





ORIGINAL ARTICLE

The impact of COVID-19 lockdown on children with recurrent wheezing and asthma in Spain

Zarife Daoud Pérez,^{1,2} Marcelo Rázquin Arias ,³ Alejandro López-Escobar ,^{4,5} Alvaro Díaz-Conradi ,⁶ Amalia Arce,⁶ Nora Ruggeri,³ Isabel Romero Blanco,⁷ Blanca Díaz-Delgado⁷ and Paula S Ventura Wichner ,^{6,8}

¹Pediatrics Pulmonology Department, ²Pediatrics Department, HM Hospitals, ⁴Pediatrics Department, Hospital Vithas Madrid La Milagrosa, ⁵Clinical Research Unit, Fundación Vithas, Grupo Vithas, Madrid, ³Pediatrics Pulmonology Department, ⁶Pediatrics Department, HM Nens, HM Hospitals, Barcelona, ⁸Pediatrics Department, Fundació Institut d'Investigació en Ciències de la Salut Germans Trias i Pujol (IGTP), Badalona, Spain and ⁷Pediatrics Department, Emirates Speciality Hospital Dubai, Dubai, United Arab Emirates

Aim: The rapid spread of a novel human coronavirus SARS-CoV-2 led to drastic measures world-wide. Most countries were forced to declare a national lockdown. We studied the effect of lockdown measures on the level of asthma control and maintenance treatment in children with recurrent wheezing and asthma during the first wave of COVID-19 in Spain.

Methods: We analysed children with recurrent wheezing or asthma before and after the implementation of the lockdown, by using a questionnaire aimed to examine pre-existing respiratory disorders, step treatment and level of asthma control before/after lockdown, COVID history and laboratory testing including IgG SARS-CoV-2.

Results: We enrolled 475 asthmatic and pre-school wheezers (60.6% males), mean age 5.6 years. There were no differences in asthma treatment comparing both periods: 81.7% maintained the same treatment ($P = 0.103$). According to child asthma-control questionnaire, 87.7% remained well controlled during confinement. Nearly, a third of children (34.9%) needed reliever treatment, mainly in older children. Determination of IgG SARS-CoV-2 was performed in 233 children (49.1%) of whom 17 (7.3%) tested positive. Seven patients positive to IgG SARS-CoV-2 were assisted in the emergency department and two required hospital admission.

Conclusions: During COVID-19 lockdown in Spain, most children with recurrent wheezing and asthma remained well controlled from their underlying disease and did not modify greatly their maintenance treatments. Unexpectedly, we also observed that those children who tested positive to SARS-CoV-2 IgG showed a significant increase in paediatric hospital admissions and attendances to urgent care settings.

Key words: anti-asthmatic agent; asthma; COVID-19.

What is already known on this topic

- 1 Asthmatic children show less severe disease manifestations when infected with SARS-CoV-2 comparing to adults.
- 2 However, pediatricians wondered at the beginning of the pandemic due to SARS-CoV-2, how this new virus and lockdown measures would affect children with underlying respiratory disease.

What this paper adds

- 1 it is one of the few studies carried out in children with respiratory pathology during the lockdown related to COVID-19.
- 2 Children with asthma and recurrent wheezing remained well controlled from their respiratory underlying disease during the COVID-19 lockdown.
- 3 The importance of maintaining good adherence to preventive asthma treatments, particularly during a lockdown due to a respiratory virus.

The pandemic due to the new respiratory virus SARS-CoV-2 has spread world-wide rapidly infecting more than 263 M people and leading to the death of nearly 5.3 million people world-wide.¹ The prevalence of COVID-19 in children younger than 18 years

at the beginning of the pandemic accounted for only 1–2% of detected COVID-19 cases.² Recent reports from CDC in the USA informed that children under 18 years of age account for approximately 14–16% of cumulative laboratory-confirmed cases.³

Correspondence: Marcelo Rázquin Arias, Pediatrics Pulmonology Department, HM Nens, HM Hospitals, Consell de Cent 437, 08009 Barcelona, Spain. Fax: +34 932655017; email: razquin.marcelo@gmail.com

Zarife Daoud Pérez and Marcelo Rázquin Arias contributed equally as co-first authors.

