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Respiratory syncytial virus and influenza epidemics disappearance in Korea during the 2020–2021 season of COVID-19

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ABSTRACT

Objectives: We investigated whether non-pharmaceutical interventions (NPIs) reduce winter-prevalent respiratory viral infections represented by a respiratory syncytial virus (RSV) and influenza virus (IFV) during the winter in Korea.

Methods: The Korean Influenza and Respiratory Virus Monitoring System database was used. From January 2016 through January 2021, the weekly positivity of respiratory viruses and the weekly number of hospitalizations with acute respiratory infections were collected. The NPI period was defined as February 2020–January 2021. We analyzed whether hospitalization and sample positivity by respiratory viruses changed after NPIs. Bayesian structural time–series models and Poisson analyses were used. Data from other countries/regions reporting positive rates of RSV and IFV were also investigated.

Results: Compared with the pre-NPI period, the positive rates of RSV and IFV decreased significantly to 19% and 6%, and 23% and 6% of the predicted value. Also, hospitalization significantly decreased to 9% and 8%, and 10% and 5% of the predicted value. The positive rates of IFV in 14 countries during the NPI period were almost 0, whereas sporadic outbreaks of RSV occurred in some countries.

Conclusions: No RSV and IFV winter epidemics were observed during the 2020–2021 season in Korea.

Introduction

Since China first reported a case of unidentified pneumonia to the WHO that occurred in Wuhan, Hubei Province on December 31, 2019, until March 16, 2021, in just 15 months, more than 120 million confirmed cases and more than 2.7 million confirmed deaths occurred globally. (WHO, 2021) Faced with the coronavirus disease 2019 (COVID-19) pandemic, many countries implemented non-pharmaceutical interventions (NPIs) to mitigate its spread. The NPI elements consist of social distancing, school closure, "test and isolate" symptomatic people, hand hygiene, respiratory etiquette, and environmental cleaning (Bo et al., 2021). These nonspecific interventions are affecting not only COVID-19 but also several infectious diseases (Huh et al., 2020). Olson SJ *et al.* reported that during April–July 2020, when influenza is traditionally prevalent in the Southern Hemisphere, the influenza virus's positive rate (IFV) decreased dramatically from 13.7% in 2017–2019 to 0.06% in 2020 (Olsen et al., 2020). Similar studies in the Northern Hemisphere, including the E.U., USA, China, Taiwan, Hong Kong, Japan, and Korea, also reported that these NPIs significantly reduced several respiratory infections (Chan et al., 2020, Hatoun et al., 2020,

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Huh et al., 2020, Lai et al., 2020a, Lee et al., 2020, Lei et al., 2020, Sunagawa et al., 2021).

However, existing studies have not investigated the actual winter in the Northern Hemisphere due to the limitation of the observation period. Also, before the winter of 2020–2021, there were concerns about the co-outbreak of respiratory viral infections, which are prevalent in winter, represented by a respiratory syncytial virus (RSV) and IFV (Hills et al., 2020, Rubin, 2020). This co-outbreak with the COVID-19 pandemic might result in a considerable burden to the community since it is difficult to distinguish SARS-CoV2 infection from RSV or IFV, thereby leading to the possibility of coinfection (Rubin, 2020).

Therefore, we investigated whether RSV and IFV epidemics occurred during the 2020–2021 winter in Korea, where national-level NPIs have been implemented since February 2020. We also investigated the epidemics of other respiratory viral infections in Korea and explored RSV and IFV epidemics in other countries during the one year of the COVID-19 pandemic.

Methods

Data source in Korea

The Korean Influenza and Respiratory Virus Monitoring System (KINRESS) database, a nationwide active sentinel surveillance network operated by the Korea Disease Control and Prevention Agency (KDCA), was used. It consisted of two surveillance systems, i.e., specimen-based and clinical surveillance systems. The former collects data from patients who visited outpatient clinics with acute respiratory infections (ARIs) at 52 participating institutions, and the latter collects data from patients requiring hospitalization due to ARI at 192 participating hospitals. These nationwide surveillance systems report the weekly number of detected cases and positive rates of eight respiratory viruses (RSV, IFV, adenovirus, bocavirus, parainfluenza virus, rhinovirus, metapneumovirus, and coronavirus) using the multiplex reverse transcription-polymerase chain reaction (RT-PCR). In clinical surveillance, some cases diagnosed with rapid antigen testing (RSV and IFV only) were additionally included. These data are accessible on the KCDA website (http://www.kdca.go.kr/npt/).

