Background: Virus mitigation measures enacted early in the coronavirus infectious disease 2019 (COVID-19) pandemic suppressed common respiratory viruses and reduced the number of obstructive lung disease exacerbations. However, many localities began to ease these precautions in the year 2021, leading to a resurgence of non-COVID viruses. How asthma and chronic obstructive pulmonary disease (COPD) activity responded to this upswing in viral abundance is unclear.

Objective: Our aim was to examine how viral resurgence during the relaxation of COVID-19 restrictions affected asthma and COPD exacerbations.

Methods: We analyzed electronic medical records for emergency department (ED) respiratory virus positivity, asthma visits, and COPD visits. We compared the 52-week interval before the COVID-19 restrictions (the pre-lockdown period [March 22, 2019–March 19, 2020]), the 52-week period immediately following enactment of the restrictions (the lockdown period [March 20, 2020–March 18, 2021]), and the 52-week period thereafter (the post-lockdown period [March 19, 2021–March 18, 2022]). We used MetaCYCLE to analyze seasonal trends in our data.

Results: The post-lockdown period was marked by a 400% increase in viral positivity compared with during the lockdown period. Asthma- and COPD-related ED visits each rose 37% compared with during the lockdown, with the rebound in asthma ED visits concentrated in individuals younger than 20 years. Interestingly, after the lockdown period, asthma ED visits overcorrected in children younger than 5 years, rising 81% compared with before the lockdown. Seasonal rhythms in asthma and COPD exacerbations were suppressed during the lockdown and recovered after the lockdown.

Conclusions: COVID-19 precautions had the unexpected effect of magnifying early-childhood asthma activity once common respiratory viruses recurred. These results may have implications for the future use of virus mitigation strategies in young children.

Key words: Asthma, COPD, COVID-19, lockdown, respiratory viruses

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic inadvertently created a natural experiment on the role of viruses in chronic lung diseases. Beginning in early 2020, the United States and many other countries adopted a series of “lockdown measures” designed to limit COVID-19 transmission; these measures included social distancing, mask use, and restriction of public venues. A side effect of these measures was a dramatic reduction in the societal burden of common respiratory viruses. In concert, the activity of several inflammatory airway diseases, especially asthma and chronic obstructive pulmonary disease (COPD), diminished. By the spring of 2021, however, COVID-19 vaccines became widely available, attitudes toward preventative measures became less strict, and common viruses began to uptrend by May 2021. Here, we report how viral rebound during the relaxation of COVID-19 precautions affected asthma and COPD exacerbations.

RESULTS AND DISCUSSION

We retrospectively analyzed emergency department (ED) visits for asthma and COPD exacerbations, as well as positivity rates for common respiratory viruses within the Barnes Jewish Christian HealthCare system, a major network of hospitals based in St. Louis, Missouri (see the Supplementary Methods in the Online Repository at www.jaci-global.org). Standard practice at our institution includes viral multiplex testing for patients presenting with respiratory chief complaints, and this standard of practice continued throughout the study period. We focused on weekly event rates occurring in the 52-week intervals before, during, and after institution of the COVID-19 lockdown, which began in our area on March 23, 2020 (Fig 1). The 52-week intervals were chosen to allow for analysis of seasonality, a major feature of respiratory viral infection and airway disease exacerbations in normal times. Using the enactment of COVID-19 restrictions as an anchor point, we defined the period from March 22, 2019, to March 19, 2020, as the pre-lockdown period;
the period from March 20, 2020, to March 18, 2021, as the lockdown period; and the period from March 19, 2021, to March 18, 2022, as the post-lockdown period. Our post-lockdown interval encompassed the roll-out of COVID-19 vaccination to the general public (phases 2 and 3), which began in Missouri on March 29, 2021, and ended proximate to the governor’s declaration of an “end” to the pandemic phase of COVID-19 on April 1, 2022.13

The pre-lockdown, lockdown, and post-lockdown periods differed visibly according to ED detection of common respiratory viruses (Fig 1, A). The pre-lockdown period exhibited the traditional seasonal pattern in viral detection, whereas the lockdown interval demonstrated greatly reduced instances of virus detection as previously described.1,2,9 The post-lockdown period demonstrated a resurgence in instances of respiratory virus detection, with a shift in the cumulative seasonal peak to the summer months (Fig 1, A). We observed similar differences between rates of viral positivity, defined as the percentage of positive tests (Fig 1, B). Interestingly, viral positivity rates adopted 2 different patterns over the study period. For respiratory syncytial virus, influenza virus, parainfluenza virus, and human metapneumovirus, viral positivity was damped during the lockdown and reemerged in the post-lockdown period (Fig 1, B). In contrast, rates of rhinovirus (RV) and adenovirus detection were less affected by lockdown measures (Fig 1). We speculate that adenovirus and RV may be more efficient at fomite transmission than other respiratory viruses and were therefore less affected by the masking and social distancing practices that typified COVID-19 precautions.

