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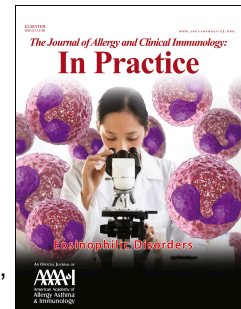
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**COVID-19 Pandemic-Related Reductions in Pediatric Asthma Exacerbations
Corresponded with an Overall Decrease in Respiratory Viral Infections**

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ABSTRACT

Background: Respiratory viruses, air pollutants, and aeroallergens are all implicated in worsening pediatric asthma symptoms, but their relative contributions to asthma exacerbations are poorly understood. A significant decrease in asthma exacerbations has been observed during the COVID-19 pandemic, providing a unique opportunity to study how major asthma triggers correlate with asthma activity.

Objective: To determine whether changes in respiratory viruses, air pollutants, and/or aeroallergens during the COVID-19 pandemic were concomitant with decreased asthma exacerbations.

Methods: Health care utilization and respiratory viral testing data between January 1st, 2015 and December 31st, 2020 were extracted from the Children's Hospital of Philadelphia (CHOP) Care Network's electronic health record. Air pollution and allergen data were extracted from U.S. Environmental Protection Agency public databases and a National Allergy Bureau-certified station, respectively. Pandemic data (2020) were compared to historical data.

Results: Recovery of in-person asthma encounters during phased re-opening (June 6th – November 15th, 2020) was uneven: primary care well and specialty encounters reached 94% and 74% of pre-pandemic levels, respectively, while primary care sick and hospital encounters reached 21% and 40% of pre-pandemic levels, respectively. During the pandemic, influenza A and influenza B decreased to negligible frequency when compared to pre-pandemic cases, while RSV and rhinovirus infections decreased to low (though

115 non-negligible) pre-pandemic levels, as well. No changes in air pollution or aeroallergen
116 levels relative to historical observations were noted.

117 **Conclusions:** Our results suggest that viral respiratory infections are a primary driver of
118 pediatric asthma exacerbations. These findings have broad relevance to both clinical
119 practice and the development of health policies aimed at reducing asthma morbidity.

Highlights Box

What is already known about this topic? While respiratory viruses, air pollutants, and aeroallergens are implicated in worsening pediatric asthma symptoms, the interplay between them and asthma exacerbations is not well understood. Asthma exacerbations decreased significantly during the COVID-19 pandemic allowing for the investigation of these major asthma triggers to asthma activity.

What does this article add to our knowledge? The sustained reductions in viral infections and acute asthma activity we observed during the COVID-19 pandemic supports a strong link between respiratory virus infections and pediatric asthma exacerbations.

How does this study impact currently management guidelines? Our findings suggest that viral respiratory infections are a primary driver of pediatric asthma exacerbations and that preventative measures taken to control exposure to these viruses may help limit exacerbating asthma symptoms

Key words: Asthma; COVID-19; Respiratory virus; Telemedicine; Aeroallergen, Pollution

142 ABBREVIATIONS

143	AC:	Acetylcholinesterase inhibitor
144	CHOP:	Children's Hospital of Philadelphia
145	COVID-19:	Coronavirus disease 2019
146	ED:	Emergency Department
147	EHR:	Electronic Health Record
148	ICD:	International Classification of Diseases
149	ICS:	Inhaled corticosteroid
150	IFV-A:	Influenza A
151	IFV-B:	Influenza B
152	LTM:	Leukotriene modifier
153	LABA:	Long-acting beta-agonist
154	Mg:	Magnesium
155	RSV:	Respiratory Syncytial Virus
156	SABA:	Short-acting beta-agonist
157	SS:	Systemic Steroid

INTRODUCTION

Symptoms of asthma, a common pediatric respiratory disease¹, worsen with exposure to respiratory viruses, air pollution, and aeroallergens². In addition, asthma patients have more frequent, severe, and longer-lasting symptoms with respiratory viral infections than people without asthma^{3, 4}. Exposure to air pollutants, including particulate pollution (PM_{2.5}, PM₁₀), ozone, and nitrogen dioxide (NO₂), has been associated with increased risk of asthma development, exacerbations, and hospitalizations⁵⁻⁹. In children with atopic asthma, aeroallergens are also a cause of asthma exacerbations^{10, 11}.

