







# Effects of the COVID-19 pandemic and lockdown on symptom control in preschool children with recurrent wheezing

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## Abstract

**Introduction:** Preschool wheezers are at high risk of recurrent attacks triggered by respiratory viruses, sometimes exacerbated by exposure to allergens and pollution. Because of the COVID-19 infection, the lockdown was introduced, but the effects on preschool wheezers are unknown. We hypothesized that there would be an improvement in outcomes during the lockdown, and these would be lost when the lockdown was eased.

**Materials and Methods:** Patients underwent medical visits before and after the COVID-19 lockdown. We recorded the childhood Asthma Control Test (cACT) and a clinical questionnaire. Data on symptoms, the need for medications and the use of healthcare resources were recorded. We compared these data with retrospective reports from the preceding year and prospectively acquired questionnaires after lockdown.

**Results:** We studied 85 preschool wheezers, mean age 4.9 years. During the lockdown, cACT score was significantly higher (median 25 vs. 23); families reported a dramatic drop in wheezing episodes (51 vs. none), significant reductions in the day and nighttime symptoms, including episodes of shortness of breath ( $p < .0001$ ); the use of salbutamol and oral corticosteroids (OCS) dropped significantly ( $p < .0001$ ) and 79 (95%) patients needed no OCS bursts during the lockdown. Finally, patients had significantly fewer extra medical examinations, as well as fewer Emergency Room visits ( $p < .0001$ ). All were improved compared with the same time period from the previous year, but outcomes worsened significantly again after lockdown (cACT median: 22).

**Conclusions:** During the national lockdown, children with persistent preschool wheeze showed a significant clinical improvement with reduction of respiratory symptoms, medication use for exacerbations, and use of healthcare resources. This trend reversed when lockdown restrictions were eased.

## KEYWORDS

COVID-19, pediatric asthma, pediatric lung disease

## 1 | INTRODUCTION

Children with asthma and preschool wheeze are at high risk of acute attacks, especially during winter and spring, caused by respiratory viruses, such as rhinovirus and respiratory syncytial virus. Other important factors include exposure to allergens<sup>1,2</sup> and atmospheric pollution.<sup>3,4</sup>

During Spring 2020, COVID-19 spread across the world and drastic interventions were introduced by most countries to reduce transmission. Asthmatic patients were initially expected to have an increased risk of attacks triggered by SARS-CoV-2. However, this fear turned out to be misplaced.<sup>5</sup>

A recent review concluded that the data on childhood asthma during the period of SARS-CoV-2 infection is of low quality<sup>6</sup> and to the best of our knowledge, data are lacking on preschool wheezers. The only published data come from emergency departments showing an overall reduction of healthcare utilization and a significant decrease in pediatric asthma admissions.<sup>7,8</sup>

The aim of this paper is to explore the effects of the pandemic and lockdown on preschool children with recurrent wheeze, using outpatient visit data, childhood Asthma Control Test (ACT), and clinical questionnaires (CQ) at three different times: before (February 2020) and immediately after (June 2020) the Italian lockdown, and at the end of October at the start of the respiratory virus season. We hypothesized that there would be an improvement in outcomes during the lockdown, and these would be lost when the lockdown was eased.

## 2 | MATERIALS AND METHODS

Data presented were extracted from an ongoing observational study on preschool wheezers carried out by the Pediatric Pulmonology Unit at the "Ospedale Pediatrico Bambino Gesù" in Rome. The original study aimed to understand differences between standard follow-up with a "treatment written plan" versus the use of a mobile app. The study was approved by the local ethics committee (study identification number: 1356\_OPBG\_2017). The study population consisted of preschool children affected by persistent wheeze<sup>9</sup> all of whom were prescribed low dose inhaled corticosteroids throughout the study period. Inclusion criteria were age between 25 and 72 months; history of recurrent wheezing ( $\geq 3$  reported episodes in the last 12 months) and/or at least one oral corticosteroid burst in the previous 6 months and/or at least one hospitalization for a respiratory exacerbation in the last 12 months. Exclusion criteria were anatomic malformation causing chronic bronchial obstruction; any severe chronic diseases (i.e., cystic fibrosis, primary immunodeficiency); intention to move away from Rome during the monitoring period.

