

The Impact of the COVID-19 Pandemic on Respiratory Syncytial Virus Infection: A Narrative Review

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Abstract: Respiratory syncytial virus (RSV) is one of the most common respiratory viruses. It not only affects young children but also the elderly and immunocompromised patients. After the emergence of SARS-CoV-2 and the corona virus disease 2019 (COVID-19) era, a dramatic reduction in RSV activity was found, which coincided with the implementation of public health and social measures (PHSMs). However, the correlation is more complicated than we initially thought. After PHSMs were gradually lifted, a seasonality shift and a delayed RSV outbreak with greater number of infected patients were found in numerous countries, such as Israel, Australia, South Africa, New Zealand, France, United States, and Japan. Several hypotheses and possible reasons explaining the interaction between SARS-CoV-2 and RSV were mentioned. Since RSV vaccinations are still under investigation, administration of palivizumab should be considered in high-risk patients. In the post-COVID-19 era, greater attention should be paid to a further resurgence of RSV. In this narrative review, we conducted a thorough review of the current knowledge on the epidemiology of RSV during the COVID-19 era, the out-of-season outbreak of RSV, and the data on co-infection with RSV and SARS-CoV-2.

Keywords: COVID-19 pandemic, SARS-CoV-2, respiratory syncytial virus, influenza virus, respiratory tract infection

Introduction

RSV belongs to the Pneumoviridae family, which is a single-stranded and negative-sense RNA virus. RSV can be grouped according to two main antigens, known as A and B subtypes.¹ Respiratory syncytial virus (RSV) is one of the most common respiratory viruses. It not only affects young children but also the elderly and immunocompromised patients. The elderly, patients with particular comorbidities, such as chronic lung disease, those who have undergone transplantation, and immunocompromised patient are more vulnerable to severe RSV infection.² In temperate countries, RSV is predominant in winter. In comparison, outbreaks of RSV may be observed during cooler months or wet months in tropical and sub-tropical countries.^{3,4} RSV infection has become a major public healthcare issue, which has caused significant hospitalization and mortality rates, partially due to the lack of vaccination against RSV.⁵ During the corona virus disease 2019 (COVID-19) era, clinicians and researchers have noted similarities and differences between RSV and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The COVID-19 era has seen the widespread implementation of public health and social measures (PHSMs), which include personal protective measures, such as mask-wearing, hand hygiene, and social distancing, environmental measures, and surveillance and response measures.⁶ PHSMs play an indispensable role against SARS-CoV-2 transmission. The implemented PHSMs have simultaneously had an enormous impact on other respiratory viral diseases. Many studies have shown a remarkable decrease in the incidence of RSV and other common respiratory pathogens during the COVID-19 era.⁷ However, while it appears that there is

a simple direct correlation, the true nature of the relationship may be more complicated. When PHSMs were gradually lifted, a seasonality shift and a delayed RSV outbreak with greater number of infected patients were found in a number of countries, such as Israel, Australia, South Africa, New Zealand, France, United States, and Japan.^{8,9} Delayed outbreaks also caused a higher hospitalization rate, even though the clinical symptoms seemed to be milder.¹⁰ Therefore, it is important to pay attention to and prepare well for the possibility of further out-of-season RSV peaks.⁹ The symptoms caused by SARS-CoV-2 may be difficult to differentiate from those of other common respiratory viruses. Since the detection of these viruses might provide potentially life-saving treatments in certain circumstances, commercial multiplex PCR assays may aid the physician in reaching a diagnosis. Research aimed at developing RSV vaccinations are currently underway, although there are still a great challenges to overcome.¹¹ As such, administration of palivizumab should be considered in patients with higher risk of developing severe clinical symptoms and fatality.¹² During the post-COVID-19 era, it is vital to recognize the clinical importance of RSV infection as well as other common upper respiratory viral infections. In this narrative review, we conducted a thorough review of the current knowledge on the epidemiology of RSV during the COVID-19 era, out-of-season outbreaks of RSV, and data on co-infections of RSV and SARS-CoV-2.

Materials and Methods

We organized published articles and current evidence on the epidemiology of RSV during the COVID-19 pandemic in comparison to the pre-COVID-19 era. This is a narrative review by performing a thorough literature search using PubMed, Embase, and Google Scholar. For the bibliographic search, MeSH terminology was used with the following search strategy: [((SARS-CoV-2[MeSH Terms]) OR (COVID-19[MeSH Terms])) AND (Respiratory Syncytial Virus [MeSH Terms])]. The searches were not restricted by date. All retrieved records (including original articles, letters to the editor, editorials, and case reports) in English and records with English translation were downloaded and evaluated. Subsequently, the abstracts were evaluated for eligibility. Articles resulting from these searches and relevant references cited in those articles were reviewed. All duplicates were eliminated. Finally, all of the articles were analyzed. The searches were not restricted by date; however, most of the studies on RSV during the COVID-19 era are still ongoing, time constraint is the major limitation to our study. The figure in this study was created with MapChart (available at mapchart.net).¹³