Public health interventions to mitigate the spread of SARS-CoV-2, the causative virus of Coronavirus Disease 2019 (COVID-19), included social distancing, mask-wearing, and quarantining of sick or exposed individuals¹²⁻¹⁵. While it was initially suspected that asthma might be a COVID-19 risk factor — a concern that may have increased preventive health behaviors among those with asthma,^{16,17} subsequent studies showed that people with asthma who contract SARS-CoV-2 were at lower risk for adverse outcomes^{18,19}. The institution and modulation of COVID-19-related public health measures offer a unique opportunity to study their effects on health outcomes beyond those directly infected, including asthma^{20,21}. Asthma symptoms and exacerbations decreased during the early stages of the COVID-19 pandemic^{22 – 25}, along with factors that impact asthma, such as respiratory viral infections^{23, 26-29}. In a prior publication, we found that during the first two months following public health interventions in Philadelphia, in-person asthma visits and steroid prescriptions decreased by more than 80%, with a concomitant decrease in rhinovirus infections and no change in air pollution compared with historical data for the years 2015-2019²³. Given that public health measures changed

181 throughout 2020 and health systems resumed more in-person services, we sought to
182 determine whether the decreased patterns of asthma activity we initially observed were
183 maintained throughout 2020, and whether levels of respiratory viral infections, air
184 pollution, and aeroallergens mirrored asthma activity.

METHODS

Study Population and Timeline

Patient-level demographic characteristics of our study population are shown in **Table E1**. We extracted asthma patient data corresponding to January 1st - December 31st encounters for the years 2015-2020 from the CHOP Care Network, which consists of 48 outpatient primary and specialty care clinical sites, 4 urgent care sites, 15 community hospital alliances, and a 557-bed quaternary care center in the greater Delaware River Valley area; the network has maintained the same number and type of providers during this time period. Asthma diagnosis was established based on encounters having International Classification of Diseases (ICD), 10th Revision code J45.nn. Public health measures during the COVID-19 pandemic in Philadelphia and surrounding counties were divided into phases. The *pre-lockdown* phase occurred from January 1st to March 17th, 2020. The first *lockdown* occurred March 18th to June 5th, 2020, while the *phased re-opening* consisted of an initial re-opening between June 6th and June 26th, 2020, and a further re-opening between June 27th and November 15th, 2020. The second lockdown was instituted on November 16th and lasted through January 4th, 2021. A more thorough description of these timeframes may be found in the **Online Repository Text**.

Variable Selection

For each encounter, its type (i.e., primary-well, primary-sick, specialty [Allergy and Pulmonary], ED, inpatient, and ICU) and date were extracted, along with the patient's gender, race, ethnicity, date of birth, and payor type. Race was based on self- or parent/guardian-selection of one of the following categories: "White", "Black", "Asian or

Pacific Islander”, or “Other”. Subjects without a race selection were coded as “Unknown.” Asthma-related drug prescription data for all outpatient asthma-related encounters (both primary and secondary diagnosis) and inpatient asthma-related encounters (primary diagnosis only) were obtained from CHOP prescription records (**Table E2**). *Outpatient* encounters included primary-well, primary-sick, and specialty care outpatient visits, while *hospital* encounters included those in the ED, ICU, or inpatient stays. Inhaled corticosteroid (ICS), leukotriene modifier (LTM), and ICS/Long-acting β_2 -agonist (ICS+LABA) drugs were considered asthma *maintenance medications*, while short-acting beta-agonist (SABA), systemic steroid, acetylcholinesterase inhibitor (AC), and ED/inpatient magnesium (Mg) were considered *acute management medications*.

Viral Infection Data

Results for respiratory viral testing from CHOP emergency department (ED) and satellite sites for adenovirus, influenza A (IFV-A), influenza B (IFV-B), metapneumovirus, non-COVID-19 coronavirus, respiratory syncytial virus (RSV), rhinovirus, parainfluenza 1, parainfluenza 2, parainfluenza 3, and COVID-19 were extracted from CHOP’s Respiratory Virus Prevalence database (**Table E3**). Four viruses most relevant to asthma exacerbations (IFV-A, IFV-B, RSV, and rhinovirus^{23,30}), as well as COVID-19, were selected for further analysis. Data for the total weekly number of positive tests during 2020 and, separately, for 2015-2019 were obtained. Data for January 1st to March 31st, 2021 was also obtained.

Air Pollution Data

Hourly PM_{2.5}, PM₁₀, ozone, and NO₂ measures obtained at EPA monitoring sites in Philadelphia for the time period January 1st to December 31st, 2020 were extracted from AirNow (an air quality data management system that reports real-time and forecast air quality estimates)³¹. Historical data from 2015-2019 for these pollutants was downloaded from Air Data (an EPA resource that provides quality-assured summary air pollution measures collected from outdoor regulatory monitors across the United States³²). AirNow did not provide historical data for pollutants considered, and Air Data did not contain 2020 data, as its data is released months after the data is reported in AirNow. For regulatory monitors included in our study, AirNow and AirData measures were obtained at the same monitoring sites.