Study design

This retrospective study evaluated the reduction in the positive rate (%) and the number of hospitalizations with respiratory viral infections in the KINRESS database one year after implementing NPIs. We defined the preintervention period as January 2016–January 2020 (pre-NPI period) and the intervention period as February 2020–January 2021 (NPI period). A Bayesian structural time–series model (BSTM) was used to predict the incidence in the NPI period from the incidence trends in the pre-NPI period. Additionally, we compared the observed incidence during the NPI period with the annual mean incidence during the same months (Feb–Jan) in the pre-NPI period. We also analyzed other respiratory viruses contained in KINRESS.

Data sources from other countries/regions

To monitor the outbreak of RSV and IFV in regions other than Korea, 13 data samples (nation or a part of the country) based on sentinel surveillance were collected and used for evaluation. Each data sample was obtained from an international organization's regional office or an infectious disease agency of a national health department (Supplemental Table). This study includes RSV and IFV monitoring data from the European regions of Northern Ireland, Ireland, England, Russia, Germany, and France. Data from Canada, United States, Mexico, Costa Rica, and Chile were used for monitoring data in the Americas. Data from other regions included data from Israel and Taiwan. Each surveillance system reported positive rates of RSV and IFV in samples collected from patients with ARI weekly from week 40 in 2019 to week 6 in 2021.

Statistical analysis

To evaluate the causal impact between the pre-NPI and NPI periods, BSTM was used. BSTM uses synthetic control for modeling the counterfactual. Counterfactual is the hypothetical outcome in a case where intervention had not been introduced. The causal impact is obtained by evaluating the effect between the counterfactual and the actual observed outcomes. Detailed methods of BSTM have been described in a previous study (Brodersen K. H., 2015). The numerical results for the BSTM have been performed using the causal impact package in R. Also, the relative risk was calculated using the Poisson regression model. As the sentinel surveillance was not based on population-based data, crude numbers of positive cases or positive rates were used. All tests were two-tailed, and *a* p-value < 0.05 was considered statistically significant. Statistical analyses were performed using R v.4.0.3 (R Foundation for Statistical Computing, Vienna, Austria) and SAS v.9.4 (SAS Institute Inc., Cary, NC,

Results

During the study period of 5 years, 53,960 positive samples in the specimen-based surveillance and 388,737 patient cases in clinical surveillance were identified. In the specimen-based surveillance, the mean weekly number of collected samples was 204.4 (mean; standard deviation (S.D.) ± 74.3) and, the mean weekly number of hospitalized cases in the clinical surveillance was 1466.9 (mean; S.D. ± 971.0).

Surveillance of RSV and IFV in Korea

During the 2019–2020 winter, RSV and IFV had a disease epidemic that began in November–December 2019 and terminated in early January 2020. Since then, these two viruses' epidemics have disappeared until January 2021 (2020–2021 winter period) under the implementation of NPIs. (Figure 1 and Figure 2) Compared with the pre-NPI period, the weekly positive rate of RSV and IFV in the specimen-based surveillance decreased significantly from 4.1% and 12.7% to 0.8% and 0.8%, respectively, resulting in an 81% and 94% reduction in the positive rates for each virus. (Table 1) Moreover, the mean weekly number of hospitalized patients with RSV and IFV in the clinical surveillance decreased significantly from 276.3 and 297.9 to 25.3 and 22.9, respectively, resulting in a 91% and 92% reduction in hospitalization for each virus. (Table 1)

In the BSTM model analysis, the observed positive rates of RSV and IFV in specimen-based surveillance decreased to 23% and 6% of the predicted values, respectively ($p = 0.001$). The observed number of hospitalized patients with RSV and IFV in the NPI period decreased to 10% and 5% of the predicted number of hospitalized patients (both, $p = 0.001$) (Table 1) (Figures 1 and 2).