Results and Discussion

Epidemiology

Before the emergence of SARS-CoV-2, Tin Tin Htar et al had conducted a systematic review and meta-analysis showing that the incidence rates of hospitalization due to RSV-related respiratory infection was 7 to 13 cases in every 10,000 people in Asia and Africa and 190 to 254 in every 10,000 people in the USA (United States of America). Furthermore, people older than 50 years old had much higher incidence rates, from 195 up to 1790 cases in every 10,000 people in the USA.² However, a considerable decrease in RSV incidence and hospitalization rate were found during the COVID-19 era. During the COVID-19 pandemic, while strict PHSMs were implemented and RSV was found to have decreased in prevalence worldwide. Moreover, it had almost disappeared in several countries and regions. The overall RSV activity after the emergence of SARS-CoV-2 is presented in [Figure 1](#).

In the USA, before the COVID-19 pandemic, RSV accounted for 5.4% in all detected positive specimens of respiratory pathogens during December 2019 to March 2020. However, after PHSMs were implemented, the RSV positive rate dramatically dropped to 0.03% during December 2020 to March 2021. Nevertheless, a delayed surge of RSV was found from April 2021 to October 2021.¹⁴ In New York City, before the COVID-19 era, RSV was the third most commonly detected respiratory virus. During the outbreak of COVID-19, Yuan et al observed a significant 86% reduction in the cumulative incidence of RSV.¹⁵ Another study conducted in New York City also revealed a similar result. During the 2020–2021 RSV season, which was from November to April, the total cases of RSV positive rate in a pediatric emergency department had dramatically decreased from 1162 cases in the 2019–2020 season to 143 cases.¹⁶ In rural Alaska, there was a dramatic decrease in RSV-related hospitalizations, which coincided with the timing of the implementation of PHSMs due to the COVID-19 pandemic.¹⁷ Groves et al analyzed data from the Canadian Respiratory

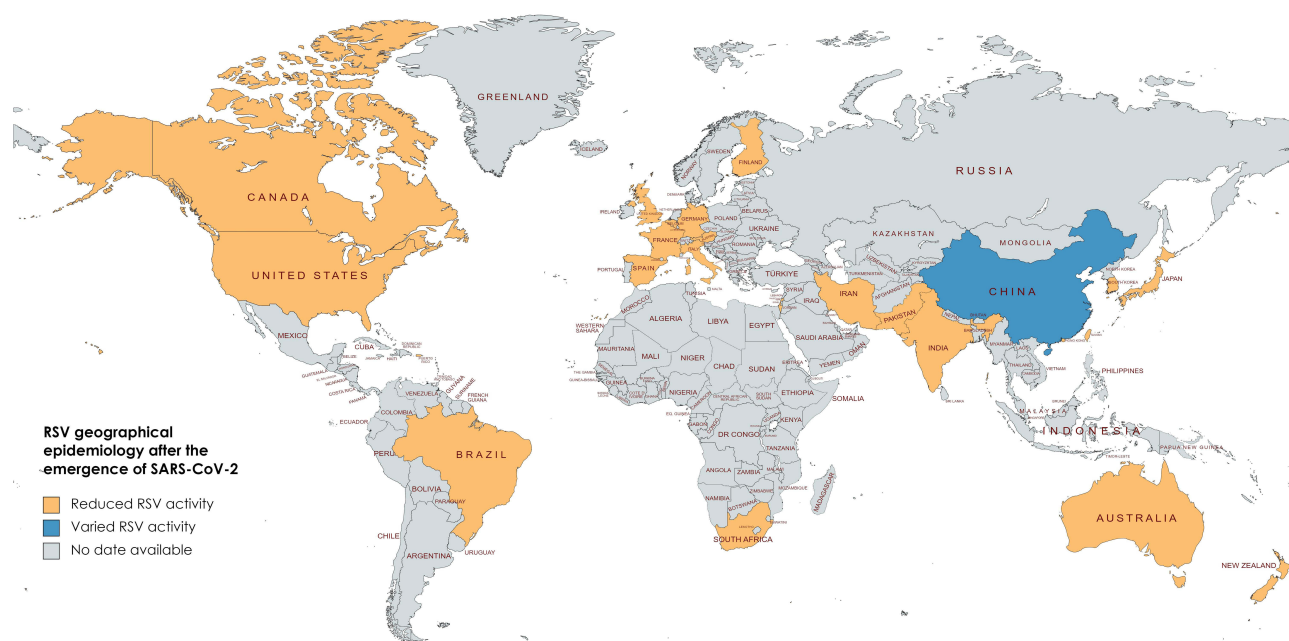


Figure 1 Regions with a decreased RSV infection rate during the COVID-19 pandemic.