Aeroallergen Data

Aeroallergen concentrations for trees, weed, mold and grass pollen were measured per Burkard device guidelines at The Asthma Center, National Allergy Bureau (NAB)-certified station in Mt. Laurel, NJ, during the period March 17th to October 29th, 2020³³. Station measures were reported as categorical variables based on historical concentrations: trees, weed and grass pollen levels were categorized as *not present*, *low concentration*, *moderate concentration*, *high concentration*, and *very high concentration* for weekly average estimate ranges 0, 1-9, 10-29, 30-59, and 60+ particles/m³ of air, respectively; weed pollen was binned into the same levels according to weekly average ranges 0, 50-599, 600-999, 1000-2499, 2500+ particles/m³ of air. Historical data for 2015-2019 from this site were not available, but the ranges used are based on historical levels observed by the same NAB station that collected the 2020 data.

Data Analysis

Summary statistics for rates of health care encounters and asthma-related medication prescriptions from 2020 were compared to those from 2015-2019. Comparisons were made between the pre-lockdown to the first lockdown period by comparing the average weekly encounter or medication prescription activity during the 8 weeks before and after the week of Mar 18th, 2020. Comparisons were made between the phased-reopening time period and prior years by determining the 'peak' weekly encounter or medication prescription activity, as defined as the highest 8-week moving average, between week 26 and 45 of 2020 or 2015-2019. Viral Testing analysis was performed via two comparisons whereby summary statistics for historical data from 2015-2019 were compared to 1) 2020 data, and 2) September 2020 to March 2021 data to cover the full influenza and RSV seasons expected for 2020-21, which often span November to March. Weekly averages of PM_{2.5}, PM₁₀, ozone, and NO₂ measures were calculated for the year 2020 and across years 2015-2019. Standard deviation was calculated for historical data. Aeroallergen data was visualized according to categorical level for each week of 2020.

Data Availability

The dataset supporting the conclusions of this article will be available in a Zenodo repository after publication.

Ethical and Regulatory Oversight

276 The CHOP Institutional Review Board reviewed our study and determined it did not meet
277 the definition of Human Subjects research.

RESULTS

Prior to enacting COVID-19-related public health measures on March 18th, 2020 in Philadelphia, pediatric asthma healthcare visit numbers and encounter types at CHOP were similar to 2015-2019 historical averages. Comparison of asthma encounters during the pre-lockdown to the first lockdown period showed that the average number of weekly outpatient encounters decreased to 12% of pre-pandemic levels (1069 encounters/week versus 130 encounters/week), with primary-well decreasing to 10% (351 vs 36 encounters/week), specialty decreasing to 12% (455 vs 53 encounters/week), and primary-sick decreasing to 16% (263 vs 41 encounters/week) (**Figure 1A**). During this time period, the average number of weekly hospital encounters decreased to 20% of pre-pandemic levels (186 vs 37 encounters/week; **Figure 1B**). In the case of both outpatient and hospital encounters, weekly rates of historical data were at similar levels before and after the week of March 18th.

During the phased re-opening June 6th to November 15th, there was a gradual return of non-acute asthma-related outpatient encounters to historical and pre-pandemic levels. Specifically, primary-well and specialty outpatient encounters rose to 94% (456 vs 486 encounters/week) and 74% of historical levels (317 vs 429 encounters/week), respectively (**Figure 1A**). In contrast, primary-sick encounters increased to 21% of historical levels (66 vs 319 encounters/week; **Figure 1A**), and hospital encounters increased to 40% of historical levels (75 vs 188 encounters/week; **Figure 1B**).

Prior to enacting COVID-19-related public health measures, pediatric asthma prescription patterns at CHOP were similar to 2015-2019 historical averages. Comparison of CHOP prescription patterns during the pre-lockdown to the first lockdown period found

that prescriptions for each asthma maintenance (**Figure 2A**) and acute management (**Figure 2B**) medication decreased relative to their pre-pandemic levels: ICS to 59% (436 vs 258 prescriptions/week), ICS+LABA to 70% (98 vs 68 prescriptions/week), LTM to 63% (122 vs 77 prescriptions/week), SABA to 46% (1146 vs 530 prescriptions/week), systemic steroids to 36% (580 vs 211 prescriptions/week), AC to 20% (129 vs 26 prescriptions/week), and ED/inpatient Mg to 38% (36 vs 14 prescriptions/week). For each of these drug classes, their levels remained similar from January to June according to historical data. We did not observe an asthma medication shortage in Philadelphia during the early stages of the pandemic.

