Family Medicine and Community Health

Time trend and seasonality in medically attended respiratory syncytial virus (RSV) infections in US children aged 0–5 years, January 2010–January 2023

Lindsey Wang,[1] Nathan Berger,[1] Pamela B Davis,[2] David C Kaelber,[3] Nora Volkow,[4] Rong Xu [5]

To cite: Wang L, Berger N, Davis PB, *et al*. Time trend and seasonality in medically attended respiratory syncytial virus (RSV) infections in US children aged 0–5 years, January 2010–January 2023. *Fam Med Com Health* 2023;**11**:e002453. doi:10.1136/fmch-2023-002453

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/fmch-2023-002453).

[1]Center for Science, Health, and Society, Case Western Reserve University, Cleveland, Ohio, USA
[2]Center for Community Health Integration, Case Western Reserve University School of Medicine, Cleveland, Ohio, USA
[3]The Center for Clinical Informatics Research and Education and the Departments ofInternal Medicine, Pediatrics, and Population and Quantitative Health Sciences, MetroHealth Medical Center, Cleveland, Ohio, USA
[4]National Institute on Drug Abuse, National Institute of Health, Bethesda, Maryland, USA
[5]Center for Artificial Intelligence in Drug Discovery, Case Western Reserve University School of Medicine, Cleveland, Ohio, USA

Correspondence to
Dr Rong Xu; rxx@case.edu

ABSTRACT

Objective The long-term time trend and seasonality variations of first-time medically attended respiratory syncytial virus (RSV) infections among young children are unknown. We aim to examine the time trend of medically attended first-time RSV infections among young children in the USA from January 2010 through January 2023.

Design This is a population-based cohort study using electronic health records (EHRs). Monthly incidence rate of medically attended first-time RSV infection (cases per 10 000 000 person-days). A time-series regression model was used to model and predict time trends and seasonality.

Setting Multicenter and nationwide TriNetX Network in the USA.

Participants The study population comprised children aged 0–5 years who had medical visits during the period of January 2010 to January 2023.

Results The data included 29 013 937 medical visits for children aged 0–5 years (46.5% girls and 53.5% boys) from January 2010 through January 2023. From 2010 through 2019, the monthly incidence rate of first-time medically attended RSV infection in children aged 0–5 years followed a consistent seasonal pattern. Seasonal patterns of medically attended RSV infections were significantly disrupted during the COVID-19 pandemic. In 2020, the seasonal variation disappeared with a peak incidence rate of 20 cases per 1 000 000 person-days, a decrease of 97.4% from the expected peak rate (rate ratio or RR: 0.026, 95% CI 0.017 to 0.040). In 2021, the seasonality returned but started 4 months earlier, lasted for 9 months, and peaked in August at a rate of 753 cases per 1 000 000 person-days, a decrease of 9.6% from the expected peak rate (RR: 0.90, 95% CI 0.82 to 0.99). In 2022, the seasonal pattern is similar to prepandemic years but reached a historically high rate of 2182 cases per 10 000 000 person-days in November, an increase of 143% from the expected peak rate (RR: 2.43, 95% CI 2.25 to 2.63). The time trend and seasonality of the EHR-based medically attended RSV infections are consistent with those of RSV-associated hospitalisations from the Centers for Disease Control and Prevention (CDC) survey-based surveillance system.

Conclusion The findings show the disrupted seasonality during the COVID-19 pandemic and a historically high surge of paediatric RSV cases that required medical attention in 2022. Our study demonstrates the potential of EHRs as a cost-effective alternative for real-time pathogen and syndromic surveillance of unexpected disease patterns including RSV infection.

KEY POINTS

⇒ **Question** What are the long-term trends and recent seasonality pattern changes in medically attended respiratory syncytial virus (RSV) infections in children aged 0–5 years in the USA?

⇒ **Findings** This population-based cohort study of 29 013 937 medical visits for children aged 0–5 years found that the monthly incidence rate of first-time medically attended RSV infections followed a consistent seasonal pattern during 2010–2019, the seasonal pattern was significantly disrupted during the COVID-19 pandemic. The seasonal variation disappeared in 2020, returned in 2021 but started earlier and reached a historical high rate of 2182 cases per 10 000 000 person-days in November 2022.

⇒ **Meaning** These data suggest that COVID-19 pandemic contributed to the disrupted seasonality and the 2022 surge of paediatric RSV cases that needed medical attention. This study demonstrates the potential of electronic health records as a cost-effective alternative for real-time surveillance of unexpected disease patterns including RSV infection.

INTRODUCTION

COVID-19 is an infectious disease caused by the respiratory SARS-CoV-2 virus. The COVID-19 pandemic caused significant morbidity and mortality in the USA and worldwide. The COVID-19 pandemic disrupted seasonal patterns of other respiratory virus infections, including respiratory syncytial virus (RSV), influenza virus, adenovirus, enterovirus, rhinovirus, human metapneumovirus, human parainfluenza virus and virus infection-associated diseases including acute respiratory illness, pneumonia, bronchiolitis, asthma and chronic obstructive pulmonary

disease.[1] These disruptions to the seasonal patterns of non-SARS-CoV-2 respiratory virus infections during the COVID-19 pandemic are attributable for multiple factors including the implementations of non-pharmaceutical interventions, change in human behaviours, viral interferences, immunity debt and waning population-level immunity.[1–4] COVID-19 infection may also play a role in the circulation patterns of other respiratory viral infections. COVID-19 has long-term adverse effects on children[5 6] and on multiple-organ systems including the immune and respiratory systems.[7–11] Individuals infected with COVID-19 can have long-lasting changes in both innate and lymphocyte-based immune functions,[7 8 12] which are engaged in defence against respiratory viruses.[13 14]

RSV is a common respiratory virus and a leading cause of lower respiratory tract infection in young children.[15] The COVID-19 pandemic disrupted RSV and other respiratory viral infection patterns in the USA for 2020–2021.[16] Unusually early and high rates of hospitalisations with RSV infections were reported in 2022, particularly among the youngest children.[17 18] Several studies from the USA and other countries reported disrupted seasonality of RSV infection during 2020–2021.[16 19–23] However, it remains unknown of the long-term time trend and seasonality of medically attended first-time RSV infections and RSV-associated diseases including bronchiolitis among young children. Leveraging a nation-wide, federated, real-time database of electronic health records (EHRs) of 61.4 million patients in the USA, including 1.7 million children 0–5 years of age, we performed time-series analyses to examine the time trend of medically attended RSV infections including both laboratory-confirmed RSV infections and RSV-associated diseases among young children in the USA from January 2010 through January 2023.