Notes: Created with mapchart.net.¹³

Virus Detection Surveillance System. They found a dramatic reduction in the average weekly RSV positive rate. It was 5.96% before the COVID-19 pandemic; however, it dropped to 0.047% during the 2020–2021 season.¹⁸ Doroshenko et al also revealed a similar reduction in RSV infections beginning in July 2020, following the implementation of PHSMs in Canada.¹⁹ In South America, in a Brazilian cohort investigated by Varela et al, no RSV was detected from May to August 2020 via RT-PCR (real-time polymerase-chain reaction) test. Meanwhile, SARS-CoV-2 was detected in 32.7% of the patients.²⁰ In Puerto Rico, the RSV test-positivity rate was 4% during 2012 to 2018. However, during the COVID-19 pandemic and the period when PHSMs were implemented, no cases of RSV were detected.²¹

In Europe, several countries, such as Austria, found a significant reduction of RSV cases beginning in March 2020, the start of COVID-19 pandemic.²² In the United Kingdom (UK), Bardsley et al extracted national data on RSV-associated disease from 2014 to March 2022. The analysis showed a dramatic reduction of RSV activity in the 2020–2021 winter season, with an estimated relative reduction of 99.6% in RSV test positivity. The observed RSV test positivity rate was only 0.1%, as well with 7 cases testing positive among 7094 tests. Since winter was typically the peak season for RSV during the pre-COVID-19 period, the 2020–2021 winter seemed to be unusual.²³ An enormous reduction in RSV cases of up to 99% was observed in Belgium in 2020 during the RSV season.²⁴ In Italy, the RSV detection rate was 99% lower during 2020 to 2021, compared to the previous two seasons, and the rate of RSV in hospitalized children decreased from 38.1% to 4.7% in 2020–2021.^{25,26} In Spain, there was a reduction of up to 86% in RSV-related disease during the RSV peak season in 2020–2021.²⁷ Moreover, a reduction of RSV infection number was found in a pediatric emergency department. The numbers of cases of RSV infection in patients younger than 2 years old totalled around 6700 to 8600 for the period 2016 to 2019. During the COVID-19 pandemic, RSV cases dropped to 2489 cases in 2020.²⁸ Another study in a pediatric emergency department in Spain also showed a dramatic reduction in RSV infections with only 21 cases detected in the 2020 winter.²⁹ As for France, although the RSV peak season showed a delay, the number of RSV cases was generally than in the 2020–2021 season.³⁰ Moreover, no patients admitted during April to November 2020 had an RSV-related infection in a tertiary hospital in Paris, France.¹⁰ In Germany, similarly, the RSV positivity rate dropped from 10–21% to 0% in the 2020/21 season until the end of March 2021.^{31,32} In Nordic countries, RSV has a biennial epidemiological pattern. In Finland, the number of cases of RSV infection declined rapidly in the beginning of the COVID-19 pandemic in March 2020, which was expected to be a high-incidence year.³³ Moreover,

RSV occurrence was significantly lower compared to the occurrence in low-incidence years during the COVID-19 pandemic between August 2020 and January 2021. This was possibly owing to implementation of PHSMs.³⁴

In the southern hemisphere, a similar pattern was observed. The detection rate of RSV infection was decreased by up to 98% in different regions in Australia as well in winter 2020, compared to 2015 to 2019.^{35–37} The low RSV detection in 2020 included both subtype A and B.³⁸ In South Africa, RSV was detected in 4.1% of outpatients and 10.5% of inpatients in 2020. Compared to 2013–2019, there was an infection rate of 6% in outpatients and 15.4% in inpatients.³⁹ A children's hospital in New Zealand revealed that RSV-positive PCR cases reduced from 200 to 300 cases annually to 2 cases in the 2022 season.⁴⁰ Another study using multiple national surveillance systems found a 98% reduction of detected RSV in 2020 compared to 2015–2019.⁴¹

In Asia, investigators in Japan found an association between implementation of PHSMs and the decrease in RSV cases. There was not only a decrease in pediatric hospitalized patients, but also a significant drop in RSV. The number of cases admitted due to RSV had dropped from 4 cases per month to 0 cases per month in Hokkaido, Japan.⁴² Moreover, Wagatsuma performed a surveillance study of data using a national database, which revealed an approximately 85% reduction in monthly RSV average cases in comparison to the preceding 6 years. This might also be evidence that PHSMs potentially curb the transmission of RSV.⁴³ Similarly, in South Korea, the RSV weekly positive rate had 81% and 91% reduction in the outpatients and inpatients, respectively, during 2020 to 2021 winter.⁴⁴ Other studies in South Korea showed a fall in RSV monthly incidence rates of up to 99% in 2020.⁴⁵ During the COVID-19 era, Taiwan found a significantly lower number of RSV cases as well in the RSV peak season.⁴⁶ Chiu et al compared the incidence rates of RSV in children during February 2020 to January 2021 with January 2016 to 2020 in Hong Kong. They found a 98% relative reduction in RSV.⁴⁷ In western region of India, the positivity rate during January 2017, to March 2020, was 7.6%, which significantly reduced to 0.6% between March 2020 and December 2020.⁴⁸ In Pakistan, the impact due to COVID-19 and the implemented PHSMs reduced RSV cases by up to 93%.⁴⁹ In Iran, Letafati et al showed no detected RSV infection in children under 5 years old between March and May of 2021, which are typically cold months during the year. Compared to the pre-COVID-19 RSV rate of 24% in acute respiratory hospitalized patient, RSV disappeared during the period of COVID-19 pandemic.⁵⁰ Table 1 summarizes the aforementioned major findings from articles focusing on the RSV activity during the COVID-19 era in different countries and region.