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COVID-19 has less incidence and severity in childhood comparing with adults, usually asymptomatic or with mild symptoms.⁴ However, the impact of this new coronavirus on children with respiratory underlying conditions (mainly pre-school transient wheezing and asthma) has not been extensively investigated. According to the International Study of Asthma and Allergies in Childhood, the prevalence of childhood asthma in the world is greater than 12% and there exists a large variability depending on age and geographical area.⁵ In Spain, the prevalence of asthma in children ranges between 7.1% and 15.3%, with an average of approximately 10%. Recurrent wheezing is estimated to affect approximately one third of pre-school children.

The rapid spread of the SARS-CoV-2 in Spain, one of the most affected countries since the beginning of the pandemic, led to the declaration of the national lockdown from 14 March to 21 June 2020;⁶ lockdown measures were taken: the opening to the public of the museums, archives, libraries, monuments as well as public shows, sports and leisure activities were suspended, and educational centres were closed for 16 weeks.

The aim of this study was to analyse the impact of lockdown measures on treatment and level of control in children with asthma and pre-school wheeze and describe the clinical outcome of children with positive IgG COVID-19 serology during the first wave of COVID-19 in Spain.

Methods

We performed an observational study to obtain information of children with pre-existing history of recurrent wheezing (≥ 3 reported episodes in the last 12 months) or asthma before and after the implementation of the lockdown in a controlled study group. The study population consisted of children younger than 16 years followed in the Pediatric Pulmonology Departments of the HM Hospitals from Madrid and Barcelona during the 2 months following the announcement of lockdown in Spain.

A survey was distributed between 18 May and 15 June to parents or responsible caregivers through institutional mailing. Informed consent was obtained from the responsible adult who voluntarily answered the questionnaire on behalf of all children living in the household. Although the survey was intended to reach children across Madrid and Catalonia, we also received information from other parts of Spain from neighbouring areas who were followed in these hospitals (total $n = 493$). Six patients refused to participate in the study and 12 who did not meet inclusion criteria were excluded. We estimated the survey reached around 700 potential participants across Catalonia and 300 across Madrid. The overall response rate was around 50%.

At the end of the survey, parents/caregivers were offered to participate in laboratory testing.

Data collection

Survey questionnaire was designed by paediatricians from HM Hospitals and approved by IRB Committee (CEIm Code: HM20.04.1615-GHM). The survey collected demographic characteristics of children such as sex, age and province of residence.

The questionnaire consisted of four sections aimed to examine (Table S1): (i) pre-existing respiratory disorders in addition to recurrent wheezing or asthma; allergy, recurrent pneumonia,

bronchiectasis, bronchopulmonary dysplasia, alpha-1-antitrypsin deficiency, bronchiolitis obliterans, apnoeas, recurrent laryngitis, diaphragmatic paralysis; (ii) step treatment and level of asthma control before/after lockdown; (iii) COVID history; and (iv) opportunity to perform laboratory testing and COVID-19 serology.

Asthma treatment steps

Six therapeutic steps were used to assess the asthma treatment in paediatric age based on the level of control, according to the Spanish Asthma Guidelines (GEMA 2020), version 5.0 (Table S2).

Asthma control assessment

We used a validated Spanish child asthma-control questionnaire (CAN)⁷ in children ≥ 2 years old that consisted of nine items selected qualitatively. Response options were in the form of a 5-point Likert scale for each item. The time frame was the 'past 4 weeks'. The total score was calculated as the sum of the scores for each item and ranges from 0 (best control) to 36 points (worst control). Patients were considered well controlled with a score equal or lower than 8.