Coincident with the aforementioned changes in viral burden, the rates of asthma- and COPD-related ED visits declined by 45% and 35%, respectively, during the lockdown period, with both rates rebounding in the post-lockdown period by approximately 37% (Table I). Although this overall effect was similar, the resurgence of asthma- and COPD-related ED visits during the post-lockdown period diverged according to patient age (Fig 2 and Table I). For asthma, ED visits were concentrated in children before the lockdown, and this age gradient flattened during lockdown as we previously described (Fig 2 [upper panel] and Table I).18 In the post-lockdown period, the childhood peak in asthma-related ED visits returned, with a leftward shift toward younger ages (Fig 2 [upper panel]). Strikingly, asthma-related ED visits overcorrected in children younger than 5 years, rising 81% on an annualized basis compared with during the pre-lockdown period whereas median weekly rates rose by 167% (Fig 2 and Table I). This overcorrection was associated with supranormal cases of virus detection in children younger than 5 years after the lockdown, driven primarily by excess RV, respiratory syncytial virus, and parainfluenza virus cases (Table I). Interestingly, in patients older than 20 years, asthma-related visits did not rise substantially in the post-lockdown period even though cases of ED virus detection rose in adults (Fig 2 [middle panel] and Table I). In contrast to asthma-related ED visits, COPD-related ED visits declined symmetrically during the lockdown across adult ages and then rebounded symmetrically in the...
TABLE I. Weekly rates of asthma-related ED visits, COPD-related ED visits, and virus detection per week in the 52-week intervals before, during, and after the institution of COVID-19 precautions