METHODS

Database description

We used the TriNetX platform to access aggregated and de-identified EHRs of 61.4 million patients including 1.7 million children 0–5 years of age from 34 healthcare organisations in the USA across 50 states, covering diverse geographic regions (31% in the Northeast, 13% in the Midwest, 42% in the South and 13% in the West), age, race/ethnic, income and insurance groups and clinical setting.[24] The data used in this study were collected during 22 February–5 March 2023 from the TriNetX 'Research USA No Date Shift' Network.

TriNetX, LLC is compliant with the Health Insurance Portability and Accountability Act (HIPAA). Any data displayed on the TriNetX Platform in aggregate form, or any patient-level data provided in a data set generated by the TriNetX Platform only contains deidentified data as per the deidentification standard defined in Section §164.514(a) of the HIPAA Privacy Rule. TriNetX built-in analytic functions (eg, incidence, prevalence, outcomes analysis, survival analysis, propensity score matching) allow for patient-level analyses, while only reporting population level data. The MetroHealth System, Cleveland OH, IRB determined research using TriNetX, in the way described here, is not Human Subject Research and therefore IRB exempt. We previously used the TriNetX platform to perform time-trend analyses and retrospective cohort studies in various populations[25–42] including young children.[25 33]

TriNetX is a platform that deidentifies and aggregates EHR data from contributing healthcare systems, most of which are large academic medical institutions with both inpatient and outpatient facilities at multiple locations, across 50 states in the USA. TriNetX Analytics provides web-based and secure access to patient EHR data from hospitals, primary care and specialty treatment providers, covering diverse geographic locations, age groups, racial and ethnic groups, income levels and insurance types including various commercial insurances, governmental insurance (Medicare and Medicaid), self-pay/uninsured, worker compensation insurance, military/VA insurance among others.

Self-reported sex (female, male), race and ethnicity data in TriNetX come from the underlying clinical EHR systems of the contributing healthcare systems. TriNetX maps race and ethnicity data from the contributing healthcare systems to the following categories: (1) race: Asian, American Indian or Alaskan Native, Black or African American, Native Hawaiian or Other, White, Unknown race and (2) ethnicity: Hispanic or Latino, Not Hispanic or Latino, Unknown Ethnicity.

TriNetX completes an intensive data preprocessing stage to minimise missing values. All covariates are either binary, categorical (which expands to a set of binary columns) or continuous but essentially guaranteed to exist. Age is guaranteed to exist. Missing sex values are represented using 'Unknown sex'. The missing data for race and ethnicity are presented as 'unknown race' or 'unknown ethnicity'. For other variables including medical conditions, procedures, lab tests and socioeconomic determinant health, the value is either present or absent so 'missing' is not pertinent.

Study population

The study population comprised children aged 0–5 years and children aged 0–1 year who had any medical visits within the TriNetx network healthcare organisations from 1 January 2010 through 31 January 2023. Age was determined as of the calendar month of the medical visit. The status of RSV infection was based on 12 lab test codes and three disease clinical diagnosis codes (details in online supplemental material).

Statistical analysis

Incidence rate analysis

We used the TriNetX built-in functions 'Incidence & Prevalence analytic' to calculate monthly incidence rate of first-time RSV infections in children aged 0–5 years