Laboratory testing

Enzyme immunoassay for the determination of IgG antibodies to SARS-CoV-2 in human serum and plasma, DIA.PRO (Milano-Italy), C-reactive protein and a complete blood count.

Statistical analysis

Data were expressed as mean (SD) for continuous variables, or as numbers/percentages for categorical variables. The normality of distribution and equality of variances were evaluated through the Kolmogorov–Smirnov test and Levene's test respectively. The Student *t*-test was used to compare independent continuous variables. A Pearson χ^2 test and/or Yates and Fisher's correction was used to compare categorical variables between groups. The Statistical Package for Social Science SPSS version 23.0 was used to perform all the statistical analyses, establishing the significance at $P < 0.05$.

Results

Treatment and asthma control data for 475 children followed up from 18 May to 15 June 2020 were included for analysis. The mean age was 5.6 years (3.6) and 60.6% were males. Regarding the place of residence, 62.3% were from Barcelona, 30.1% from Madrid and 7.6% from neighbouring areas. In addition to recurrent wheezing or asthma, allergy was the most frequent respiratory disorder referred by 188 patients (39.6%), of whom 71.8% were sensitised to house dust mite, 51.1% to pollen and 32.4% to animal dander. Serological analysis for SARS-CoV-2 infection was performed during July 2020 in 233 children (49.1%) of whom 17 (7.3%) tested positive to IgG SARS-CoV-2.

Asthma treatment steps, need for change in maintenance treatment before and after lockdown, as well as asthma control and need of reliever treatment during confinement by age range, are shown in Table 1.

Regarding to treatment steps, nearly 80% of the children were on steps 2–4 both before and after lockdown (Fig. 1). Our study revealed that the group of children aged 6–11 years were in higher therapeutic steps (steps 4–5) both before and after

Table 1 Asthma treatment steps and asthma control by age range

	Total <i>n</i> = 475 <i>n</i> (%)	<6 years† <i>n</i> = 275 (57.90%)	6–11 years† <i>n</i> = 163 (34.30%)	12–15 years† <i>n</i> = 37 (7.80%)	<i>P</i> value
Gender					
Male	288 (60.6%)	61.5	61.3	51.4	0.480
Asthma treatment steps before lockdown					
Step 1	81 (17.1%)	14.5	19.6	24.3	<0.001
Step 2	128 (26.9%)	32.7	16.6	29.7	
Step 3	111 (23.4%)	24.7	22.1	18.9	
Step 4	139 (29.3%)	27.3	33.7	24.3	
Step 5	16 (3.4%)	0.7	8	2.7	
Step 6	0	0	0	0	
Asthma treatment steps after lockdown					
Step 1	85 (17.9%)	17.8	17.8	18.9	0.001
Step 2	143 (30.1%)	33.8	23.3	32.4	
Step 3	111 (23.4%)	25.1	20.2	24.3	
Step 4	117 (24.6%)	22.2	28.8	24.3	
Step 5	19 (4%)	1.1	9.8	0	
Step 6	0	0	0	0	
Change in asthma treatment before and after lockdown					
Escalation	30 (6.3%)	4	8.6	13.5	0.103
Unchanged	388 (81.7%)	84	78.5	78.4	
De-escalation	57 (12%)	12	12.9	8.1	
Asthma control after lockdown CAN‡					
Well-controlled	378 (87.7%)	89.2	87.1	81.1	0.364
Uncontrolled	53 (12.3%)	10.8	12.9	18.9	
Needed reliever treatment after lockdown	166 (34.9%)	30.5	38	54.1	0.011

† Values expressed in %. Note: Bold numbers represent statistically significant values for an alpha level <0.05. ‡ Child asthma-control (CAN) questionnaire in children ≥2 years old.