Italian lockdown in response to COVID-19 started on March 9 and lasted until May 19. All patients satisfying inclusion criteria and who signed informed written consent were consecutively included. Only five families refused to take part in the study.

The study was structured in three distinct periods: (1) before lockdown: November 2019–February 2020; (2) immediately after

lockdown: March–June 2020; and (3) from July–until the end of October. All patients underwent several visits: a first visit (V1) 3 months after recruitment, in February 2020, before lockdown, and the second visit in June (V2) immediately after lockdown. At V1 and at V2, a clinical history was obtained, a CQ answered by parents/caregivers with the help of a physician, and finally, cACT completed by patients  $\geq 4$  years old. The CQ was structured to collect retrospective data over the previous 3 months and explored 12 items (Table 1). cACT is a validated tool designed to be used in children 4–11 years old (Q1–4) and their parents (Q5–7, referring to the last 4 weeks). The higher the number, the better is control. As above, only patients  $\geq 4$  years old were asked to complete the cACT score. Visit 2 was completed by 83 patients (two patients withdrew from the study for family reasons). At the end of October 2020, we telephoned parents and asked them to answer the CQ questionnaire to obtain data a few months postlockdown.

Moreover, medical records of all 85 patients (83 considered for the second-period analysis) included in our study were reviewed and data retrospectively collected from the previous (non-COVID) year 2018–2019 (winter and spring season). To be consistent, we reviewed medical records from the same patients although one year younger.

The sample size was opportunistic as there are no published data to inform a power calculation. Statistical analyses were performed with SAS 9.4 software. Data were summarized as numbers (N) and frequencies (%) if they were categorical and as mean/median and standard deviation (SD)/interquartile range (IQR) if quantitative, depending on whether normally distributed or not. Wilcoxon and McNemar's tests were used to evaluate the differences in cACT score at three different time points.  $\chi^2$  or Fisher tests were used to compare CQ responses at three different time points and to compare results from the study period with those from the previous year's exacerbations in the winter and spring seasons.

A  $p < .05$  was considered statistically significant.

## 3 | RESULTS

Eighty-five patients, 48 (56%) males, mean age  $\pm$  SD (range)  $4.2 \pm 1.1$  (2–5.9), affected by persistent preschool wheeze were enrolled for prospective data collection. Visit 2 was completed by 83 patients. Sixty-two (73%) patients were  $\geq 4$  years old and filled in the cACT test. Twelve (14%) were sensitized to allergens with 10 (83%) being sensitized to house dust mite. Only two patients were sensitized to outdoor allergens.

Results from cACT and CQ for the three periods before, during, and after lockdown are presented in Table 1. At the end of October, cACT was sent to the homes of families and all patients completed the telephone questionnaire. There were statistically significant differences between V1 and V2 for cACT median 23 (IQR: 21–25) versus 25 (24–25). At the end of October, cACT median dropped again to 22 (20–25). The number of children whose cACT increased by  $\geq 2$  points was 19 (38%) and the number of children that then decreased by  $\geq 2$  points (the minimally important clinical difference) was 27 (54%).<sup>10</sup> Moreover, the numbers of patients who were poorly