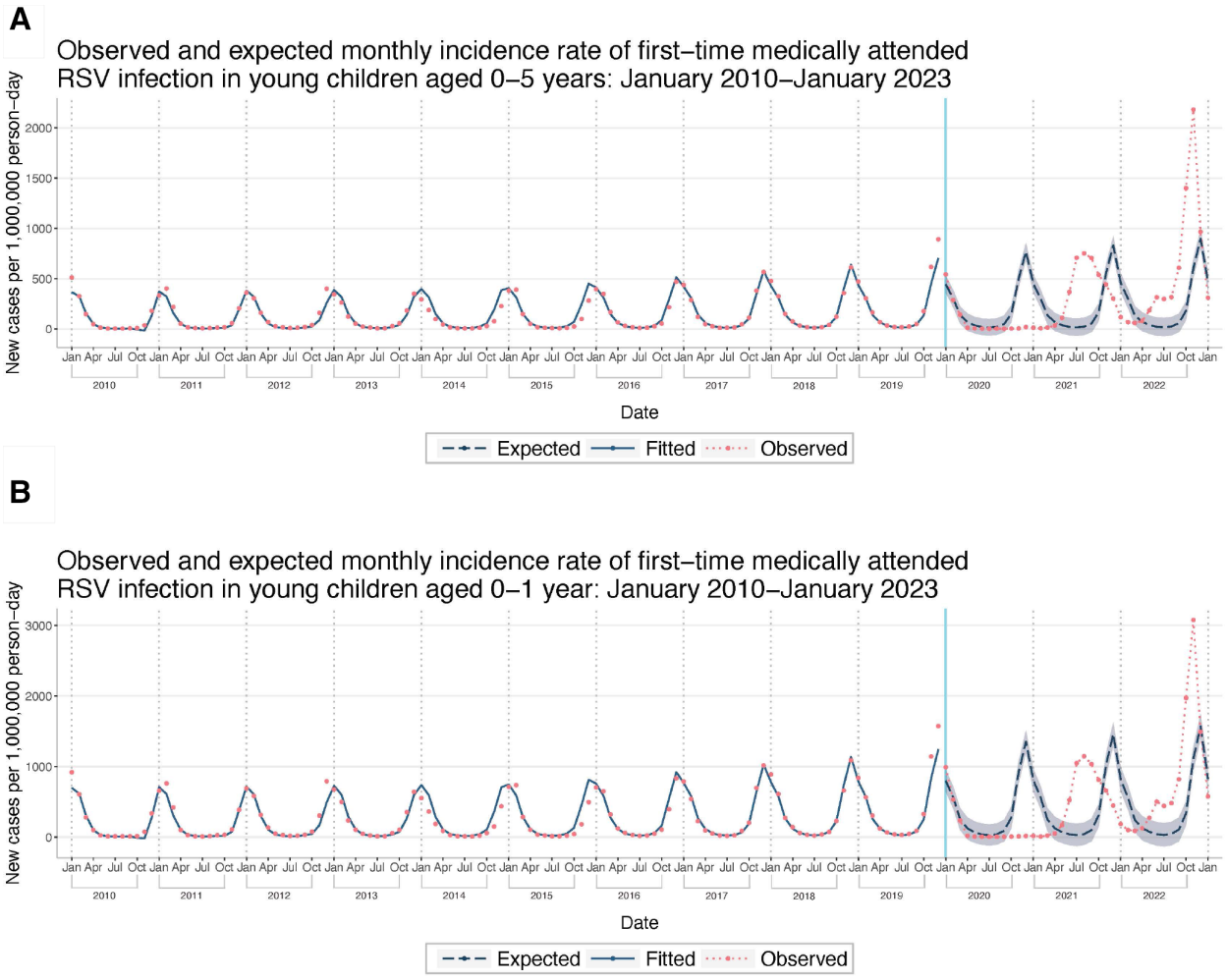

Figure 1 Observed and expected monthly incidence rate of first-time medically attended RSV infections from 1 January 2010 through 31 January 2023 among (A) children aged 0–5 years and (B) children aged 0–1 year. Monthly incidence rates were calculated as the number of incident cases per 1 000 000 person-days for each month. The blue vertical line marks the beginning of COVID-19 pandemic (January 2020). RSV, respiratory syncytial virus.

and children aged 0–1 year separately. For a given time window (each calendar month in our study), the incidence proportion denominator includes all and only those patients in the cohort under analysis (children ≤5 years of age as of that month when they had a medical visit), whose fact record overlaps the time window by at least 1 day, whose fact record does not contain the event of interest (RSV in this study) during the lookback period. For this study, the lookback time was any time to 1 day before the start of each month; therefore, we examined first-time medically attended RSV infections. The incidence proportion numerator includes all and only those patients who are in the denominator and whose record includes the event of interest on a date within the time window. For each month, the incidence rate denominator is the product of the number of patients in the incidence proportion denominator and the number of days covered by the time interval. The incidence rate numerator is equivalent to the incidence proportion numerator.

Time-series analysis

We used a linear time-series regression model with Fourier terms[43] to model the time trend and seasonality of the prepandemic (January 2010 through December 2019) RSV infections. Using the model, we predicted the monthly incident rate of RSV infection during the pandemic months (January 2020 through January 2023). The predicted monthly incidence rate was compared with the observed rate during the same period by calculating rate ratios and 95% CIs.

Comparison with the CDC reported weekly rates of RSV-associated hospitalisations

The Centers for Disease Control and Prevention (CDC) Respiratory Syncytial Virus Hospitalization Surveillance Network (RSV-NET) is a network that conducts population-based surveillance for laboratory-confirmed RSV-associated hospitalisations in 12 states based on voluntary reporting from state health departments.[22] Hospitalisation rates are calculated as the number of residents in a surveillance area who are hospitalised with

laboratory-confirmed RSV divided by the total population estimate for that area. RSV-NET surveillance began tracking RSV-associated hospitalisations in children in the 2018–2019 season. We downloaded the data from the RSV-NET Surveillance System for children aged 0–4 years of age.[44] We compared the seasonality and time trends of the EHR-based monthly incidence rates of medically attended first-time RSV infection in children aged 0–5 years of age with weekly rates of RSV-associated hospitalisation among children aged 0–4 years of age from October 2018 through January 2023.

Stratified analysis of seasonality

In this study, the medically encountered RSV infection was defined by 12 lab test codes and three disease clinical diagnostic codes for RSV-associated diseases (details in online supplemental material). The clinical diagnosis-based RSV infection included 'Respiratory syncytial virus pneumonia' (International Classification of Diseases, Tenth Revision (ICD-10) code J12.1), 'Acute bronchiolitis due to respiratory syncytial virus' (ICD-10 code J21.0) and 'Respiratory syncytial virus as the cause of diseases classified elsewhere' (ICD-10 code B97.4). We performed separate analysis for: clinical diagnosis-based RSV diseases (J12.1, J21.0, B97.4), positive lab test confirmed RSV infection (12 lab test codes) and RSV-associated bronchiolitis (J21.0). In addition, we also examined unspecified bronchiolitis (J21.9), which could be caused by other severe respiratory viruses such as influenza, to investigate whether the seasonality disruption was unique to RSV infection.

All statistical tests were conducted within the TriNetX Advanced Analytics Planform during 22 February 22–5 March 2023, at significance set at p value <0.05 (two-sided). Data and code (R statistical software V.4.2.2) for time-series analysis are available at https://github.com/liwang0904/RSV. R package V.4.4.4 was used for calculating rate ratios of incidence rates. All R packages are freely available.

Patient and public involvement

As the data were derived from patient records, there was no patient involvement.

RESULTS

Seasonal pattern of monthly incidence rate of medically attended RSV infection among young children in the USA during January 2010–January 2023

We examined EHR data from 29 013 937 medical visits for children aged 0–5 years (46.5% girls and 53.5% boys) and 13 169 955 medical visits from children aged 0–1 year (46.4% girls and 53.6% boys) from 1 January 2010 through 31 January 2023. From 2010 through 2019, the monthly incidence rate of medically attended RSV infection in children aged 0–5 years followed a consistent seasonal pattern: rising from September to November, peaking from December to January, then dropping from February to April, with sustained low rate during May to August (figure 1A).

During the COVID-19 pandemic, the seasonal pattern changed. In 2020, the seasonal variation disappeared, and the incidence rate was consistently low from April through December ranging from 13 to 20 cases per 1 000 000 person-days. Compared with an expected December peak incidence rate of 770 cases per 1 000 000 person-days from the prepandemic trend, the incidence rate of 20 cases per 1 000 000 person-days in December 2020 corresponded with a relative decrease of 97.4% (rate ratio or RR: 0.026, 95% CI 0.017 to 0.040) (figure 1A).