When examining the phased re-opening period, prescription patterns for all medications showed a recovery towards historical and pre-pandemic levels, but all remained lower through December 2020 (**Figure 2**). Specifically, SABA prescriptions were 61% of historical levels (761 vs 1240 prescriptions/week), systemic steroid prescriptions were 58% of historical levels (338 vs 576 prescriptions/week), AC prescriptions were 34% of historical levels (53 vs 153 prescriptions/week), and ED/inpatient Mg prescriptions were 66% of historical levels (23 vs 35 prescriptions/week). In comparison, ICS prescriptions were 56% of historical levels (308 vs 551 prescriptions/week), LTM prescriptions were 65% of historical levels (97 vs 149 prescriptions/week), and ICS+LABA prescriptions were 84% of historical levels (85 vs 101 prescriptions/week).

Testing for all viruses continued during 2020 though the number of non-COVID-19 tests performed decreased when compared to historical testing figures. During the pre-lockdown phase, an increase in the number of positive IFV-A and IFV-B tests was

observed as compared with historical averages²³. Additionally, both the number of positive RSV and positive rhinovirus tests decreased during this time period when compared to historical averages. Just as the first lockdown was instituted, the number of positive results for rhinovirus increased. However, this increase (as a percentage of total rhinovirus tests) was similar to the historical average (**Table E3**). The weekly total positive tests for IFV-A, IFV-B, RSV, and rhinovirus during the first lockdown, phased re-opening, and second lockdown were significantly lower than 2015-2019 historical averages even as the number of positive COVID-19 tests increased (**Figure 3**). When investigating seasonal trends, and focusing on months of peak viral transmission, the respiratory viral data from September 2020 to March 2021 showed that positive tests for IFV-A, IFV-B, and RSV were at or near zero when compared to their historical averages. Positive rhinovirus tests, while non-zero, also remained significantly lower than antecedent averages (**Figure 4**).

Air pollution and aeroallergen trends did not substantially change during the pandemic compared to historical or expected seasonal data^{11, 28}, respectively (**Figure 5**). While seasonal variability of daily average PM_{2.5}, PM₁₀, NO₂ and ozone was observed, the variability was similar to historical trends across the years 2015-2019. Aeroallergen concentrations during most weeks of 2020 were *not present* or *low concentration*, with *high concentration* of weed pollen in September; *very high concentration* of tree pollen in March-May; *high concentration* to *very high concentration* of mold pollen in mid-March-October; and *moderate concentration* of grass pollen in May-June.

DISCUSSION

In addition to the devastating morbidity and mortality arising directly from COVID-19^{29-30, 34-36}, there have been indirect negative effects on various health outcomes^{20-21, 26, 28}. In the case of asthma, however, COVID-19-related public health measures during the initial months of the pandemic reduced disease burden^{23-25, 27, 37-38}. As a continuation of our previous initial observations²³, the in-depth analyses of the effects of COVID-19-related public health measures on asthma activity over a longer period of time provide a unique opportunity to study the environmental triggers of asthma exacerbations. Our current results show that while the relaxation of COVID-19-related public health measures resulted in a recovery of non-acute asthma care to near pre-pandemic levels, there was a persistence of historically low acute asthma care that corresponded with low respiratory virus positivity until the end of 2020. The current study allows for the analysis of viral trends following deviations from public health interventions during the course of the study, as well as a closer look at the seasonality of the viruses when compared to historical averages due to the increased duration of the observation period. Allergen data during this span has also been included in the current analysis. Additionally, analysis of well vs sick outpatient encounters was performed, as was a more detailed analysis of asthma medication prescriptions during this timeframe.

The COVID-19 pandemic has resulted in a substantial decrease in respiratory viral infections^{23,26,29,38}, including influenza^{23,28,39-40}. Consistent with these reports, our results show that the number of positive virus tests decreased and remained lower than the historical average. Specifically, in the ED and satellite care centers between September 2020 to March 2021, when peaks in the number of IFV-A, IFV-B and RSV infections were

observed in prior years, no positive IFV-A, IFV-B, or RSV infections were identified. In addition, the number of positive cases of rhinovirus, a key virus linked to asthma exacerbations^{41,42}, remained lower than historical averages. These trends may not be solely due to behavioral responses or public health interventions, in that after the major U.S. 2020 fall and winter holidays that were accompanied by ill-advised gatherings (e.g., Thanksgiving, Christmas and New Year's Eve), the number of respiratory viruses, other than SARS-CoV-2, remained very low even as COVID-19 rates increased. Given the known role of respiratory viral infections as a trigger of asthma exacerbations, it is likely that the sustained decrease in respiratory virus levels strongly contributed to the decrease in asthma encounters in 2020.