**TABLE 1** cACT and CQ results classified in all time periods

	(A) Nov–Feb	(B) Mar–June	(C) Jul–Oct	
cACT score, median (interquartile range; 95% CI)	23 (21–25; 22–24)	25 (24–25; 24–25)	22 (20–25; 21–23)	<b>&lt;0.0001</b>
Episodes of wheezing, N (%)				<b>&lt;0.001</b>
Yes	51 (61)	0 (0)	19 (23)	
No	32 (39)	83 (100)	64 (77)	
Cough attacks/last 3 months, N (%)				<sup>a</sup> <b>&lt;0.001</b>
Once or ≥twice	64 (77)	7 (8)	50 (60)	
Never	19 (23)	76 (92)	33 (40)	
Nighttime symptoms, N (%)				<b>&lt;0.001</b>
Once or ≥twice/week	58 (70)	5 (6)	32 (38)	
Never	25 (30)	78 (94)	51 (62)	
Wheeze affecting daily activities, N (%)				<b>&lt;0.001</b>
Yes	39 (47)	2 (2)	9 (11)	
No	44 (53)	81 (98)	74 (89)	
Episodes of shortness of breath, N (%)				<b>&lt;0.001</b>
Once, twice, or >2/week	41 (48)	2 (2)	21 (25)	
Never	42 (52)	81 (98)	62 (75)	
Use of salbutamol, N (%)				<b>&lt;0.001</b>
≥Twice a week	52 (63)	5 (6)	31 (37)	
Once a week/never	31 (37)	78 (94)	52 (63)	
Oral steroids courses ≥3 days, N (%)				<b>&lt;0.001</b>
≥1 course	50 (60)	4 (6)	13 (16)	
Never	33 (40)	79 (94)	70 (84)	
Total days of oral steroids, N (%)				
≥5 days	29 (34)	1 (1)	5 (6)	<b>&lt;0.001*</b>
<5 days	22 (27)	3 (4)	8 (10)	<b>&lt;0.001*</b>
Never	32 (39)	79 (95)	70 (84)	<b>&lt;0.001*</b>
Extra medical visits, N (%)				<b>&lt;0.001</b>
Once or ≥twice	67 (81)	4 (5)	29 (35)	
Never	16 (19)	79 (95)	54 (65)	
Emergency room visits, N (%)				<b>&lt;0.001</b>
≥Once a week	12 (14)	1 (1)	3 (4)	
Never	71 (86)	82 (99)	80 (96)	
Hospital admission, N (%)				<b>0.018</b>
Yes	4 (5)	0 (0)	0 (0)	
No	79 (95)	83 (100)	83 (100)	
Asthma family perception, N (%)				<b>&lt;0.001<sup>a</sup></b>
Not well-controlled	14 (17)	0 (0)	21 (25)	
Well-controlled	69 (83)	83 (100)	62 (75)	

Note: cACT analysis includes only 59 patients (68%) ≥4 years old.

Abbreviations: cACT, childhood Asthma Control Test; CQ, clinical questionnaire.

<sup>a</sup>A versus B; B versus A and C.

\*p Value has been analyzed among the three groups for each variable. The difference resulted in significance for the three groups (A, B, and C).

**TABLE 2** Questionnaires' results on study period and last year exacerbations for winter and spring seasons

	Nov-Feb	Mar-Jun	
Study period (2019–2020)			$p < .0001$
>3 attacks, <i>n</i> (%)	15(18)	0(0)	
1 or 2 attacks, <i>n</i> (%)	49(58)	7(8)	
Never, <i>n</i> (%)	21(24)	76(92)	
Previous year (2018–2019)			$p < .4296$
>3 attacks, <i>n</i> (%)	29 (34)	21(25)	
1 or 2 attacks, <i>n</i> (%)	19 (23)	23(28)	
Never, <i>n</i> (%)	37 (43)	39(47)	

controlled ( $cACT \leq 19$ ) were 5 (10%), 0, and 12 (24%) before, during, and after lockdown, respectively. A more detailed analysis for  $cACT$  measured in the three considered periods (November–February; March–June; July–October) can be found in Table S2.

There was a dramatic drop in wheezing (51 vs. 0) and only minor episodes of cough were recorded during the lockdown. There were significant reductions in the day and nighttime symptoms, including episodes of shortness of breath (see Table 1). However, from the same questionnaire a few months after lockdown, cough, nighttime symptoms, and episodes of wheezing and shortness of breath all increased again (see Table 1).

The use of salbutamol and oral corticosteroids (OCS) dropped significantly and 79 (95%) patients needed no OCS bursts during the lockdown. Finally, the use of healthcare resources for respiratory exacerbations or wheezing symptoms was significantly lower. There was a weak statistically significant reduction in nights spent in the hospital. Most families felt that their children's symptoms were well-controlled. Again, this worsened significantly after the end of the lockdown.

Hospital medical records of all patients were also reviewed and data on a number of exacerbations retrospectively collected from the previous non-COVID year 2018–2019 (winter and spring season) and there was no equivalent drop in symptoms, over the corresponding time period (Table 2). We completed the analysis by comparing the respiratory exacerbations in spring (the period affected by national lockdown) of the two consecutive years 2018/19 and 2019/20. We observed, for the same patients, a statistically significant difference in the number of exacerbations between Spring 2019 and 2020 ( $p < .0001$ ) with the latter being dramatically lower (Table S1).

Finally, none of the children were infected with the COVID-19 coronavirus during the study period.