In 2021, the seasonality returned but started earlier than expected. The incidence rate peaked in August, 4 months earlier than the expected peak in December. In August, the incidence rate was 753 cases per 1 000 000 person-days, corresponding with a relative decrease of 9.6% from the expected peak incidence rate (RR: 0.90, 95% CI 0.82 to 0.99). The RSV season in 2021 extended to 9 months (May 2021–January 2022), longer than the expected 5 months in the winter (figure 1A).

In 2022 and January 2023, the seasonal pattern is similar to prepandemic years with a winter peak in November (2182 cases per 1 000 000 person-days), 1 month earlier and 143% higher than the expected December peak (897 cases per 1 000 000 person-days) (RR: 2.43, 95% CI 2.25 to 2.63). The incidence rate in May through November 2022 was significantly higher than expected, corresponding to a related increase of 365%–1576%. The incidence rate returned to the expected level in December (RR: 1.08, 95% CI 0.98 to 1.18). In January 2023, the incidence rate was 311 cases per 1 000 000 person-days, 33% lower than the expected rate (RR: 0.67, 95% CI 0.58 to 0.77) (figure 1A).

The incidence rate in children aged 0–1 year followed the same seasonal pattern as for children aged 0–5 years, but with higher rates. In 2022, the incidence rate peaked in November (3077 cases per 1 000 000 person-days), representing a 96.4% increase from the expected December peak rate of 1569 cases per 1 000 000 person-days (RR: 1.96, 95% CI: 1.85 to 2.09) (figure 1B).

Consistent time trend and seasonality between EHR-based incidence rate of medically attended RSV infection and CDC-reported RSV-associated hospitalisation among young children from October 2018 to January 2023

The CDC RSV-NET is a population-based surveillance network for laboratory-confirmed RSV-associated hospitalisations in 12 states covering almost 8% of the USA,[22] which began tracking RSV-associated hospitalisations in children during the 2018–2019 season. The time trend and seasonality of the EHR-based incidence rate of medically attended RSV infections in children aged 0–5 years (figure 2A) are consistent with the CDC-reported RSV-associated hospitalisation in children aged 0–4 years (figure 2B): low RSV infection during 2020, early shift of

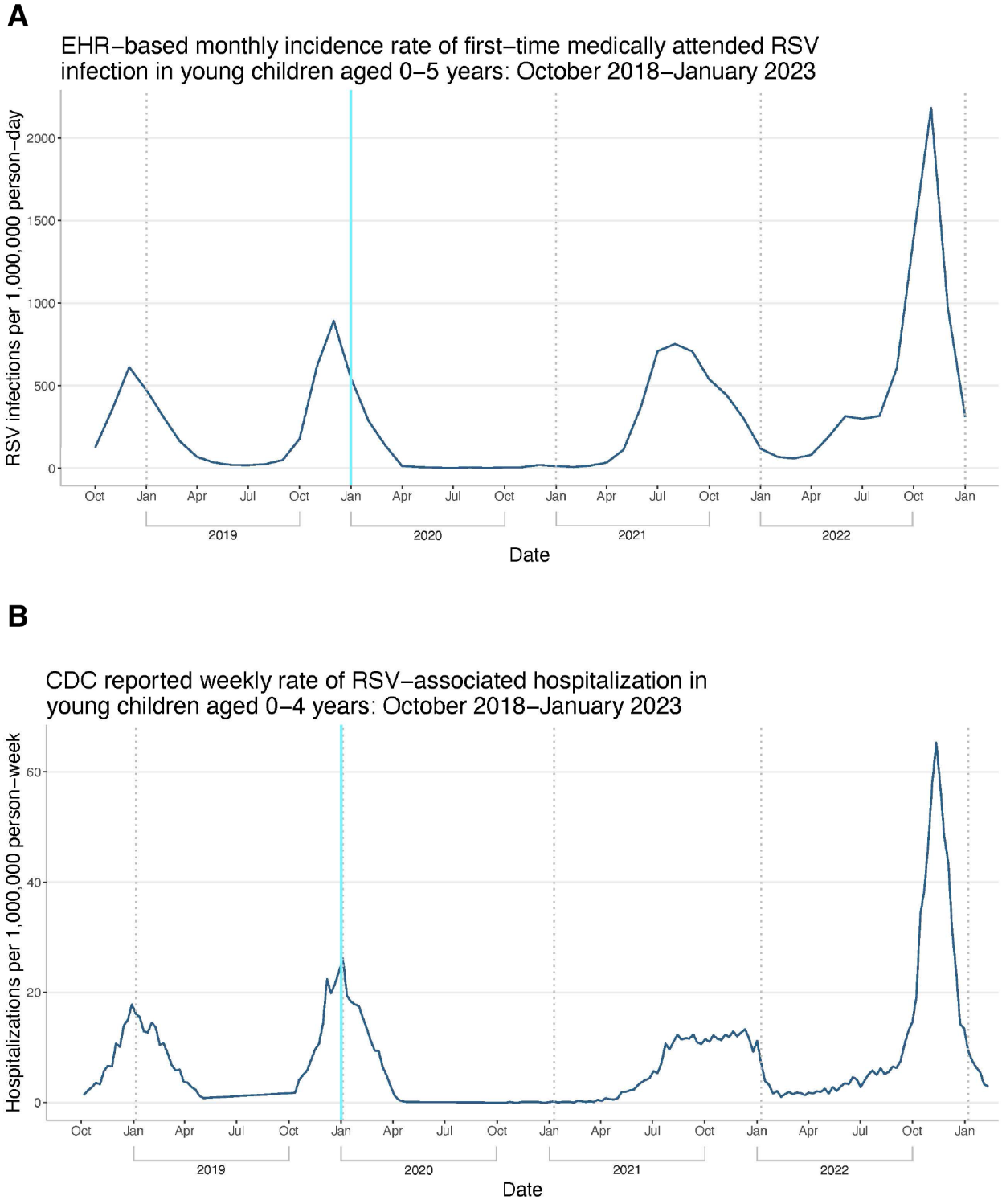

Figure 2 Time trend and seasonality of (A) EHR-based monthly incidence rate of first-time medically attended RSV infection among children aged 0–5 years from 1 October 2018 to 31 January 2023 and (B) the CDC reported rate of RSV-associated hospitalisations among young children aged 0–4 years from 1 October 2018 to 31 January 2023. CDC, Centers for Disease Control and Prevention; EHR, electronic health record; RSV, respiratory syncytial virus.

the RSV season in 2021, surge in 2022 winter and decline in January 2023. In the prepandemic 2018–2019 seasons, the peak of medically attended RSV infection preceded the RSV-associated hospitalisations. In the 2021–2022 seasons, the peaks were aligned.