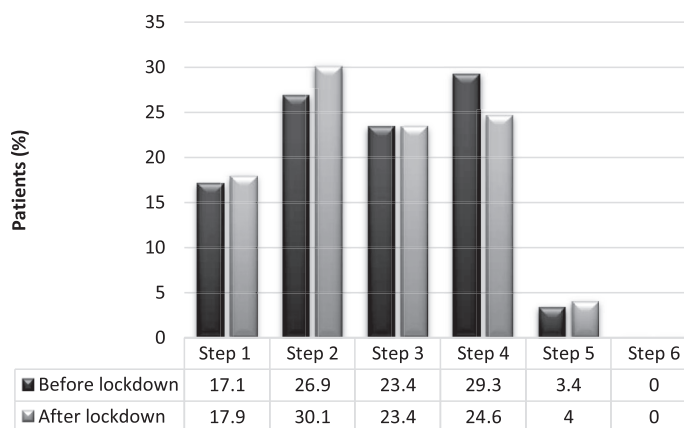


Fig. 1 Asthma treatment steps (GEMA) before and after lockdown. Each column represents the percentage of patient’s asthma treatments steps before and after lockdown.

Each column represents the percentage of patient’s asthma treatments steps before and after lockdown.

lockdown. There were no differences in asthma treatment comparing both periods, since 81.7% maintained the same treatment (*P* = 0.103) (Table 1).

According to CAN questionnaire in 431 children ≥2 years old, most of them (87.7%) remained well controlled (CAN <8) during confinement and there were no differences between age groups.

Forty-four children <2 years old did not answer the questionnaire. Nearly a third of children (34.9%) needed reliever treatment with salbutamol during confinement, mainly in older children.

Comparing children who tested positive versus negative for SARS-COV-2 IgG, there were no differences in maintenance

Table 2 Asthma treatment steps and control according to IgG SARS-CoV-2 result

	IgG SARS-COV-2			P value
	Total	Positive†	Negative†	
	n = 233	n = 17 (7.3%)	n = 216 (92.7%)	
Age (years), mean (SD)	6.3 (3.7)	6.7 (3.8)	6.3 (3.7)	0.673
Gender				
Male	136 (58.4%)	47.1	59.3	0.326
Inhaled corticosteroid				
Low dose	77 (33%)	52.9	31.5	0.070
Medium dose	88 (37.8%)	29.4	38.4	0.460
High dose	12 (5.2%)	5.9	5.1	0.887
LTRA	58 (24.9%)	29.4	24.5	0.654
Asthma treatment steps before lockdown				
Step 1	39 (16.7%)	11.8	17.1	0.945
Step 2	62 (26.6%)	23.5	26.9	
Step 3	53 (22.7%)	29.4	22.2	
Step 4	68 (29.2%)	29.4	29.2	
Step 5	11 (4.7%)	5.9	4.6	
Step 6	0	0	0	
Asthma treatment steps after lockdown				
Step 1	38 (16.3%)	11.8	16.7	0.108
Step 2	71 (30.5%)	17.6	31.5	
Step 3	50 (21.5%)	47.1	19.4	
Step 4	64 (27.5%)	17.6	28.2	
Step 5	10 (4.3%)	5.9	4.2	
Step 6	0	0	0	
Change in asthma treatment before and after lockdown				
Escalation	11 (4.7%)	11.8	4.2	0.276
Unchanged	204 (87.6%)	76.5	88.4	
De-escalation	18 (7.7%)	11.8	7.4	
Asthma control				
Well controlled‡	184 (84%)	87.5	83.7	0.693
Uncontrolled	35 (16%)	12.5	16.3	
Needed reliever treatment	99 (42.5)	64.7	40.7	0.054

† Values expressed in %. ‡ CAN \leq 8 in children older than 2 years. LTRA, leukotriene.

treatment, with either inhaled corticosteroids (ICS) or leukotriene receptor antagonist, neither in level of asthma control comparing both groups since 87.5% and 83.7% were well controlled, respectively (Table 2).