Surveillance of other respiratory viruses in Korea

Hospitalizations with respiratory viruses other than RSV and IFV in the NPI period decreased to 3%–26% compared to those in the pre-NPI period, 2%–20% of the predicted value. In the case of specimen-based surveillance, the positive rates of parainfluenza virus, metapneumovirus, and coronavirus were significantly lower than those in the pre-NPI period and predicted values. However,

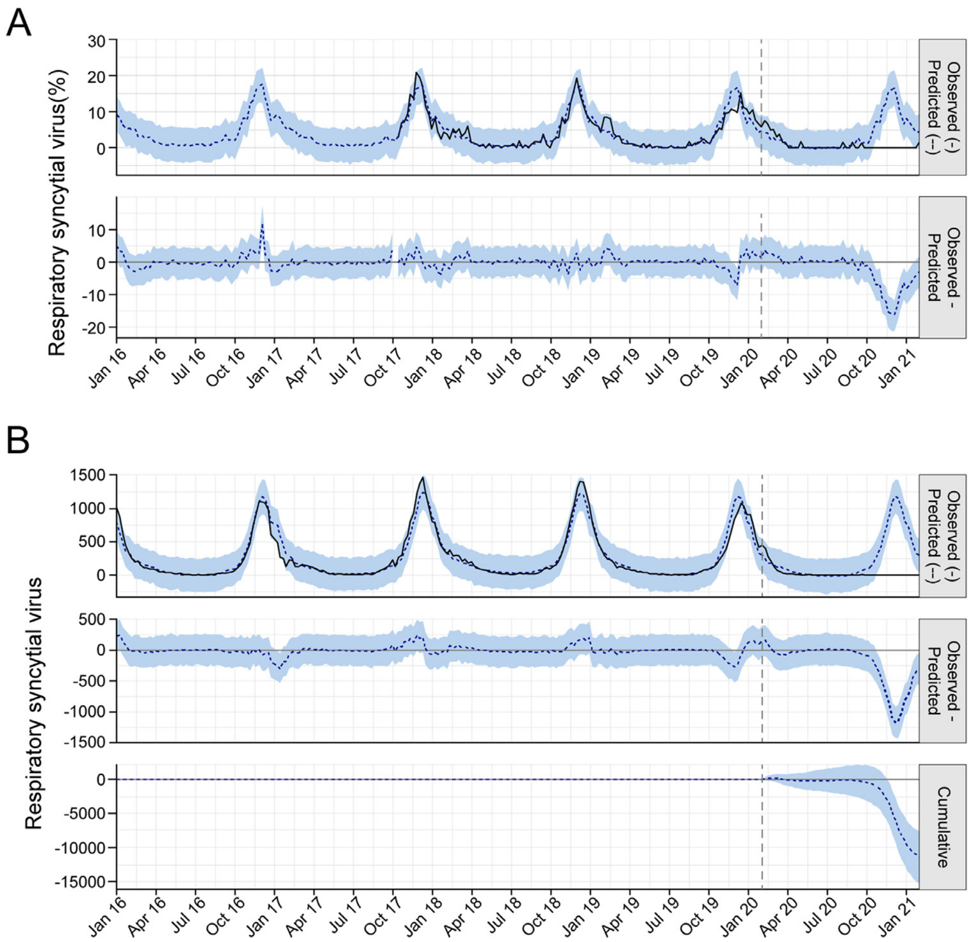

Figure 1. The weekly trend of respiratory syncytial virus (RSV) from the Korean Influenza and Respiratory Virus Monitoring System, January 2016–January 2021. The solid lines denote the observed value, the blue-dotted lines denote the predicted value, and the gray-dotted lines denote February 2020, when the NPI began in Korea; blue shades, 95% confidence intervals of the predicted value. (a) The RSV-positive rate in the specimen-based surveillance (b) RSV-related hospitalization cases in the clinical surveillance

the positive rate of rhinovirus and bocavirus increased to 34%–55% compared to those in the pre-NPI period, 1.34 and 2.45 times higher than that of the predicted values. There was no difference in the positive rate of adenovirus in the NPI than in the pre-NPI period. Still, it significantly decreased by 22% compared with the predicted value. (Table 1)

Surveillance of RSV and IFV in other countries/regions (Figure 3)