Exposure to air pollution and aeroallergens contribute to asthma exacerbations⁵⁻¹¹. Consistent with our prior publication that studied the early phases of the pandemic²³, we did not observe changes to levels of air pollutants that diverged from historical trends, i.e. seasonal variability in PM_{2.5}, PM₁₀, ozone that peaked during summer 2020, and NO₂ that peaked during winter 2020, were consistent with 2015-2019 trends^{43, 44}. Similarly, seasonal peaks were observed among aeroallergens from April to June and early September, according to pollen type^{11,45}, but these changes were consistent with historical trends. Previously, we explicitly confirmed that the seasonal decrease in levels of four air pollutants in the two month period following Philadelphia's first lockdown period was not statistically significant when compared to historical trends via interrupted time series analysis²³. Here, having expanded the time period of observation, there were even fewer differences between pollution levels across 2020 compared with historical patterns, suggesting that the implementation and relaxation of COVID-19-related public health

measures had little effect on levels of PM_{2.5}, PM₁₀, ozone and NO₂ in Philadelphia as measured with regulatory monitors. Similarly, COVID-19-related measures did not influence aeroallergen levels, as illustrated by our results for weed, tree, mold and grass pollens which followed expected seasonal trends. We note however, that our data has limitations. First, the EPA data used comprised monitoring sites that sparsely cover of the greater Philadelphia region and do not account for all pollutants that may have changed as a result of public health measures. Second, our aeroallergen data was sourced from a single monitoring site and did not have detailed historical measures available (only ranges). Third, public health interventions may have altered the outdoor pollution and aeroallergen exposure profiles of children due to increased usage of masks, decreased outdoor activity and commuting, and school closures^{46,47}. Given the complex behavioral, environmental and biological issues relevant to fully understanding the effects of public health interventions on asthma studies, capturing individual-level data is necessary to more fully quantify changes in children's exposure profiles, as well as to distinguish the impact of these changes on atopic versus non-atopic children with asthma⁴⁸.

The recovery of non-acute asthma care during the reopening phases suggests that people were willing and able to access healthcare during this time. Thus, reduced access was not a major driver of the persistently low acute outpatient and inpatient asthma encounters. The persistently decreased prescription levels of maintenance and acute management medications during phases in which routine asthma care encounters were recovering further supports that a decrease in asthma exacerbations and symptoms occurred. However, it is possible that fear of coming to the pediatrician's office or hospital, out of concern for increased SARS-CoV-2 infection risk, drove some of the effect on acute

asthma care that we observed. There are additional limitations to our study. Our results showing a substantial decrease in the number of asthma exacerbations along with extremely low levels of respiratory viral infections reflect a single pediatric healthcare network and may not generalize to other populations. Using an ICD-10 classification of asthma may potentially miss asthma admissions that were coded primarily as COVID-19-related. Nevertheless, the observed trends of a decrease in weekly positive respiratory virus tests during the first lockdown, phased re-opening and second lockdown, together with the decrease in acute asthma episodes during the same timeframe, suggests that limiting routes through which respiratory viruses are communicable likely substantially decreased asthma exacerbations.

While the restrictive COVID-19 public health interventions would not be feasible or acceptable long-term given their detrimental consequences on other aspects of health⁴⁹⁻⁵¹, the insights gained during this period may foster greater awareness for the importance of practicing effective strategies to reduce exacerbations. Continued education of patients with asthma and their parents to encourage handwashing, provide anticipatory guidance about travel, adhere to asthma action plans as children return to school⁵², consider voluntary masking during respiratory viral seasons in certain settings (e.g., large indoor gatherings or while traveling), and follow other CDC guidelines to reduce viral transmission^{53,54}, could effectively curb asthma exacerbations. As the COVID-19 pandemic subsides and related public health measures are reduced, continued studies of the relationship between viral infection rates and asthma are needed to identify the most effective and acceptable long-term strategies that will maintain reduced asthma exacerbations.

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Figure Legends

Figure 1. Outpatient and hospital asthma encounters during 2020. **(A)** Weekly averages for outpatient asthma encounters from January 1st - December 31st, 2020. Primary care well visits (Well), Primary care acute care visits (Sick), and specialty care visits (Specialty; Allergy and Pulmonary) are shown. **(B)** Weekly averages for hospital asthma encounters from January 1st to December 31st, 2020. Emergency department (ED), inpatient admissions (Inpatient), and pediatric intensive care unit admissions (ICU) are shown. Five-year historical averages (January 1st to December 31st, 2015-2019) with one standard deviation from the mean are shown. Phases of Philadelphia COVID-19-related public health measures are shown.