| Age (y) | Asthma (n = 19,337) | COPD (n = 20,963) | Positive virus tests (n = 39,350) |
|---------|---------------------|-------------------|----------------------------------|
|         | Before the lockdown | During the lockdown | After the lockdown | Before the lockdown | During the lockdown | After the lockdown | Before the lockdown | During the lockdown | After the lockdown |
| Total   | 159.5 (132.5-183)   | 86.5 * (72.5-97.75) | 116 * (96.5-135.75) | 159.5 (142.5-178)   | 102.5 * (85-109.75) | 131 * (116.5-142.75) | 173 (150.25-200.25) | 66 * (52.5-78) | 305.5 * (217.5-367.25) |
| 0-5     | 13 (9-17)           | 7 * (4-10)        | 22 * (14-27)       | 9 (6-14)           | 15 * (11-24.5)      | 21 * (13-30)        | 27 (14-82.75)      | 8 * (5-12) | 29 * (21-25-48)         |
| 5-10    | 20 (16-26)          | 5 * (3-7)         | 27 * (19-35)       | 14 (11-15)         | 11 * (8-15)         | 14 * (10-20)        | 19 (14-52.75)      | 5 (3.5-9) | 19 (13-21)          |
| 10-15   | 18 (11-25-24)       | 7 * (5-9)         | 11 * (8-14)        | 11 (7-15)          | 6 * (4.25-8.25)     | 7 * (4-10)          | 9.5 (5.75-15)      | 3 (2-5) | 12 (7-21.75)         |
| 15-20   | 11 (7-15)           | 5 * (3-7)         | 7 * (3-10)         | 10 (8-12)          | 8 * (6-10)          | 7 * (4-10.75)       | 8 (4.16)          | 2 * (1-4) | 9 (6.5-15)          |
| 20-25   | 10 (8-12)           | 8 * (5-9)         | 5.5 * (3-8)        | 10 (8-12)          | 8 * (6-10)          | 7 * (4-10.75)       | 4.5 (1.25-11.75)   | 1 * (0.2) | 5 (2.8-7.5)          |
| 25-30   | 30 (23-32.75)       | 2 * (1-3)         | 30 * (21-35)       | 28 (23-32.75)      | 20 * (16-25.25)     | 20 * (13-27)        | 8 (6.25-19.25)     | 1 * (0.2) | 3 (1.25-5)          |
| 30-35   | 12 (9-15)           | 7 * (5-9)         | 7 * (4-10)         | 9 (6-12)           | 6 * (4-8)           | 7 * (4-9.75)        | 7 (2.5-12.5)       | 1 * (0.2) | 3 (1.25-5)          |
| 35-40   | 9 (7-11)            | 6 * (4.75-8.75)   | 6 * (3-8)          | 9 (7-11)           | 6 * (4.75-8.75)     | 6 * (4-9)           | 3.5 (2.11)        | 1 * (0.2) | 2 (1.5-4)           |
| 40-45   | 8 (6-10)            | 6 * (4.75-8.75)   | 6 * (3-8)          | 6 * (4.75-8.75)    | 6 * (4-8)           | 6 * (4.75-8.75)     | 5.5 (2.11)        | 1 * (0.2) | 2 (1.5-4)           |
| 45-50   | 8 (5-25-10)         | 4 * (3-6.75)      | 4 * (3-6.75)       | 8 (5-25-10)        | 4 * (3-6.75)        | 4 * (3-6.75)        | 3.5 (2.11)        | 1 * (0.2) | 2 (1.5-4)           |
| 50-55   | 6 (4-8)             | 4 * (3-6.75)      | 4 * (3-6.75)       | 6 (4-8)            | 4 * (3-6.75)        | 4 * (3-6.75)        | 3.5 (2.11)        | 1 * (0.2) | 2 (1.5-4)           |
| 55-60   | 6 (5-8.75)          | 4 * (3-6.75)      | 4 * (3-6.75)       | 6 (5-8.75)         | 4 * (2.5)           | 3 * (2-4)           | 4.5 (2.5-7.5)     | 1 * (0.2) | 3 (1.25-5)          |
| 60-65   | 6 (4.25-8)          | 4 * (3-6.75)      | 3 * (1-4)          | 6 (4.25-8)         | 4 * (2-5)           | 3 * (2-4)           | 3.5 (2.11)        | 1 * (0.2) | 3 (1.25-5)          |
| 65-70   | 4 (3-6)             | 2 * (1-3.75)      | 2 * (1-3.75)       | 4 (3-6)            | 2 * (1-3.75)        | 2 * (1-3.75)        | 3.5 (2.11)        | 1 * (0.2) | 2 (1.5-4)           |
| 70-75   | 3 (2-5)             | 1 * (0-2)         | 1 * (0-2)          | 3 (2-5)            | 1 * (0-2)           | 1 * (0-2)           | 3.5 (2.11)        | 1 * (0.2) | 2 (1.5-4)           |
| 75-80   | 1 (1-2)             | 0 (0-1)           | 0 (0-1)            | 1 (1-2)            | 0 * (0-1)           | 0 * (0-1)           | 3.5 (2.11)        | 1 * (0.2) | 2 (1.5-4)           |
| 80-85y  | 1 (1-2)             | 0 (0-1)           | 0 (0-1)            | 1 (1-2)            | 0 * (0-1)           | 0 * (0-1)           | 3.5 (2.11)        | 1 * (0.2) | 2 (1.5-4)           |
| 85-90y  | 0 (0-1)             | 0 (0-1)           | 0 (0-1)            | 0 (0-1)            | 0 * (0-1)           | 0 * (0-1)           | 3.5 (2.11)        | 1 * (0.2) | 2 (1.5-4)           |

All values in columns 2 through 10 are medians followed by interquartile ranges in parentheses. *P value less than .05 versus before the lockdown (according to the Mann-Whitney U test). †P value less than .05 versus during the lockdown (according to the Mann-Whitney U test).

FIG 2. Supranormal levels of ED visits for asthma in young children after the lockdown data, we analyzed the correlation between airway disease exacerbations and virus detection across the entire study period as a function of age. Histograms depicting cumulative clinical events during the post-lockdown period (Fig 2). Emphasizing the differences between viral detection and asthma- (red circles) or COPD-related ED visits (red squares) across the entire study period as a function of age. Best-fit trend lines and goodness of fit (R2) are depicted.
both asthma and COPD seasonality as reflected by ED visits (Fig 3). In the post-lockdown period, the amplitude in asthma seasonality increased nearly to pre-lockdown levels, although the peak in this rhythm shifted toward the summer months. For COPD-related ED visits, seasonality increased in the post-lockdown period, but with a diminished amplitude and shortened periodicity (Fig 3). Thus, the rebound in virus detection in the post-lockdown period came with a resumption of asthma and COPD seasonality, albeit with altered and disease-specific features.