During the 2019–2020 season, the RSV epidemic trend began 1–2 months earlier than the IFV epidemic. The peak of the RSV epidemic occurred before January 2020 in most regions, and IFV peaked after January 2020, except in the Southern Hemisphere, where seasonally, January of 2020 is summer. After the RSV epidemic reached its peak, Northern Ireland, Ireland, and England had IFV peak in December 2019. In specimens of ARIs during the 2019–2020 season, the positive rate of RSV varied from country to country but showed a distribution of 0%–20%. Alternatively, IFV's positive rate showed a 0%–60% distribution, and the positive rate of infections in an epidemic period increased. The RSV epidemic has gradually decreased and disappeared smoothly despite the implementation of NPIs to prevent COVID-19 in the spring of 2020. However, the IFV epidemic showed a sharp decrease in the positive rate of specimens due to NPI's implementation, so that the ascending phase was gentle to the peak, while the descending phase was rapid. In the 2020–2021 season, the positive rate of RSV varied depending on the country, but it was hardly detected. Ireland, Germany, France, South Korea, Taiwan, Costa Rica, and Chile, which intermittently reported the number of positive samples, also reported significantly lower sample positivity rates than in the previous epidemic period. However, IFV was positive in France and Russia for only a few weeks and was not detected in most countries during the 2020–2021 season.

Discussion

This study demonstrates that in the 2020–2021 season, the first winter since the NPI was implemented, the positive rates of RSV and IFV in Korea and hospitalizations for these viruses were nearly zero by January 2021. The 2020–2021 winter is the first season that had not issued an influenza season advisory since the 2000–2001 season when KDCA issued a seasonal influenza advisory for the first time in Korea (KCDC, 2020b). Also, the 2020–2021 winter season is the first season when there has been no RSV epidemic since the KINRESS conducted PCR-based respiratory virus surveillance in 2010 (KCDC, 2020a).

The implementation of NPIs in countries has significantly reduced physical contact frequency, which is related to the transmission of infectious diseases. A cross-sectional survey conducted in the Netherlands between April and June 2020 reported that community contacts' frequency decreased by 41%–76% compared with before the NPI (Backer et al., 2021). In the U.K., the average daily number of contacts also decreased to 74%, which has been reported to reduce the R0 value of SARS-CoV-2 infection from 2.6 to