Stratified analysis by RSV severity: positive lab test RSV infection, RSV-associated diseases, RSV-associated bronchiolitis and unspecified bronchiolitis

During the 2022 peak season in November and December, clinically diagnosed RSV diseases had the highest

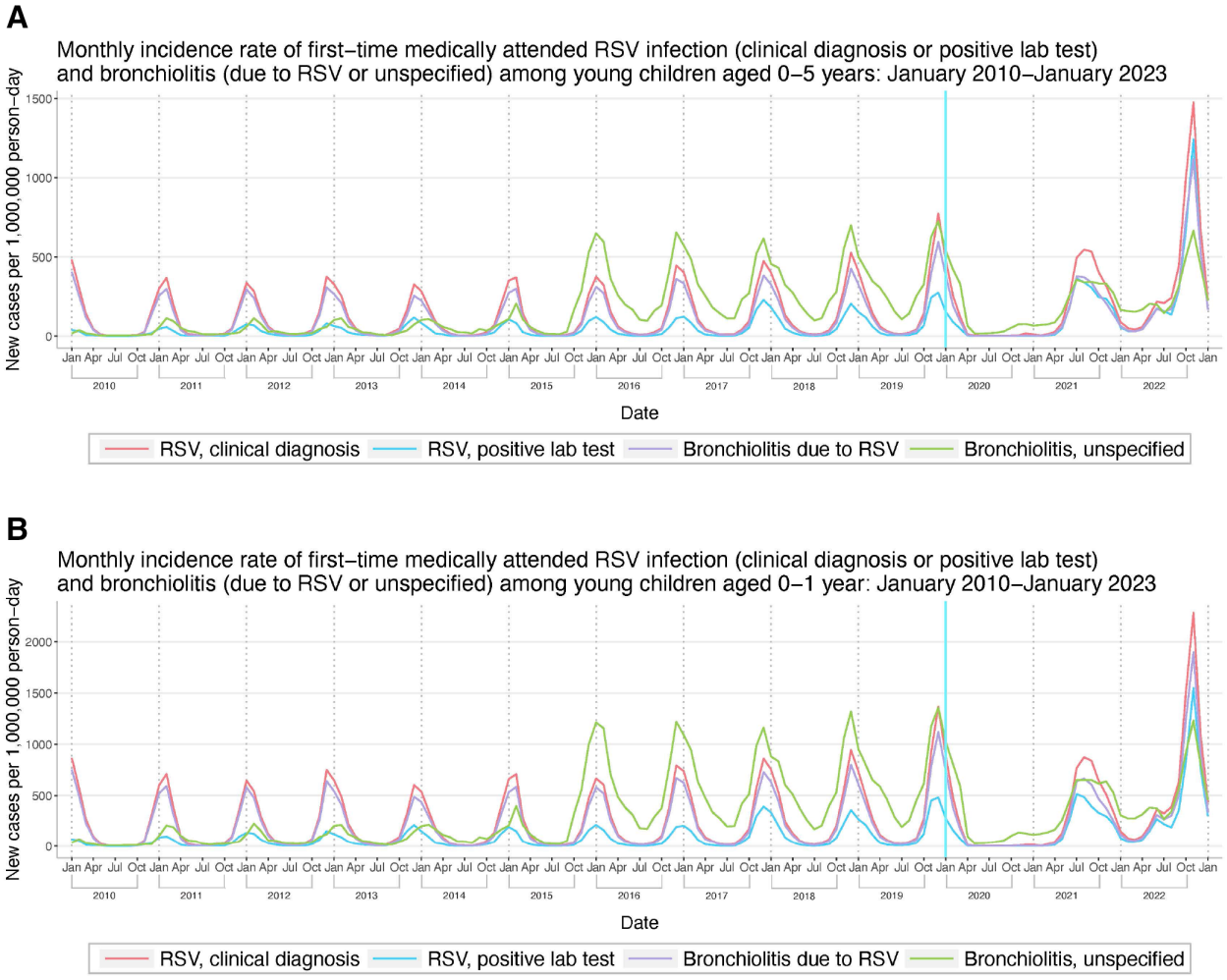

Figure 3 Stratified analysis of monthly incidence rate of first-time medically attended RSV infection from 1 January 2010 through 31 January 2023 among (A) children aged 0–5 years and (B) children aged 0–1 year. Monthly incidence rates were calculated as the number of incident cases per 1 000 000 person-days for each month. The blue vertical line marks the beginning of COVID-19 pandemic (January 2020). RSV infection was stratified by clinical diagnosis (J12.1, J21.0, B97.4), positive lab tests (12 lab-test codes), RSV-associated bronchiolitis (J21.0). Unspecified acute bronchiolitis (J21.9), which could be caused by other severe respiratory viruses such as influenza, was also shown. RSV, respiratory syncytial virus.

incidence rate in children aged 0–5 years, followed by positive lab test-confirmed RSV and RSV-associated bronchiolitis, all reaching a historically high rate. For comparison, the peak incidence rate of unspecified bronchiolitis in 2022 was similar to that from the prepandemic period of 2015–2019 but higher than in 2020 and 2021 (figure 3A). Starting in 2015, there was a marked increase in incidence rate of unspecified bronchiolitis cases (figure 3A). Among children 0–1-year old, clinically diagnosed RSV diseases had the highest incidence rate during the 2022 RSV peak season, followed by RSV-associated bronchiolitis and positive lab test-confirmed RSV, all of which reached a historically high rate (figure 3B). On the other hand, the rate of unspecified bronchiolitis in 2022 was similar to that during the prepandemic period of 2015–2019. In summary, these stratified analyses of different indicators showed differential trends between RSV infection and non-RSV respiratory viral diseases, indicating the specificity of the 2022 surge in RSV infection children.