To our knowledge, our data represent a first look at how the recurrence of common respiratory viruses late in the COVID-19 pandemic influenced emergent asthma and COPD activity. Our data suggest that although asthma and COPD are both strongly influenced by viral triggers, the diseases differ in terms of the role of age in the expression of exacerbations. The strengths of our study include the inclusion of 52-week intervals to capture seasonal variations; the use of data across a regional health care system encompassing multiple EDs; and parallel observations of asthma, COPD, and viral activity from the same care locations.

Our study also has several limitations, including the following: its retrospective design; its reliance on International Classification of Diseases, 10th Revision, codes to specify asthma and COPD exacerbations; the inability of our data to distinguish asthma from self-limited viral wheeze in young children; and the fact that asthma and COPD frequently overlap in older patients. It is possible that ED avoidance might have masked asthma and COPD cases occurring in the community during the lockdown. However, we did not detect a signal for this in a recent analysis of pediatric asthma exacerbations, although in another study, patient avoidance proved to be a minor factor for asthma in the ED setting. Even if present, patient avoidance would bias us toward underestimating the observed rebound in viruses and airway disease exacerbations during the post-lockdown period. Finally, patients made highly individualistic and fluid choices in their adherence to COVID-19 precautions, and as a result, demarcating periods of time as either lockdown or post-lockdown periods is inherently inexact. Nevertheless, our definitions are consistent with local experience, and they succeeded in parsing the arc of the COVID-19 pandemic into clear intervals of normal, low, and resurgent respiratory virus levels in our patient population. The clear distinction in viral abundance between the lockdown and post-lockdown periods helps to contextualize the changes in asthma and COPD clinical activity observed by us, as well as to strengthen our conclusions.

One key finding is that COVID-19 precautions had the unexpected effect of magnifying early-childhood asthma activity once common respiratory viruses recurred. Recently, some authors have suggested that viral mitigation measures such as masking may be an effective approach for managing asthma and COPD going forward based on the dramatic reductions in disease exacerbations during lockdown. However, our data would suggest caution in applying viral mitigation strategies to young children with asthma because withdrawal of these measures led to an overcorrection in viral positivity and asthma cases. Such an overcorrection is biologically plausible because young children are immunologically naive. The enhanced hygiene that is central to COVID-19 precautions might have delayed the normal introduction of infectious flora, impeding immune education and herd immunity as predicted by some authors. Because viral infections during early life are statistically associated with asthma later in childhood, whether the “lockdown generation” of toddlers will be better or worse off in the long term with regard to asthma pathogenesis and natural history remains to be seen.

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Key messages

- Relaxation of COVID-19 precautions in 2021 was associated with a rebound in asthma and COPD exacerbations in concert with a resurgence in common respiratory viruses.
- The rise in asthma exacerbations after the COVID lockdown was selective for children and included an 81% overcorrection of cases in children younger than 5 years old compared with before the COVID lockdown.
- These results suggest an unintended consequence of COVID-19 precautions and may have implications for the future use of such measures to improve asthma control in children.