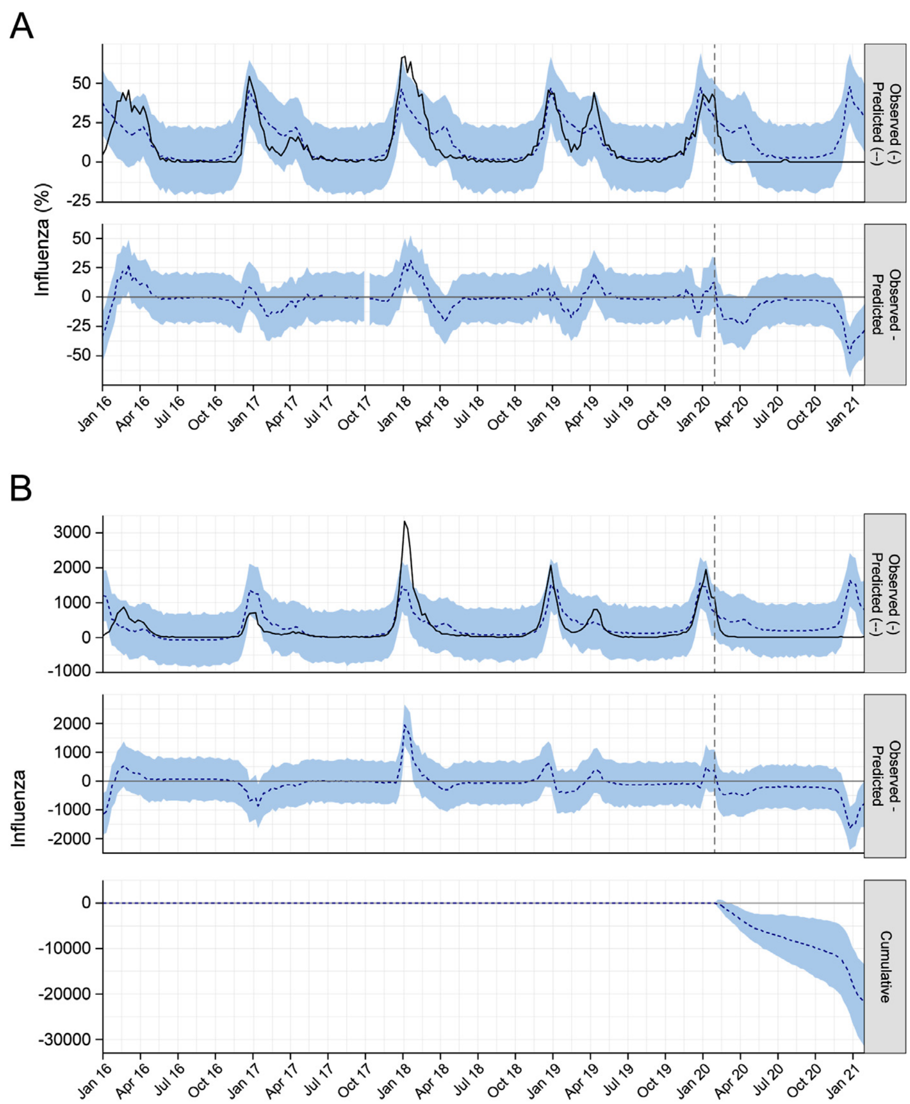

Figure 2. The weekly trend of influenza virus (IFV) from the Korean Influenza and Respiratory Virus Monitoring System, January 2016–January 2021. The solid lines denote the observed value. The blue-dotted lines denote the predicted value, and the gray-dotted lines denote February 2020, when the NPI began in Korea; blue shades, 95% confidence intervals of the predicted value. (a) The IFV-positive rate in the specimen-based surveillance (b) IFV-related hospitalization cases in the clinical surveillance

0.6 (Jarvis et al., 2020). In South Korea, the rate of wearing masks reached approximately 80%, and the daily movement of people decreased up to 38% in February 2020, which was even before the government-led mandates (Park and Yum, 2020). Physical distancing and mask-wearing, along with other NPI elements, such as hand hygiene, respiratory etiquette, and environmental cleaning, may have affected the reduction of existing airborne and droplet transmitted communicable infections, especially respiratory viruses (Chan et al., 2020, Hatoun et al., 2020, Huh et al., 2020). Our results showed that during winter, no RSV and IFV epidemic was recorded in Korea in the Northern Hemisphere and during summer in the Southern Hemisphere (Olsen et al., 2020). Also, in Korea's case, school opening was postponed until May 20, and the term was maintained until the end of December, showing that the transmission of respiratory viruses can also be suppressed when NPIs are maintained after school opening (van den Berg et al., 2021, Yoon et al., 2020).

Interestingly, the RSV and IFV epidemic patterns after the implementation of NPIs slightly differ by country. Regarding IFV, in all 14 countries included in the analysis, the positive rate of IFV was almost 0% after May 2020. In contrast, sporadic RSV cases were seen in countries such as Taiwan, Germany, Ireland, France, and Korea. Notably, in Taiwan, one of the best countries that controlled the COVID-19 pandemic, the positive rate of RSV in November (week 45) 2020 was the highest at 9.6%. The infectivity of RSV is 0.9–1.8, which is similar or slightly lower than 0.9–2.1 of IFV, especially in adults (Falsey and Walsh, 2000, Huang, 2008, Otomaru et al., 2019). Therefore, it is difficult to explain this phenomenon by the difference in the two viruses' infectivity. Of course, there is a possibility that the sentinel surveillance systems in countries were not well operated compared with the pre-COVID-19 era, but rather, IFV appears to be almost zero in the COVID-19 era. Still, it is difficult to explain that only RSV is sporadic. One explanation is that there is a possibility that the elements of the NPI that specifically influence RSV and IFV epidemics are different (Flaxman et al., 2020). As of September 2020, 156 countries, including 14 countries in our study, required 1–2 weeks of quarantine or self-isolation for people entering the country from abroad regardless of symptoms (Bielecki et al., 2020). This isolation period exceeded the incubation period of RSV (3–7 days) or IFV (1–4 days), and therefore, RSV or IFV influx from other countries is theoretically interrupted (Lessler et al., 2009).