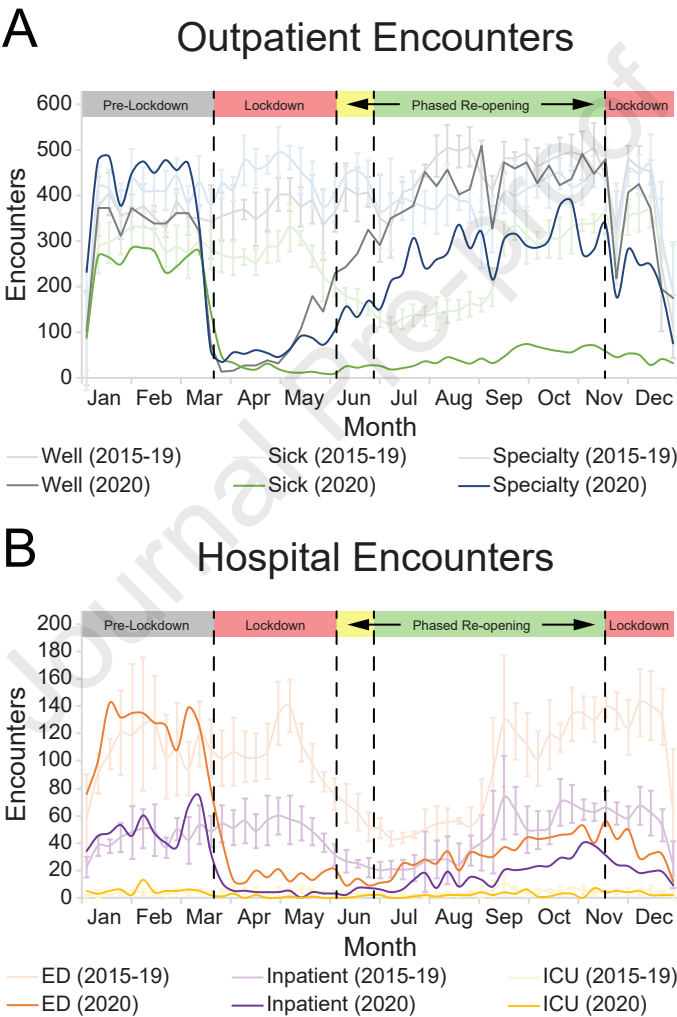
Figure 2. Asthma prescriptions during 2020. **(A)** Weekly averages for asthma maintenance medication prescriptions from January 1st - December 31st, 2020. Inhaled corticosteroid (ICS), leukotriene modulator (LTM), and ICS + long acting beta agonist (ICS+LABA) prescriptions are shown. **(B)** Weekly averages for asthma acute management medication prescriptions from January 1st - December 31st, 2020. Short-acting beta-agonist (SABA), systemic steroid (SS), anticholinergic (AC), and magnesium (Mg) prescriptions are shown. Five-year historical averages (January 1st - December 31st, 2015-2019) with one standard deviation from the mean are shown. Phases of Philadelphia COVID-19-related public health measures are shown.

Figure 3. Viral respiratory testing data using deidentified institutional ED and satellite sites virology testing results for the period of 2015-2020. Time series plots comparing

historical average data (dark grey lines) and $\pm$ 1SD (light grey shaded areas) from 2015-2019 to 2020 data (dark blue lines) for total number of weekly positive influenza A, influenza B, RSV, rhinovirus, and COVID-19 tests respectively. Phases of Philadelphia COVID-19-related public health measures are shown.

Figure 4. Viral respiratory testing data comparing September 2020 to March 2021 to historical data (2015- 2019). Total number of weekly positive influenza A, influenza B, RSV, rhinovirus and COVID-19 testing data (dark blue lines with blue markers) from the ED and satellite sites are compared to the 2015-2019 historical average (dark grey lines) $\pm$ SD (light grey shaded areas) during the same period. Weeks during which tests were not performed are without markers.

Figure 5. Levels of air pollutants and aeroallergens in Philadelphia during the COVID-19 pandemic. **(A)** Trendlines of weekly averages of daily NO₂, ozone, PM₁₀ and PM_{2.5} measures from 2020 and 2015-2019 sourced from AirNow and AirData, respectively, for the period January 1st to December 31st in Philadelphia. ppb = parts per billion; $\mu\text{g}/\text{m}^3$ = micrograms per cubic meter. **(B)** Heatmap of weekly aeroallergens concentrations for tree, weed, mold and grass pollen measured by a National Allergy Bureau (NAB)-certified station near Philadelphia during the period March 17th to October 29th, 2020. Phases of Philadelphia COVID-19-related public health measures are shown.