REFERENCES

1. Cookson W, Moffatt M, Rapeport G, Quint J. A pandemic lesson for global lung diseases: exacerbations are preventable. Am J Respir Crit Care Med 2022;205:1271-80.
2. Redlberger-Fritz M, Kundi M, Aberle SW, Puchhammer-Stockl E. Significant impact of nationwide SARS-CoV-2 lockdown measures on the circulation of other respiratory virus infections in Austria. J Clin Virol 2021;137:104795.
3. Kuitunen I, Artama M, Makela L, Backman K, Heiskanen-Kosma T, Renko M. Effect of social distancing due to the COVID-19 pandemic on the incidence of viral respiratory tract infections in children in Finland during early 2020. Pediatr Infect Dis J 2020;39:e423-7.
4. Olsen SJ, Winn AK, Budd AP, Prill MM, Steel J, Midgley CM, et al. Changes in influenza and other respiratory virus activity during the COVID-19 pandemic – United States, 2020-2021. MMWR Morb Mortal Wkly Rep 2021;70:1013-9.
5. Ferraro VA, Zamanaro A, Spaggiari S, Di Riso D, Zanconato S, Carraro S. Pediatric asthma control during the COVID-19 pandemic. Immun Inflamm Dis 2021;9:561-8.
6. Kouis P, Michaelidou E, Kinni P, Michanikou A, Anagnostopoulou P, Dimitriou H, et al. Pediatric asthma symptom control during lockdown for the COVID-19 pandemic in spring 2020: a prospective community-based study in Cyprus and Greece. Pediatr Pulmonol 2022;57:386-94.
7. Shah SA, Quint JK, Nwaru BI, Sheikh A. Impact of COVID-19 national lockdown on asthma exacerbations: interrupted time-series analysis of English primary care data. Thorax 2021;76:860-6.
8. Ullmann N, Allegorico A, Bush A, Porcaro F, Negro V, Onofri A, et al. Effects of the COVID-19 pandemic and lockdown on symptom control in preschool children with recurrent wheezing. Pediatr Pulmonol 2021;56:1946-50.
9. Hazan G, Fox C, Eiden E, Anderson N, Friger M, Haspel J. Effect of the COVID-19 lockdown on asthma biological rhythms. J Biol Rhythms 2022;37:152-63.
10. Simonneau T, Greco KF, Hammond A, Nelson K, Gaffin JM. Impact of the COVID-19 pandemic on pediatric emergency department use for asthma. Ann Am Thorac Soc 2021;18:717-9.
11. Taueichel K, Divadkar AR, Sayed S, Dudley JW, Grundmeier RW, Kenyon CC, et al. Pediatric asthma health care utilization, viral testing, and air pollution changes during the COVID-19 pandemic. J Allergy Clin Immunol Pract 2020;8:3378-87.e11.
12. Maison N, Peck A, Bli S, Meyer-Buehn M, von Mutius E, Hubner J, et al. The rising of old foes: impact of lockdown periods on “non-SARS-CoV-2” viral respiratory and gastrointestinal infections. Infection 2022;50:519-24.
13. Impact of opening and closing decisions by state: a look at how social distancing measures may have influenced trends in COVID-19 cases and deaths, Missouri. Available at: https://coronavirus.jhu.edu/data/state-timeline/new-confirmed-cases/missouri/90. Accessed May 11, 2022.
14. Olsen SJ, Winn AK, Budd AP, Prill MM, Steel J, Midgley CM, et al. Changes in influenza and other respiratory virus activity during the COVID-19 pandemic - United States, 2020-2021. MMWR Morb Mortal Wkly Rep 2021;70:1013-9.
15. St. Louis, Missouri, Government. COVID-19 emergency orders. Available at: https://www.stlouis-mo.gov/government/departments/health/communicable-disease/covid-19/orders/index.cfm. Accessed January 30, 2022.
16. Cohen HA, Blau H, Hoshen M, Batat E, Balicer RD. Seasonality of asthma: a retrospective population study. Pediatrics 2014;133:e923-32.
17. Donaldson GC, Wedzicha JA. The causes and consequences of seasonal variation in COPD exacerbations. Int J Chron Obstruct Pulmon Dis 2014;9:1101-10.
18. Hazan G, Eubanks A, Gierasch C, Atkinson J, Fox C, Hernandez-Leyva A, et al. Age-dependent reduction in asthmatic pathology through reprogramming of post-viral inflammatory responses. J Immunol 2022;208:1467-82.
19. Gastaldi A, Donà D, Barbieri E, Giaquinto C, Bont LJ, Baraldi E. COVID-19 lesson for respiratory syncytial virus (RSV): hygiene works. Children (Basel) 2021;8:1144.
20. Sanz-Munoz I, Tamames-Gomez S, Castrodeza-Sanz J, Eiros-Bouza JM, de Lejarazu-Leonardo RO. Social distancing, lockdown and the wide use of mask; a magic solution or a double-edged sword for respiratory viruses epidemiology? Vaccines (Basel) 2021;9:595.
21. Gern JE, Busse WW. Association of rhinovirus infections with asthma. Clin Microbiol Rev 1999;12:9-18.
22. Jartti T, Bönnyäkke K, Elenius V, Feleszko W. Role of viruses in asthma. Semin Immunopathol 2020;42:61-74.