DISCUSSION

In this study, we focused on medically attended RSV infections, which was based on the presence of clinical diagnosis codes for RSV-associated diseases, including pneumonia and bronchiolitis or positive lab test results for RSV infections that are documented in patient's EHR and required medical care or hospitalisation. Children with mild infections are often not sick enough to present to a healthcare setting. Even in a healthcare setting, most providers do not test for RSV unless the patient is being hospitalised. Therefore, these medically attended RSV infections are more likely severe RSV infections. In fact, among the 19 936 incident cases of medical attended RSV cases occurred in children aged 0–5 years during October 2022–December 2022, 14 103 (70.7%) were RSV-associated diseases, including RSV-associated bronchiolitis (54.5%). In this study, we used first-time medically attended RSV infections in order to not double count two different clinical visits for the same RSV infection,

since it is difficult to discern whether two close RSV visits recorded in patient EHRs were for two different or the same RSV infection.

In 2020, the incidence rate of RSV infection was low throughout the year, which is likely due to non-pharmaceutical interventions such as lockdown, masking and social distancing that prevented RSV from spreading. Computational models that simulated non-pharmaceutical interventions and associated immunity debt predicted a large outbreak in the 2021 winter.[45 46] However, our data showed that the seasonal pattern returned in 2021, but the incidence rate was lower for severe diseases, including RSV-associated bronchiolitis than expected. Positive lab test-confirmed RSV infection reached prepandemic levels for children aged 0–1 year and was higher for children aged 0–5 years. Certain COVID-19 preventative measures remained in place in 2021 that limited the spread of RSV infections. In April 2022, the CDC lifted the mask mandate but still recommended that people wear masks at public transportation settings.[47] Interestingly, very young children aged 0–1 year (as of 2021), many of whom were born after 2020, also showed increased RSV infection in 2021. Waning maternal immunity due to low RSV exposure during the COVID-19 pandemic and the consequent decrease in transplacental RSV antibody transfer may have contributed to increased RSV infections in 2021 compared with 2020. However, RSV infections in 2021 did not reach the levels in 2022, largely because of the preventive measures and fewer COVID-19-infected children.

In 2022, medically attended RSV infection including both clinically diagnosed severe RSV diseases and positive lab test-confirmed infections reached a historically high rate, higher for RSV diseases than the positive lab test-confirmed RSV infection. Among children aged 0–1, the peak incidence rate of RSV-associated diseases in November 2022 was 47% higher than lab test-confirmed RSV. These data suggest that the 2022 RSV surge was disproportionately driven by more severe cases of RSV diseases, which could not be fully explained by possibility of increased testing practices, awareness or transmission through day-care or siblings alone. While non-pharmaceutical interventions in 2021 and immunity debt might have contributed to the increased rate of RSV infection, these factors alone could not fully explain the huge surge in November 2022, representing 4–5 times as many severe RSV-associated diseases as in 2021. For children aged 0–1 year (as of 2022), if the immune debt due to waning maternal immunity was the main contributor, we would expect that the level of RSV infection in 2022 to be similar to that in 2021. Instead, the peak incidence rate of severe RSV diseases in children aged 0–1 year was 2285 cases per 1 000 000 person-days in November 2022, a 161% increase compared with the peak rate of 874 cases per 1 000 000 person-days in August 2021. These data suggest that together with the effects of RSV-specific immunity debt and other factors, the large buildup of COVID-19-infected children and the potential long-term adverse effects of COVID-19 on the immune and respiratory systems[7–11] may have contributed to the 2022 winter surge of severe RSV diseases. Future work is warranted to examine whether prior COVID-19 infection was associated with increased risk for medically attended RSV infections while accounting for other risk factors.

RSV is the most common virus associated with bronchiolitis. However, many other viruses cause bronchiolitis, including human rhinovirus, coronavirus, metapneumovirus and adenovirus.[48] In the winter of 2015, there was a marked increase in incidence rate of unspecified bronchiolitis, which remained stable from 2015 through 2019. Starting in 2017–2018, there was an increase in the incidence rate of lab test-confirmed RSV but was not accompanied by a proportional increase in clinically diagnosed RSV diseases until in 2019–2020. The underlying reasons for these changes remain unknown but may be attributable to advances in genomic surveillance, increased detection of respiratory viruses in the laboratory, the emergence of new viral strains, increased awareness, among others. The linear time-series regression model used a linear term to model the increasing time trend; however, the observed peak incidence rate of RSV in 2022 was 143% higher than expected, suggesting that these factors may not be the sole contributing factor for the 2022 surge.

Several studies from the USA and other countries reported disrupted seasonality of RSV infection during 2020–2021.[16 19–23] Our study is the first to report the long-term time-series data of medically attended first-time RSV infection among young children from 2010 to 2023. We show that our EHR-based incidence rate of medically attended RSV infection corresponds closely with the CDC-reported RSV-associated hospitalisations. In addition, our study provides information that is complementary to the CDC data. First, the EHR-based data reported both laboratory-confirmed cases and RSV-associated diseases, which allowed use to perform separate analyses for different types of RSV infection and compared with unspecified bronchiolitis. Second, our study population was drawn from a nation-wide database of EHRs collected in diverse clinical settings across 50 states in the US, representing demographically and clinically diverse RSV cases. The database also contains longitudinal patient data of more than 20 years, which allowed us to build robust time-series models. The CDC RSV-NET began data collection in children in 2018 based on voluntary reporting from state health departments. The EHR database is updated daily, which allows for real-time surveillance. Together, these complementary data resources provide a comprehensive overview of updated RSV activity and outcomes at both medical and general population levels in the USA.

Currently, the changes in the epidemiology of RSV especially the unusual surge in 2022 remain unknown. Multiple factors may have contributed to RSV circulation and its associated diseases in the community, including non-pharmaceutical interventions, change in human behaviours, viral interferences, immunity debt, waning population-level immunity and the long-term adverse

effects of COVID-19 infection on the immune and respiratory systems. While non-pharmaceutical interventions have been largely lifted, other factors may still play a significant role, which makes the postpandemic monitoring of respiratory virus infections necessary and complicated.