## 4 | DISCUSSION

Contrary to initial expectations, and in accord with our hypothesis, children affected by preschool wheeze had better outcomes during the lockdown. This is consistent with findings of reduction in emergency visits and admissions for asthma attacks in school-age children.<sup>7,11</sup> Both

$cACT$  and CQ showed similar results. A possible explanation of the discrepancies between the two tests probably relates to the fact that the former relates only to the previous 4 weeks. Were only data on emergency visits been available, a possible interpretation could have been that Italian parents avoided hospitals, for example, because of the risk of COVID? However, the significant reduction in the day and nighttime respiratory symptoms and in medication use (both salbutamol and OCS) shows there was a real improvement in outcomes. Our innovative results in children with preschool wheeze confirm the benefit found by Sheehan et al. in DC asthmatic patients during fall 2020.<sup>12</sup> Unfortunately, we recorded a significant worsening again at the end of October with a new increase in respiratory symptoms, even if not as bad as that registered from the winter season 2020–2021. We believe that there are two possible reasons for this difference: (a) in July lockdown was over but people kept wearing masks and were aware of the importance of social distancing and (b) the period under consideration after lockdown included also part of the summer and data was available for only 2 months of autumn (September and October). However, the new increase of symptoms after the strict lockdown was eased, suggests that the clinical improvement, registered during the lockdown, was not just a manifestation of the natural trend for children affected by preschool wheeze to improve over time.

Moreover, the lack of improvement in the previous, non-COVID year, over the corresponding time period, also suggests the improvement in outcomes during lockdown was not artefactual.

The possible causes of these findings remain speculative. Lockdown and home-schooling may have limited respiratory viral transmissions. Other potential hypotheses include less environmental pollution and better adherence to preventive medications, as well as possibly less exposure to outdoor aeroallergens. Clearly, the improvements were the results of some behavioral and exposure changes, and it would be important to try to understand and recapitulate these, without returning to lockdown.

The strengths of the study include well-characterized medical visits (immediately before and after COVID-19 lockdown) and clinical data collection from a good size cohort affected by preschool wheeze. The limitations of the study include the use of  $cACT$ . This is a well-validated tool designed to be used in children 4–11 years old (Q1–4) and their parents (Q5–7). Therefore, only patients  $\geq 4$  years old used this tool. The use of a nonvalidated CQ could be considered a limitation, however, this tool seemed reliable as parents' answers accorded with the clinical history recorded at each visit. Symptoms recall was retrospective and thus may be biased, and we did not perform a skin prick test in this young population, which could explain the low incidence of atopy, measure lung function, or any inflammatory biomarker.

There are difficulties with studying recurrent wheeze. The known seasonal variation in symptoms and exacerbations, and the tendency for these to improve over time, are potentially important confounding factors. However, the fact that symptoms worsened after easing lockdown is against the suggestion that improvement during lockdown merely represented the known natural history of preschool wheeze, and the matching of data with the corresponding season from the previous year is also against attributing the changes

to mere seasonal variation. Finally, our findings may not be generalizable to countries in which there was a less severe lockdown.

In summary, we have shown for the first time that children with recurrent wheeze improved significantly during the lockdown, with a reduction of respiratory symptoms, and less use of medication and healthcare resources. We need to understand the exact factors leading to this improvement and find ways of sustaining the improvements during the lockdown, without the rigors of the confinement in that period. Future work should include a longer follow-up in children in those countries wherein lockdown is reinstated to reconfirm our findings.

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#### AUTHOR CONTRIBUTIONS

**Nicola Ullmann:** Conceptualization (lead); data curation (equal); supervision (equal); writing original draft (equal). **Annalisa Allegorico:** Data curation (equal); writing original draft (equal). **Andrew Bush:** Data curation (equal); writing review and editing (equal). **Federica Porcaro:** Data curation (equal); methodology (equal); validation (equal); writing review and editing (supporting). **Valentina Negro:** Formal analysis (equal); methodology (equal). **Alessandro Onofri:** Formal analysis (equal); investigation (equal); methodology (equal). **Claudio Cherchi:** Data curation (equal); investigation (equal). **Simone De Santis:** Data curation (equal); formal analysis (equal). **Lorenza Rosito:** Data curation (equal); formal analysis (equal); methodology (equal). **Renato Cutrera:** Conceptualization (equal); supervision (equal); validation (equal); writing review and editing (equal).

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#### SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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