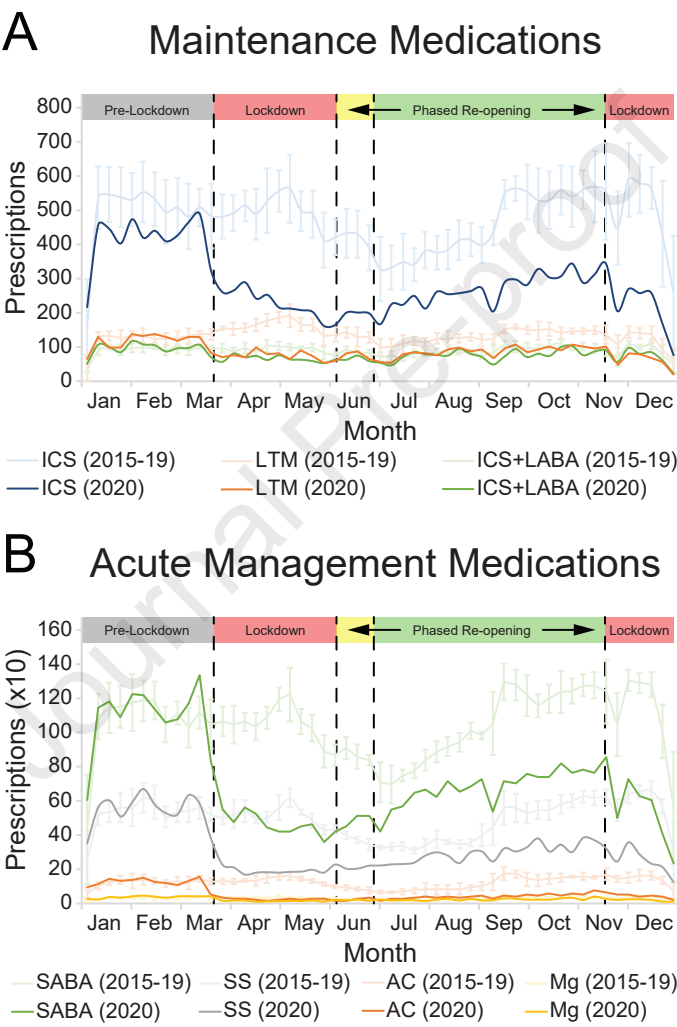


Figure 3

Weekly Total Positive Tests

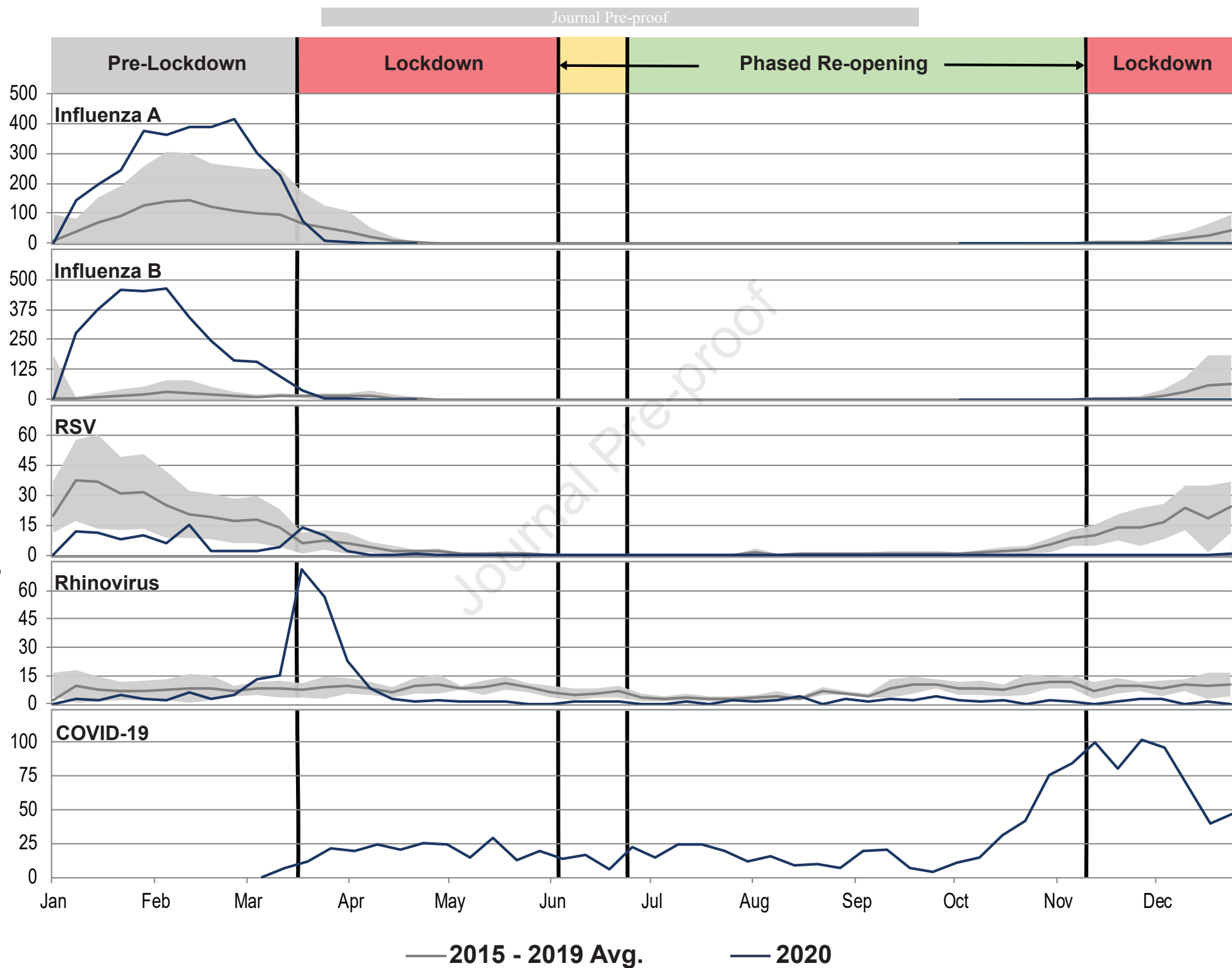


Figure 4

Weekly Total Positive Tests

Journal Pre-proof

2020