Analysing the subgroup of 17 children positive for SARS-CoV-2 IgG, the mean age was 6.7 years (3.8), 47.1% were males, and 14 children received maintenance therapy. Although we found that these children showed a tendency to escalation in the treatment (11.8% vs. 4.2%), the global difference was not significant. Eleven children (64.7%) needed reliever treatment and two (11.8%) required further escalation. Two of these children needed reliever and escalation treatment (Table 2). Seven patients were assisted in the emergency department. Two of these children needed reliever and escalation treatment, requiring hospital admission for supplementary oxygen therapy; one of them was admitted to PICU. Regarding the symptoms they presented, the most frequent

was cough/respiratory distress (41.2%), followed by fever (29.4%), headache (17.6%), gastrointestinal problems (17.6%), sore throat (5.9%) and 6 (35.3%) were asymptomatic. No significant differences were observed in the frequency of symptoms compared to children with negative IgG SARS-CoV-2 (Table 3). Almost all made a complete recovery within a week, except two patients that had respiratory symptoms for at least 1 month. None of the children died during the study period. Regarding the source of infection, 12 (70.5%) children were supposedly infected by their parents or grandparents, 4 (23.5%) by other children and 1 (5.9%) unknown. Eleven (64.7%) children referred were infected during confinement, five (29.4%) before and one (5.9%) unknown.

Regarding the values of the blood count and C-reactive protein, no significant differences were found when positive and negative SARS-CoV-2 IgG patients were compared. Four clotted blood samples were not included (Table S3).

Table 3 Clinical characteristics according IgG SARS-CoV-2 result

	Total <i>n</i> = 233	IgG SARS-CoV-2		<i>P</i> value
		Positive† <i>n</i> = 17	Negative† <i>n</i> = 216	
COVID-19 clinical manifestations				
Asymptomatic	131 (56.2%)	35.3	57.9	0.071
Symptomatic				
Cough/respiratory distress	53 (22.7%)	41.2	21.3	0.06
Sore throat	43 (18.5%)	5.9	19.4	0.165
Headache	42 (18%)	17.6	18.1	0.966
Fever	39 (16.7%)	29.4	15.7	0.146
Vomiting/diarrhoea	29 (12.4%)	17.6	12	0.5
COVID-19 contact				
Suspicious	74 (31.8%)	76.5	28.2	<0.001
Confirmed	29 (12.4%)	47.1	9.7	<0.001
Emergency care for COVID-19 symptoms	44 (18.9%)	41.2	17.1	0.023
Hospital admission for COVID-19 suspicion	4 (1.7%)	11.8	0.9	0.028

† Values expressed in %. Bold numbers represent statistically significant values for an alpha level <0.05.

Discussion

Our study showed that during confinement, most children with recurrent wheezing and asthma remained well controlled on their maintenance therapies and those treatments preserved unchanged, both in the group with positive and negative serology IgG SARS-CoV-2. The subgroup of children positive to IgG referred mild symptoms, but significant increase in paediatric hospital admissions and attendances to urgent care settings.

Respiratory viruses are the most common triggers of asthma; it is estimated that up to 90% of exacerbations in children are related to viral infections. Non-epidemic coronaviruses are found commonly in the respiratory tracts of children with an asthma exacerbation.⁸ It has been suggested that SARS-CoV-2 infection in asthmatic children may increase the risk of acute respiratory disease. CDC listed moderate to severe asthma as a risk factor for COVID-19 morbidity and mortality and some authors suggested that uncontrolled asthma might represent a condition for severe SARS-CoV-2 infection.^{9,10} However, in our study the two 'uncontrolled' children positive to IgG SARS-CoV-2 did not refer severe symptoms.