Limitations

Our study has several limitations: first, the paediatric population from the TriNetX network are those who had medical encounters with healthcare systems that contribute data to TriNetX. Though the population is large (1.7 million children aged 0 to 5 years in our study), they do not necessarily represent the entire US population. Although our study showed a time trend that is well-aligned with that from the CDC population-based surveillance data, results from this study need to be validated in other populations. Second, though the EHR data were drawn from 34 healthcare organisations across 50 states, covering diverse geographic regions, we were unable to further break down the trend patterns by region due to TriNetX's deidentification restrictions. Third, this is a retrospective cohort study of monthly incidence of medically attended RSV infections based on analysing patient EHRs and there may be overdiagnosis/misdiagnosis/underdiagnosis of RSV infection and associated diseases in patient EHRs.

CONCLUSIONS

The findings show the disrupted seasonality and historically high surge of paediatric RSV cases that needed medical attention during the COVID-19 pandemic. Our study demonstrates the potential of EHRs as a cost-effective alternative for real-time pathogen and syndromic surveillance of unexpected disease patterns including RSV infection. Further studies are needed to examine how pandemic-related factors including COVID-19 infections contribute to the 2022 RSV surge among young children and how preventive measures such as vaccinations would be beneficial in preventing severe RSV infection and associated diseases.

Acknowledgements We acknowledge support from the National Institute on Aging (grants numbers AG057557, AG061388, AG062272, AG07664), National Institute on Alcohol Abuse and Alcoholism (grant number AA029831), the Clinical and Translational Science Collaborative (CTSC) of Cleveland (grant number TR002548-01), National Cancer Institute Case Comprehensive Cancer Center (CA221718, CA043703).

Contributors RX conceptualised the project, designed and supervised the study. LW performed data analysis and prepared tables and figures. RX drafted the manuscript. PBD, NB, DCK, NV critically contributed to result interpretation and manuscript preparation. We confirm the originality of the content. RX had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information. This study used population-level aggregate and de-identified data generated by the TriNetX Platform. Due to data privacy, patient-level data were not used and cannot be shared. Population-level data and code (R statistical software V.4.2.2) for time-series analysis for this study are publicly available at https://github.com/liwang0904/RSV. All R packages are freely available.

ORCID iD

Rong Xu http://orcid.org/0000-0003-3127-4795

REFERENCES

1 Chow EJ, Uyeki TM, Chu HY. The effects of the COVID-19 pandemic on community respiratory virus activity. *Nat Rev Microbiol* 2023;21:195–210.
2 Cohen R, Ashman M, Taha M-K, *et al*. Pediatric infectious disease group (GPIP) position paper on the immune debt of the COVID-19 pandemic in childhood, how can we fill the immunity gap *Infectious Diseases Now* 2021;51:418–23.
3 Hatter L, Eathorne A, Hills T, *et al*. Respiratory syncytial virus: paying the immunity debt with interest. *Lancet Child Adolesc Health* 2021;5:e44–5.
4 Billard M-N, Bont LJ. Quantifying the RSV immunity debt following COVID-19: a public health matter. *Lancet Infect Dis* 2023;23:3–5.
5 Morello R, Martino L, Buonsenso D. Diagnosis and management of post-COVID (long COVID) in children: a moving target. *Curr Opin Pediatr* 2023;35:184–92.
6 Zimmermann P, Pittet LF, Curtis N. How common is long COVID in children and adolescents *Pediatr Infect Dis J* 2021;40:e482–7.
7 Davis HE, McCorkell L, Vogel JM, *et al*. Long COVID: major findings, mechanisms and recommendations. *Nat Rev Microbiol* 2023;21:133–46.
8 Iwasaki A, Putrino D. Why we need a deeper understanding of the pathophysiology of long COVID. *Lancet Infect Dis* 2023;23:393–5.
9 Phetsouphanh C, Darley DR, Wilson DB, *et al*. Immunological dysfunction persists for 8 months following initial mild-to-moderate SARS-Cov-2 infection. *Nat Immunol* 2022;23:210–6.
10 Liu J, Yang X, Wang H, *et al*. Analysis of the long-term impact on cellular immunity in COVID-19-recovered individuals reveals a profound NKT cell impairment. *mBio* 2021;12:e00085-21.
11 Haunhorst S, Bloch W, Javelle F, *et al*. A scoping review of regulatory T cell dynamics in Convalescent COVID-19 patients - indications for their potential involvement in the development of long COVID? *Front Immunol* 2022;13:1070994.
12 Buonsenso D, Valentini P, De Rose C, *et al*. Recovering or persisting: the Immunopathological features of SARS-Cov-2 infection in children. *J Clin Med* 2022;11:4363.
13 Beňová K, Hancková M, Koči K, *et al*. T cells and their function in the immune response to viruses. *Acta Virol* 2020;64:131–43.
14 Rogers MC, Lamens KD, Shafagati N, *et al*. CD4+ regulatory T cells exert differential functions during early and late stages of the immune response to respiratory viruses. *J Immunol* 2018;201:1253–66.
15 Hall CB, Weinberg GA, Iwane MK, *et al*. The burden of respiratory syncytial virus infection in young children. *N Engl J Med* 2009;360:588–98.
16 Olsen SJ, Winn AK, Budd AP, *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.