Figure 3. Heatmap of positive rates of (A) respiratory syncytial virus and (B) influenza virus in the national sentinel surveillance of 14 countries/regions
*Gray means data do not exist: some countries do not operate surveillance systems during non-epidemic periods.

Meanwhile, the degree of NPI within each country varies. In particular, the domestic NPI in Taiwan is loose compared with other countries due to the strict prevention of COVID-19 influx from other countries (Lai et al., 2020b). If the origin of RSV is endemic and that of seasonal IFV is overseas, it may be possible to explain these viruses' different epidemic patterns. To support this hypothesis, further research with long-term surveillance data according to the degree of NPIs and research on RSV and IFV epidemics in other countries, such as Vietnam and New Zealand, with less domestic NPI and strict isolation of overseas entrants, is also required (Geoghegan et al., 2021, Nguyen et al., 2021).

A sharp decrease in RSV or IFV infections during the NPI period does not indicate the elimination of these infections. Instead, it can decrease herd immunity in the community by increasing the susceptible population to these viral infections. Baker *et al.* predicted large-scale RSV and IFV outbreaks in the U.S. after NPI in their epidemic modeling study and reported that the longer the NPI period, the larger the outbreak (Baker et al., 2020). Therefore, monitoring these transmissible infections and measures for proper prevention, including universal vaccination and immunoprophylaxis for high-risk groups, needs to be continued. One of the notable findings of our study is that incidence reduction after NPI implementation varies according to respiratory viruses. In particular, the portion occupied by bocavirus and rhinovirus in specimen-based surveillance increased significantly, and there was no reduction in adenovirus. A similar phenomenon has recently been reported in other countries.

A surveillance study by Loren Rodgers et al. on respiratory-related emergency department visits in the United States reported an increase in rhinovirus percent positivity in 2020 (34%) during the COVID-19 era compared to 2019 (26%) (Rodgers et al., 2021). In addition, the decrease in adenovirus positivity was reported to be less than that in influenza, RSV, metapneumovirus, or parainfluenza virus. After reopening schools as part of easing the lockdown during the COVID-19 era, Southampton, U.K., and Hong Kong also reported an increase in rhinovirus epidemics in schools (Fong et al., 2021, Poole et al., 2020). It is unclear why these viruses appear to be relatively less affected by NPIs. One hypothesis is that these non-enveloped viruses are resistant to lipophilic disinfectants, so it is possible that they survived longer on surfaces with infectivity (Leung, 2021). However, additional data are needed to support this hypothesis.

There are some limitations. First, this study did not aggregate the total number of RSV cases and influenza in Korea. Therefore, incidence rates of RSV and influenza could not be directly calculated. However, total-case surveillance of respiratory viral infections at the national level, which are too common and mild, is impossible. Second, the rapid antigen test was used in clinical surveillance, but the number of identified cases by rapid antigen test was not presented in the surveillance. This makes it difficult to assess

Table 1
The weekly positive rate (%) and weekly number of hospitalizations with respiratory viral infections in the Korean Influenza and Respiratory Virus Monitoring System, January 2016–January 2021

