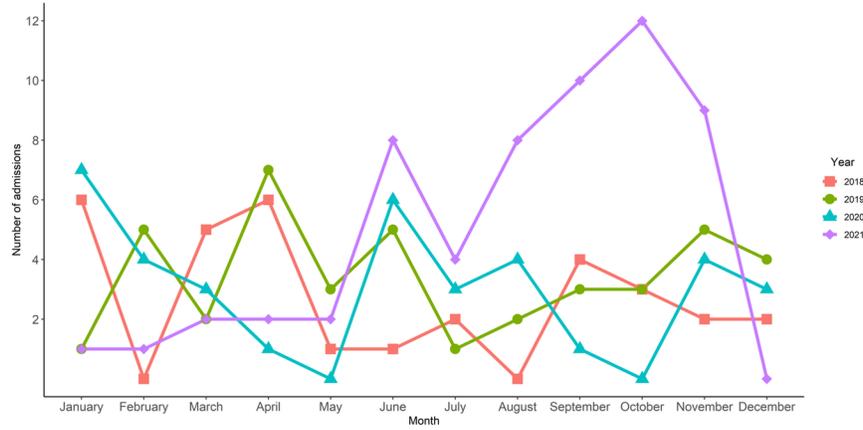


Figure 1 | The number of PICU admissions for SAA in 2018-2021. The monthly pediatric intensive care unit (PICU) admissions for severe acute asthma (SAA) are shown for the years 2018-2021.

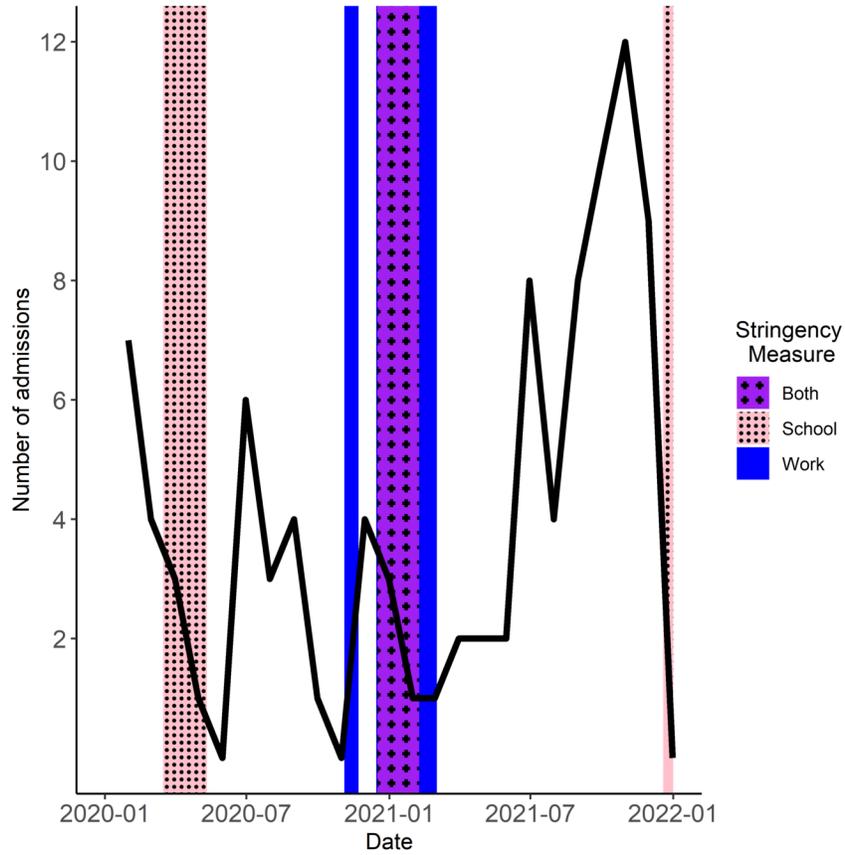


Figure 2 | The number of PICU admissions for SAA in 2020 and 2021 and the stringency measures. The monthly pediatric intensive care unit (PICU) admissions for severe acute asthma (SAA) are shown for the years 2020 and 2021 of the COVID-19 pandemic. Additionally, the stringency lockdown measures that were applicable in that time period (i.e. closure of schools, only allowing to work from home or both) in the Netherlands are also shown as colored bars.