Although most countries and regions revealed a significant reduction of RSV infection after the outbreak of COVID-19 pandemic, China showed conflicting data. In Zhejiang, China, RSV positive cases in children during COVID-19 outbreak from February to April in 2020 showed a decrease compared to 2018 and 2019.⁵¹ However, in Hangzhou, China, Du et al evaluated the RSV positivity rate before and during the COVID-19 pandemic, ie, October 2017 to February 2021. Compared with the season before 2020, no obvious reduction was found. The RSV positivity rate remained high, although the number of samples was lower than in the previous season.⁵² In another study conducted by Li et al there was even a prominent increase in the RSV infection rate from 6.6% to 20.1%, during September to December in 2019 and 2020, respectively. There were 2298 cases in 2019 and 3398 in 2020.⁵³ Ye et al also demonstrated an increase in the positive rate of RSV in 2020, which was 9.35%, compared to 6.31% in 2019.⁵⁴ Nevertheless, in Shanghai, China, there was an obvious drop in RSV infections during the COVID-19 pandemic and school closures, during the period from February to May in 2020.⁵⁵ Overall, the conflicting data may have been partly due to China's large geographic size. As the world's third largest country, China spans five geographical time zones, and therefore, there might have been regional differences and relatively wide range of RSV activity. Another possible reason is that proper wearing of masks is more difficult in children under 2 years old and there is greater susceptibility to RSV infection in children younger than 2 years old.^{52,53}

Overall, the most important reason for such a significant reduction of RSV during the COVID-19 pandemic is likely the implementation of PHSMs. Since the beginning of the SARS-CoV-2 outbreak, governments have paid considerable attention to these measures, which include personal protective measures, such as facial coverings, mask-wearing, hand hygiene, social distancing, environmental measures, and surveillance and response measures.⁶ Moreover, border controls of many countries as well as mandatory quarantine after arrival all limited the viral transmission among countries.⁴⁰ It seems highly probable that these measures played an essential role protecting against SARS-CoV-2 transmission. The implemented PHSMs simultaneously appeared to have an enormous impact on the transmission of RSV.^{14,38} Another

Table I Summary of Major Findings from Articles Focusing on RSV Activity During the COVID-19 Era in Different Countries and Regions

References	Country or Region	Findings of the Study
Katharine Uhteg et al 2022 ¹⁴	Maryland, USA	The RSV positive rate dramatically dropped to 0.03% during December 2020 to March 2021
Haokun Yuan et al 2022 ¹⁵	New York City, USA	During the outbreak of COVID-19 from March 2022 to May 2021, a significant 86% reduction in the cumulative incidence of RSV was observed.
Katia C. Halabi et al 2022 ¹⁶	New York City, USA	During the 2020–2021 RSV season, the total cases with an RSV positive rate in a pediatric emergency department dramatically decreased from 1162 cases in 2019–2020 season to 143 cases.
Helen E. Groves et al 2021 ¹⁸	Canada	The data from Canadian Respiratory Virus Detection Surveillance System showed a dramatic reduction of the average weekly RSV positive rate, which dropped from 5.96% before the COVID-19 pandemic to 0.047% during the 2020–2021 season.
Fernanda Hammes Varela et al 2021 ²⁰	Southern Brazil	No RSV was detected from May to August 2020 via RT-PCR (real-time polymerase chain reaction) test. Meanwhile, SARS-CoV-2 was detected in 32.7% of the patients.
Talia M. Quandelacy et al 2022 ²¹	Puerto Rico	RSV test-positivity rate was 4% during 2012 to 2018. However, during the period of COVID-19 pandemic and PHSMs were implemented, no case of RSV were detected.
Monika Redlberger-Fritz et al 2021 ²²	Austria	Compared with the previous season, RSV after the lockdown in March 2020 showed only 19 cases were detected. The estimated number of cases in the same period in previous years was 82.
Megan Bardsley et al 2022 ²³	United Kingdom	A dramatic reduction of RSV activity was observed in 2020–2021 winter with the estimated relative reduction of 99.6% in RSV test positivity. The observed RSV test positivity rate was only 0.1%, with 7 cases positive in 7094 tests.
Van Brusselen. et al 2021 ²⁴	Belgium	An enormous reduction of RSV cases (by 99%) was observed in 2020 during the RSV season.
Raffaella Nenna. et al 2022 ²⁶	Rome, Italy	The rate of RSV in hospitalized children decreased from 38.1% to 4.7% in 2020–2021
Ermengol Coma et al 2022 ²⁷	Spain	A reduction of RSV-related disease of up to 86% was noted during the RSV peak season in 2020–2021.
Ana Isabel Reyes Domínguez et al 2022 ²⁸	Spain	The number of cases of RSV infection in patients younger than 2 years old was around 6700 to 8600 in 2016 to 2019 in the pediatric emergency department. During the outbreak of COVID-19 pandemic, RSV cases dropped to 2489 cases in 2020.
Paul Stamm et al 2021 ³¹	Germany	The RSV positivity rate dropped from 10–21% to 0% in the 2020/21 season until the end of March 2021.
Daniel K. Yeoh et al 2021 ³⁵	Western Australia	A reductions in RSV detections of 98% was reported in Western Australian children in the winter of 2020.
El-Heneidy, A. et al 2022 ³⁶	Queensland, Australia	A significant decrease of RSV detection was noted during the COVID-19 pandemic year of 2020 with a delayed surge in the non-RSV peak season.
Yara-Natalie Abo et al 2021 ³⁷	Melbourne, Australia	A tertiary paediatric hospital has shown a 68% reduction in the RSV positive rate during the COVID-19 pandemic compared to previous years.
Stefano Tempia et al 2021 ³⁹	South Africa	RSV was detected in 4.1% of outpatients and 10.5% of inpatients in 2020. Compared to the years between 2013 and 2019, 6% of outpatients and 15.4% of in patients had RSV.
Adrian Trenholme et al 2021 ⁴⁰	New Zealand	A children's hospital revealed that RSV positive PCR cases had reduced from 200–300 cases annually to 2 cases in the 2022 season.