2021

Influenza A

Influenza B

RSV

Rhinovirus

COVID-19

Sep

Oct

Nov

Dec

Jan

Feb

Mar

— 2015 - 2019 Avg. —•— Sep. 2020 - Mar. 2021

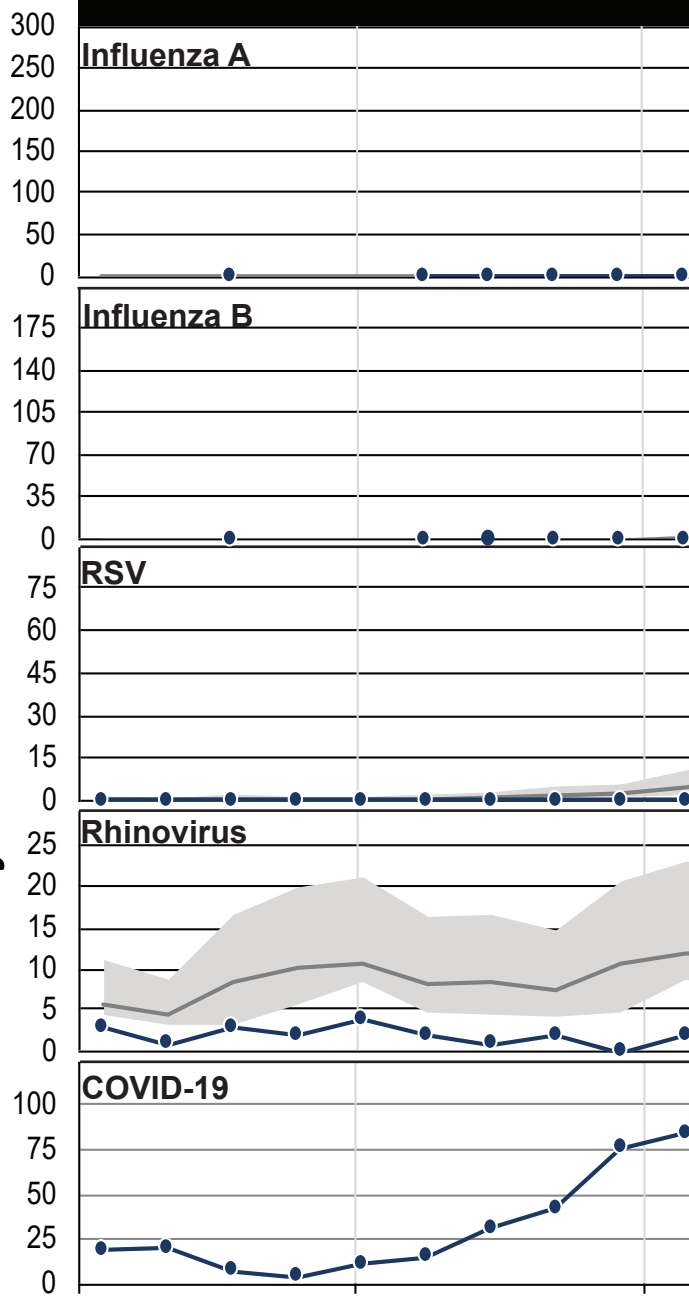


Figure 5