There is low evidence whether the administration of ICS might affect the outcome or prevent the development of symptomatic infection or severe acute respiratory infections due to SARS-CoV-2.¹¹ Asthmatic patients were widely advised to continue their controller medications.^{12,13} In our study, we observed that most children maintained good therapeutic adherence after lockdown, differing from what was published by other authors.¹⁴ It is likely that due to fear of respiratory complications and avoidance of the healthcare setting due to fear of contracting COVID-19, parents/caregivers may have been more vigilant that their children maintain prescribed treatments.^{15,16}

As similar findings recently published,^{17,18} the high rates of well-controlled asthma that we observed (according to CAN questionnaire) could be explained by different reasons: better

therapeutic adherence,¹⁹ lower circulation of respiratory viruses (mainly rhinovirus and RSV) due to the measures of confinement,²⁰ interruption of extracurricular activities⁶ and improvement in air quality.²¹

Regarding the use of reliever treatment, we found that nearly a third of children required the use of salbutamol during confinement, especially in the group of older children, likely because of the lower therapeutic adherence in adolescents²² and increased exposure to indoor allergens.²³

Compared with adults, the symptoms related to COVID-19 were mild, being the most frequent cough and fever.⁴ In our study, 40% of the children with serology positive to IgG SARS-CoV-2 referred cough and shortness of breath, symptoms that are also found in asthma exacerbation. These overlapping of symptoms that are also found in asthma exacerbation, representing a diagnostic and therapeutic challenge for pediatricians. Fever, headache and odynophagia, present in 29%, 17% and 5.9% of our children respectively, may help to differentiate COVID-19 from an asthma exacerbation, although can be also present in virus-triggered asthma. Regarding symptoms, no differences were observed in those who presented positive versus negative IgG SARS-CoV-2 serology. This finding would not allow us, according to symptoms, to infer if the children suffered from COVID-19 disease or not. However, despite the fact the sample size was very small, our results suggest that children IgG positive showed significant increase in paediatric hospital admissions and attendances to urgent care settings, suggesting a worse general condition in these children.

As described in the early stage of the pandemic, we observed that exposure to family cluster with confirmed COVID-19 was the most common source of infection among children, probable related to difficulties in self-isolation. Although children were not considered major drivers of the SARS-CoV-2 and did not greatly represent household clusters of infection,²⁴ the transmission from children to household contacts occurs; however, the relative

frequency of transmission from young children compared with other age groups is uncertain.²⁵

Our study has some limitations. First, it was performed during the first period of the pandemic, and the availability of molecular detection tests for SARS-CoV-2 was very limited, especially in children with mild symptoms. The low number of patients that resulted positive to IgG SARS-CoV-2 represents a limitation to reach relevant conclusions in this group. However, we found a SARS-CoV-2 IgG seroconversion of 7.3%, as also showed the results of the National Study of Seroepidemiology of infection by SARS-CoV-2 in Spain.²⁶ Second, the serology test was performed 3–4 months after the lockdown; it is unknown the duration of the antibody responses to SARS-CoV-2 infection, and if children with negative results could pass the infection without seroconversion. Third, spirometry was not performed since respiratory function tests were not recommended during this period.¹³

The strengths of this study include the follow-up of treatment and level of disease control in a large cohort of children with the most frequent respiratory disorders (recurrent wheezing and asthma), particularly in those positive to IgG SARS-CoV-2. Another strength is the fact that we could have assessed the outcome of the underlying condition in young children, by using a validated questionnaire in children ≥ 2 years old.

To date, there are limited published studies that describe the level of control and clinical outcomes of children with recurrent wheezing and asthma during the first wave of COVID-19. We consider that our study sheds light on this population group, especially those who passed the SARS-CoV-2 infection.

Conclusions

During the COVID-19 lockdown, most of the children with asthma and recurrent wheezing maintained their preventive treatments unchanged, showing good therapeutic adherence. Therefore, they remained well controlled from their underlying disease. Although the subgroup of children with positive IgG SARS-CoV-2 did not show severe symptoms of COVID-19 disease, we observed a significant increase in paediatric hospital admissions and attendances to urgent care settings.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1. Survey questions and response options.

Table S2. Asthma treatment steps in paediatric age according to level of control (GEMA).

Table S3. Laboratory results of paediatric patients according to IgG SARS-CoV-2.