(Continued)

Table I (Continued).

References	Country or Region	Findings of the Study
Q. Sue Huang et al 2021 ⁴¹	New Zealand	A study using multiple national surveillance systems found a 98% reduction of detected RSV in 2020 compared to 2015–2019.
Yuji Maruno et al 2022 ⁴²	Hokkaido, Japan	The number of cases of patients admitted due to RSV dropped from 4 cases per month to 0 cases per month.
Keita Wagatsuma et al 2021 ⁴³	Japan	A reduction of about 85% in monthly RSV average cases in comparison to the preceding 6 years was found in a nationwide surveillance study.
Jong-Hun Kim et al 2021 ⁴⁴	South Korea	The RSV weekly positive rate had an 81% and 91% reduction in outpatients and inpatients, respectively, during the 2020–2021 winter.
Chiu. et al 2022 ⁴⁷	Hong Kong	The RSV incidence rates in children during February 2020 to January 2021 had a 98% relative reduction compared to the period January 2016 to 2020.
Sumit Bhardwaj et al 2022 ⁴⁸	India	The positivity rate during January, 2017, to March, 2020, was 7.6%, which was significantly reduced to 0.6% between March 2020 and December 2020.
Arash Letafati et al 2022 ⁵⁰	Iran	Compared to the RSV rate of 24% in acute respiratory hospitalized patients in the era before COVID-19, no RSV was detected during the cold months from March to May 2021
Xinke Du et al 2021 ⁵²	Hangzhou, China	Compared with the season before 2020, no obvious reduction was found. RSV positivity rate remained high, although the number of samples was lower than in the previous season.
Li Li et al 2021 ⁵³	Shenzhen, China	A prominent increase in the RSV infection rate was noted from 6.6 to 20.1%, during September to December in 2019 and 2020, respectively.

Notes: Table I summarizes the data of RSV infection rates during the COVID-19 era.

reason for this finding is the hypothesized competition among respiratory viruses.²⁰ In the initial outbreak of the COVID-19 pandemic, Leuzinger et al observed the fact that SARS-CoV-2 had quickly and nearly completely replaced other common seasonal respiratory viruses.⁵⁶ The phenomenon of competition and viral interference between SARS-CoV-2 and RSV has been described and further supported by an Italian multicenter study. Nenna et al observed a resurgence of RSV in the fall with a major peak in November 2021; meanwhile, the SARS-CoV-2 activity was relatively low. In contrast, when the outbreak of the Omicron variant of SARS-CoV-2 occurred, RSV saw a sharp reduction immediately.⁵⁷ However, some might question this hypothesis because several studies showed a substantial rate of co-infection with SARS-CoV-2 and other respiratory viruses.⁵⁸ Some experts argued that the reduction of RSV cases was in part because of the decrease in the sample number and hospital visits during the COVID-19 pandemic.⁵⁹ Nevertheless, another study disproved this possibility because the number being tested in 2020 was as twice that observed than in previous years.³⁸ Bardsley et al has also demonstrated the reduction of laboratory testing could not explain the decrease in RSV since the RSV positivity rate was also reduced by a similar order of magnitude.²³ In sum, the implementation of PHSMs appears to be the most commonly mentioned factor associated with the reduction of RSV activity during the beginning of the COVID-19 era, but other factors also seemed to play an important role.