	Mean	Bayesian structural time–series model				Poisson regression	
	(Pre-NPI period)*	Observed (NPI period)†	Predicted (95% CI)	Relative effect (95% CI)	p-value (1)	Relative ratio** (95% CI)	p-value (2)
Specimen-based surveillance, %/week							
Influenza	12.69	0.80	13.36 (8.60, 18.28)	−0.94 (−1.31, −0.58)	0.001	0.06 (0.05, 0.09)	<.0001
Respiratory syncytial virus	4.11	0.78	3.45 (2.18, 4.61)	−0.77 (−1.11, −0.40)	0.001	0.19 (0.14, 0.26)	<.0001
Other Respiratory viruses							
Adenovirus	6.45	6.55	8.41 (6.86, 10.01)	−0.22 (−0.41, −0.04)	0.017	1.02 (0.90, 1.14)	0.80
Bocavirus	2.09	5.12	3.30 (2.41, 4.24)	0.55 (0.26, 0.82)	0.002	2.45 (2.11, 2.86)	<.0001
Parainfluenza virus	6.62	0.09	7.07 (5.68, 8.39)	−0.99 (−1.17, −0.79)	0.001	0.01 (0.01, 0.03)	<.0001
Rhinovirus	17.25	23.15	17.33 (14.99, 19.65)	0.34 (0.20, 0.47)	0.001	1.34 (1.26, 1.43)	<.0001
Metapneumovirus	4.48	0.48	5.29 (3.68, 6.83)	-0.91 (−1.20, −0.61)	0.001	0.11 (0.07, 0.16)	<.0001
Coronavirus	4.41	0.94	2.65	−0.64	0.001	0.21	<.0001
Clinical surveillance, hospitalization/week							
Influenza	297.94	22.92	443.69 (272.83, 605.87)	−0.95 (−1.31, −0.56)	0.001	0.08 (0.07, 0.08)	<.0001
Respiratory syncytial virus	276.27	25.25	242.77 (171.48, 317.37)	−0.90 (−1.20, −0.60)	0.001	0.09 (0.09, 0.10)	<.0001
Other Respiratory viruses							
Adenovirus	229.95	28.37	253.64 (141.50, 371.59)	−0.89 (−1.35, −0.45)	0.001	0.12 (0.12, 0.13)	<.0001
Bocavirus	99.74	26.02	131.47 (107.78, 156.26)	−0.80 (−0.99, −0.62)	0.001	0.26 (0.25, 0.28)	<.0001
Parainfluenza virus	181.95	6.27	276.64 (242.06, 313.15)	−0.98 (−1.11, −0.85)	0.001	0.03 (0.03, 0.04)	<.0001
Rhinovirus	457.80	112.25	637.97 (596.47, 679.93)	−0.82 (−0.89, −0.76)	0.001	0.25 (0.24, 0.25)	<.0001
Metapneumovirus	108.51	7.17	156.18 (118.01, 194.29)	−0.95 (−1.20, −0.71)	0.001	0.07 (0.06, 0.07)	<.0001
Coronavirus	104.20	25.67	132.16 (104.18, 161.82)	−0.81 (−1.03, −0.59)	0.001	0.25 (0.23, 0.26)	<.0001

NPI = non-pharmaceutical intervention, CI = confidence interval
* The pre-NPI period was defined from January 2016 to January 2020
† The NPI period was defined from February 2020 to January 2021
** R.R. = observed value in the NPI period/annual mean value in the pre-NPI period

the likelihood and degree of false-positive and false-negative cases due to the antigen-based method's limitation. However, we also collected and analyzed specimen-based data collected only by PCR and minimized the possibility of errors in clinical monitoring data. Third, other factors indirectly related to NPIs, such as healthcare-seeking behaviors, may have increased bias. Fourth, only countries with disclosed data on monitoring RSV and influenza-positive rates, even during the COVID-19 pandemic, were included in the study. Therefore, countries that do not operate national sentinel surveillance or have not been updated during the COVID-19 pandemic were excluded from this study, so the results of this study have limitations in representing the global RSV and IFV epidemics.

Nevertheless, this study has the strength to demonstrate that there was no winter epidemic of RSV and IFV in the 2020–2021 season, which had been prevalent yearly in Korea. Further research is needed to determine if these declines continue into the following winter and how the epidemics of these viruses will change as the NPIs gradually ease with the introduction of COVID-19 vaccines in this COVID-19 era.

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None

Author contributions

Drs. Kim JH, Roh YH, and Kang JM had full access to the study data and take responsibility for the integrity and accuracy of the analysis. Drs. Kim JH and Roh YH contributed equally to this study.

Concept and design: Kim JH and Kang JM

Acquisition, analysis, and interpretation of data: Kim JH, Roh YH, Huh K, Kim MY, Jung J, Ahn G.Y., and Kang JM

Drafting of the manuscript: Kim JH, Roh YH, and Kang JM

Statistical analysis: Kim JH and Roh YH

Conflict of Interest Disclosures

The authors have no conflicts of interest to declare.

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Ethics

This research was ethically conducted following the World Medical Association and the Declaration of Helsinki. The institutional review board (No. 4-2021-0013) approved the study.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2021.07.005.

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