17 Abbasi J. This is our COVID"—what physicians need to know about the pediatric RSV surge. *JAMA* 2022;328:2096.
18 Willyard C. Flu and colds are back with a vengeance — why now? *Nature* 2022.
19 Eden J-S, Sikazwe C, Xie R, *et al*. Off-season RSV epidemics in Australia after easing of COVID-19 restrictions. *Nat Commun* 2022;13:2884.
20 Bardsley M, Morbey RA, Hughes HE, *et al*. Epidemiology of respiratory syncytial virus in children younger than 5 years in England during the COVID-19 pandemic, measured by laboratory, clinical, and syndromic surveillance: a retrospective observational study. *Lancet Infect Dis* 2023;23:56–66.
21 Groves HE, Piché-Renaud P-P, Peci A, *et al*. The impact of the COVID-19 pandemic on influenza, respiratory syncytial virus, and other seasonal respiratory virus circulation in Canada: a population-based study. *Lancet Reg Health Am* 2021;1:100015.
22 Centers for Disease Control and Prevention. RSV-NET: respiratory syncytial virus hospitalization surveillance network. 2023. Available: https://www.cdc.gov/rsv/research/rsv-net/dashboard.html [Accessed 21 Feb 2023].
23 Hamid S, Winn A, Parikh R, *et al*. Seasonality of respiratory syncytial virus - United States, 2017-2023. *MMWR Morb Mortal Wkly Rep* 2023;72:355–61.
24 TriNetX. TriNetX, Available: https://trinetx.com/ [Accessed 24 Dec 2022].
25 Wang L, Berger NA, Kaelber DC, *et al*. Incidence rates and clinical outcomes of SARS-Cov-2 infection with the Omicron and Delta variants in children younger than 5 years in the US. *JAMA Pediatr* 2022;176:811.
26 Wang L, Davis PB, Kaelber DC, *et al*. Comparison of mRNA-1273 and BNT162b2 vaccines on breakthrough SARS-Cov-2 infections, hospitalizations, and death during the Delta-predominant period. *JAMA* 2022;327:678.
27 Wang L, Davis PB, Kaelber DC, *et al*. COVID-19 breakthrough infections and hospitalizations among vaccinated patients with dementia in the United States between December 2020 and August 2021. *Alzheimers Dement* 2023;19:421–32.
28 Wang W, Kaelber DC, Xu R, *et al*. Breakthrough SARS-Cov-2 infections, hospitalizations, and mortality in vaccinated patients with cancer in the US between December 2020 and November 2021. *JAMA Oncol* 2022;8:1027.
29 Wang L, Kaelber DC, Xu R, *et al*. COVID-19 breakthrough infections, hospitalizations and mortality in fully vaccinated patients with hematologic malignancies: a clarion call for maintaining mitigation and ramping-up research. *Blood Rev* 2022;54:100931.
30 Wang L, Berger NA, Xu R. Risks of SARS-Cov-2 breakthrough infection and hospitalization in fully vaccinated patients with multiple myeloma. *JAMA Netw Open* 2021;4:e2137575.
31 Wang L, Davis PB, Volkow ND, *et al*. Association of COVID-19 with new-onset Alzheimer's disease. *J Alzheimers Dis* 2022;89:411–4.
32 Pan Y, Davis PB, Kaebler DC, *et al*. Cardiovascular risk of gabapentin and Pregabalin in patients with diabetic neuropathy. *Cardiovasc Diabetol* 2022;21:170.
33 Kendall EK, Olaker VR, Kaelber DC, *et al*. Association of SARS-Cov-2 infection with new-onset type 1 diabetes among pediatric patients from 2020 to 2021. *JAMA Netw Open* 2022;5:e2233014.
34 Wang L, Xu R, Kaelber DC, *et al*. Time trend and association of early-onset colorectal cancer with diverticular disease in the United States: 2010-2021. *Cancers* 2022;14:4948.
35 Wang L, Wang Q, Davis PB, *et al*. Increased risk for COVID-19 breakthrough infection in fully vaccinated patients with substance use disorders in the United States between December 2020 and August 2021. *World Psychiatry* 2022;21:124–32.
36 Wang L, Volkow ND, Berger NA, *et al*. Association of COVID-19 with endocarditis in patients with cocaine or opioid use disorders in the US. *Mol Psychiatry* 2023;28:543–52.
37 Olaker VR, Kendall EK, Wang CX, *et al*. Association of recent SARS-Cov-2 infection with new-onset alcohol use disorder. *JAMA Netw Open* 2023;6:e2255496.
38 Gao Z, Winhusen TJ, Gorenflo M, *et al*. Repurposing ketamine to treat cocaine use disorder: integration of artificial intelligence-based prediction, expert evaluation, clinical corroboration and mechanism of action analyses. *Addiction* 2023;118:1307–19.
39 Gao Z, Gorenflo M, Kaelber DC, *et al*. Drug repurposing for reducing the risk of cataract extraction in patients with diabetes mellitus: integration of artificial intelligence-based drug prediction and clinical corroboration. *Front Pharmacol* 2023;14:1181711.
40 Gorenflo MP, Davis PB, Kendall EK, *et al*. Association of aspirin use with reduced risk of developing Alzheimer's disease in elderly ischemic stroke patients: A retrospective cohort study. *J Alzheimers Dis* 2023;91:697–704.
41 Wang L, Volkow ND, Berger NA, *et al*. Cardiac and mortality outcome differences between methadone, buprenorphine and Naltrexone prescriptions in patients with an opioid use disorder. *J Clin Psychol* 2023.
42 Wang L, Volkow ND, Berger NA, *et al*. Cardiac and mortality outcome differences between methadone, buprenorphine and Naltrexone prescriptions in patients with an opioid use disorder. *J Clin Psychol* 2023;16.
43 Ord K, Fildes RA, Kourentzes N. Principles of business forecasting. 2017. Available: https://eprints.lancs.ac.uk/id/eprint/88208/1/POBF_2e_handout_pages.pdf [Accessed 23 Feb 2023].
44 Weekly rates of laboratory-confirmed RSV hospitalizations from the RSV-NET surveillance system. 2022. Available: https://data.cdc.gov/Case-Surveillance/Weekly-Rates-of-Laboratory-Confirmed-RSV-Hospitali/29hc-w46k [Accessed 04 Mar 2023].
45 Baker RE, Park SW, Yang W, *et al*. The impact of COVID-19 nonpharmaceutical interventions on the future dynamics of Endemic infections. *Proc Natl Acad Sci U S A* 2020;117:30547–53.
46 Messacar K, Baker RE, Park SW, *et al*. Preparing for uncertainty: endemic paediatric viral illnesses after COVID-19 pandemic disruption. *Lancet* 2022;400:1663–5.
47 CDC, Centers for Disease Control and Prevention. Wearing masks in travel and public transportation settings. 2022. Available: https://www.cdc.gov/coronavirus/2019-ncov/travelers/masks-public-transportation.html [Accessed 26 Feb 2023].
48 Meissner HC. More on viral bronchiolitis in children. *N Engl J Med* 2016;375:1200.