Out-of-Season Epidemic and Delayed Surge of RSV

During the COVID-19 era, the interaction between RSV and SARS-CoV-2 has been widely discussed. In 2009 influenza pandemic, RSV showed a seasonal delay of up to 2.5 months, compared with the previous RSV season. A viral interference effect and the implementation of non-pharmaceutical interventions have been postulated to explain these findings.⁶⁰ Recent data have identified a seasonal change in RSV circulation in both northern and southern hemispheres.³ The resurgence of RSV after the lightning of PHSMs is a major concern that has been raised by many experts. Lina et al developed a model simulating the RSV season after the end of PHSMs in 2022–2023 in Tokyo, Japan. The result showed

a possible severe outbreak partly because of the increased size of populations that are susceptible to RSV during the period of PHSM implementation for COVID-19.⁶¹ Similarly, Baker et al in the US also reported this concern using an epidemic model.⁶² In fact, the resurgence of RSV infection had already been found in Australia during January to March 2021.⁶³ Moreover, since the start of 2021 summer in the northern hemisphere, an unusual circulation of RSV was observed in the USA by the New Vaccine Surveillance Network (NVSN).⁶⁴ A study in Western Australia found an unusual RSV resurgence in late 2020. In patients admitted due to respiratory tract admission, the RSV positive rate was relatively low during May to September 2020. However, during November and December 2020, which is summer in the southern hemisphere, Foley et al found RSV positive rate of 81.7%.⁶⁵ In addition, a similar interseasonal increase in RSV cases was reported in other studies, in regions such as in New South Wales, Australia, and New York, USA.^{66,67}

In Europe, an unexpected resurgence of RSV was detected in summer 2021 in the UK. Moreover, the number of reported cases was even greater than in the pre-COVID-19 era.²³ An interseasonal surge of RSV infection was found during the first half of 2021 in Switzerland. Hammerstein et al reported a shift in the usual RSV season in both infants and children, which coincided with the lifting of PHSMs and a local decline in COVID-19 cases.⁶⁸ A change in RSV seasonality was also found in Germany. A dramatic decrease of RSV cases was observed in winter during 2020 to 2021. However, once the requirements for PHSMs were officially lifted, a delayed RSV epidemic occurred.⁶⁹ Southern Italy also suffered a seasonal shift of RSV epidemic beginning in August 2021. Moreover, a delayed peak with increasing RSV cases was also noted in November 2021.⁷⁰ An early RSV season was detected in Finland after the lifting of PHSMs in September 2021.⁷¹ A seasonality shift was observed in Portugal as well. The RSV peak season used to occur during December and January, however, a significant delay in the RSV peak season to July and August was documented in 2021.⁷² In France, a late RSV outbreak was found in the 2020–2021 season. The RSV season used to begin in the fall, around October. However, it was not until December 2020 that the RSV epidemic began, peaking between February and March 2021.¹⁰ In Italy, no RSV specimens were detected in 2020. However, there was a surge in RSV in the fall of 2021. In those positive nasopharyngeal specimens, RSV account for 14.5%, which was only less than SARS-CoV-2 of 25.6%.⁷³

In eastern Asia, an unusual outbreak of RSV infection with a greater magnitude than in the pre-COVID-19 season occurred in Tokyo, Japan in the spring of 2021. This outbreak was associated with the return to school.⁷⁴ In Shanghai, China, the RSV positivity rate in the post-COVID-19 period, from June 2020 to January 2021 increased. The resurgence was also accompanied by a seasonal shift, with RSV being detected during the whole post-COVID-19 period and peaking in the summer.⁵⁵ As in Taiwan, the usual peak RSV season is in spring and fall. However, in the 2020–2021 season, Lee et al noted a delay in the RSV season, which occurred in the winter of 2020. The delay was mainly related to the COVID-19 mitigation measures.⁴⁶ In Iran, the first RSV outbreak in 2022 among children less than 5 years old occurred after the emergence of SARS-CoV-2. A local children's hospital in southwest Iran reported that as many as 53% of children admitted due to acute respiratory infection suffered from RSV.⁷⁵

Several factors have been reported described to be responsible for the seasonality change in RSV and its resurgence. First, PHSMs were not as strictly enforced as at the beginning of COVID-19 pandemic. As the COVID-19 pandemic wore on, requirements for PHSMs were loosened; children could return to schools and day care centers, and restrictions on social gatherings were lifted.¹⁰ Among all of the PHSMs, a thorough analysis of RSV surveillance data from 11 countries revealed a strong association of school reopenings and lifting of stay-at-home requirements with increased RSV activity.⁷⁶ Moreover, the role of adults in RSV transmission seems to be more important than previously thought. During the COVID-19 era, PHSMs were mainly aimed at older children and adults, partly because of the difficulty of strictly implementing these measures in infants, toddlers, and younger children. The resurgence of RSV was associated with the lifting of PHSMs and the reopening of borders rather than the opening of childcare facilities. This result has given rise to speculation that it was the change in daily habits in adult is actually affecting RSV activity.⁷⁷ Second, decreasing immunity in older children and adults to RSV is another prominent factor. Due to the COVID-19 era, there was a RSV-naïve infant cohort that possessed increased susceptibility to RSV.^{30,78} One of the reasons for this concern was a phenomenon termed “immunity debt”. Before the COVID-19 pandemic, most children less than 2 years old would become infected with RSV sooner or later and then develop a certain level of immunity against severe disease.⁷⁹ It has become apparent that because of the significant decrease of RSV activity since the emergence of SARS-CoV-2, there is now a cohort of children who are more susceptible to severe RSV infection due to their immunologically naïve status.⁸⁰

In fact, entire populations, especially those who are younger than 2 years old, lack immune stimulation because of the reduction of RSV circulation.⁸¹ This might result in very young children having greater susceptibility to RSV as well as a decrease in adult immunity.³ The hypothesis of waning immunity has been further supported by Reicherz et al. Serum prefusion RSV F protein IgG level and RSV neutralization titers were examined in women of reproductive age and in infants before and during the COVID-19 pandemic. The results showed a significant reduction of RSV antibody levels after the emergence of SARS-CoV-2.⁸² Furthermore, Foley et al also found the median patient age during the RSV resurgence was 18.4 months, which was significantly higher than in the previous season, which ranged from 7.3 to 12.5 months.⁶⁶ The “immunity debt” might raise the risk to the whole population of a serious outbreak and potentially more severe RSV infection.⁸³ Moreover, household transmission was shown, to some degree, to be partially responsible for the RSV surge.⁸⁴ Other possible factors include the reopening of travel between countries and climatic factors.^{30,78} Importantly, the RSV resurgence was not associated with a novel RSV strain. A study conducted in Greece in 2021–2022 reported a sudden RSV outbreak, which was caused by both RSV subtype A and B. An analysis revealed that the genotypes were the same as in the pre-COVID-19 season.⁸⁵ This suggests the possibility of a novel strain-related outbreak is low.

Although the implementation of PHSMs disrupted the transmission of RSV, it is unlikely that they completely eliminated infections. An interseasonal shift of the RSV peak season has already been found. Therefore, we should pay more attention to a resurgence of RSV in the near future with the possibility of a more severe outbreak and impact.⁸⁶ Moreover, an out-of-season RSV outbreak might make preventive RSV screening on the ward a potential measure for physicians to detect positive cases earlier. Once a case of RSV has been noted, quarantine could stop transmission between high-risk patients, such as those with hematological disease. Considering the potentially serious outcomes in such patients, a further strategy on RSV prevention should be reviewed and investigated.⁸⁷ Clinicians should be aware of the possibility of future outbreaks of a more serious RSV epidemic following the easing of strict PHSMs. Surveillance of certain common respiratory infections, especially RSV, will be important as we enter the post-COVID-19 era.⁷⁹

SARS-CoV-2 Co-Infection with Respiratory Syncytial Virus

Physicians have raised concerns about co-infection with SARS-CoV-2 and RSV. Although a resurgence of RSV was noted in the post-COVID-19 era, the rate of co-infection with SARS-CoV-2 and RSV was substantially lower than expected. During the COVID-19 pandemic in the USA, Uhteg et al found only two patients had co-infection. One had SARS-CoV-2 and enterovirus/rhinovirus and the other was co-infected with enterovirus/rhinovirus and adenovirus. In sum, the co-infection rate of SARS-CoV-2 was only 0.8% between December 2019 and October 2021 in the study.¹⁴ A retrospective review in the USA showed only 1.4% of cases were infected with SARS-CoV-2 and RSV simultaneously in 2021.⁸⁸ In Italy, the co-infection rate of SARS-CoV-2 and other respiratory viruses was around 7.6% in all positive samples. None of these cases showed co-infection with SARS-CoV-2 and RSV.⁷³ In another study conducted in Warsaw, Poland, no cases of co-infection with SARS-CoV-2 and RSV were found.⁸⁹ In South Africa, no co-infection was found for either SARS-CoV-2 or RSV during March to October 2020.³⁹ In the UK, the co-infection rate among SARS-CoV-2-positive patients with RSV between February 2020 and December 2021 was around 3.2%. Meanwhile, the co-infection rates of SARS-CoV-2 with influenza viruses and adenoviruses was 3.3% and 2.0%, respectively. Nevertheless, only co-infection of SARS-CoV-2 with influenza virus was associated with increased odds of mechanical ventilation use and in-hospital mortality.⁹⁰ Cong et al conducted a systematic review on the impact of SARS-CoV-2 and RSV co-infection on mortality, which included 12 published studies. The review showed no obvious effect on the overall mortality; however, due to the lack of high-quality studies, the results revealed insufficient evidence. Therefore, further investigation on this topic is necessary.⁹¹

However, a high co-infection rate was found in several regions. In Brazil, Alvares et al conducted an observational retrospective study that included 32 children younger than 24 months of age who suffered from COVID-19 during March to September 2020. Among these patients, an RSV co-infection rate of 18.7% was observed. Although patients with co-infection did not have a high risk of intensive care unit admission, use of mechanical ventilation, or death, length of stay was longer.⁹² Hashemi et al observed an RSV co-infection rate of 9.7% in children who died from SARS-CoV-2 infection in Iran. However, the co-infection rate was as high as 22.3% in the cases with influenza virus.⁹³

In contrast to patients infected with SARS-CoV-2, those with RSV were more likely to have bacterial co-infection.⁹⁴ Clinicians should be aware of the substantial rate of co-infection with RSV and other respiratory viruses, especially SARS-CoV-2. Early recognition might alter the further treatment plan for such patients. In practice, it might be necessary to carefully detect all suspected respiratory pathogens, not only for accurate clinical diagnosis and management but also for further investigation of these respiratory viruses.

Diagnostic Approach for RSV in COVID-19 Era

Laboratory confirmation of RSV could assist in the clinical diagnosis of RSV infection. Evidence of an RSV infection should alert the physician to the possibility that further testing may be needed, especially for patients at high risk of developing severe illness or hospitalization, such as preterm birth, comorbidity of underlying lung disease, Down syndrome, immunocompromised patients, as well as the elderly with chronic pulmonary disease or functional disability.^{95–97} Nucleic acid amplification test is the preferred method, rather than antigen detection or viral culture. The specimen can be collected via nasopharyngeal swab of bronchoalveolar lavage fluid.^{98,99} When PHSMs were lifted, increasing cases of RSV as well as influenza viruses were detected, which led to increased testing demand to examine these viruses.¹⁴ The World Health Organization (WHO) has suggested testing other common respiratory viruses, which include influenza viruses and SARS-CoV-2, once RSV infection is suspected.¹⁰⁰

Table 2 lists some of the currently available multiplex PCR assay that can detect SARS-CoV-2, RSV, and influenza virus simultaneously. Most of the listed PCR assays received emergency use authorization (EUA) by the United States Food and Drug Administration (FDA). The first EUA-approved multiplex PCR assays for detecting these viruses was the Cepheid Xpert Xpress SARS-CoV-2/Flu/RSV Test, which has showed high accuracy and a good correlation with to standard-of-care tests.^{101–103} Both the NeuMoDx™ Flu A-B/RSV/SARSCoV-2 Vantage Assay and the Alinity m Resp-4-Plex have also provided high sensitivity and accuracy as well, which may aid

Table 2 Summary of the Currently Available Commercial Multiplex PCR Assay for Detecting SARS-CoV-2, Influenza Viruses, and RSV

Multiplex PCR Assay in Detecting SARS-CoV-2, Influenza Viruses, and RSV	Eligibility
Cepheid Xpert Xpress SARS-CoV-2/Flu/RSV Test ^{101–103}	USA FDA
Abbott Alinity m resp-4-plex ^{104,124,125}	USA FDA
PKamp™ Respiratory SARS-CoV-2 RT-PCR Panel I ¹²⁶	USA FDA
BioFire FilmArray Respiratory Panel 2.1 ^{127,128}	USA FDA
ePlex Respiratory Pathogen Panel 2 ^{127,128}	USA FDA
QIAstat-Dx Respiratory SARS-CoV-2 Panel ^{127,128}	USA FDA
STANDARD™ M Flu/SARS-CoV-2 Real-time Detection Kit ¹⁰⁵	USA FDA ¹²⁸
NeuMoDx™ Flu A-B/RSV/SARSCoV-2 Vantage Assay ^{104,128}	USA FDA ¹²⁸
AusDiagnostics SARS-CoV-2, Influenza and RSV 8-well assay ¹⁰⁶	Therapeutic Goods Administration (TGA) in Australia
Allplex™ SARS-CoV-2/FluA/FluB/RSV Assay ^{105,129}	Ministry of Food and Drug Safety in Korea
PowerChek™ SARS-CoV-2, Influenza A&B Multiplex Real-time PCR Kit ^{105,108}	Ministry of Food and Drug Safety in Korea
TaqMan SARS-CoV-2, Flu A/B, RSV RT-PCR Multiplex Assay ¹³⁰	Not yet been approved
AMPLIQUICK® Respiratory Triplex assay ¹³¹	Not yet been approved
LabTurbo AIO 48 open platform SARS-CoV-2, influenza A/B, and respiratory syncytial virus ¹³²	Not yet been approved
Labcorp Seasonal Respiratory Virus RT-PCR DTC Test * ¹⁰⁷	USA FDA ¹²⁸

Notes: Labcorp Seasonal Respiratory Virus RT-PCR DTC Test is a home collection kit.

physicians in performing diagnosis and differential diagnosis.¹⁰⁴ The Allplex™ SARS-CoV-2/FluA/FluB/RSV Assay and the PowerChek™ SARS-CoV-2, Influenza A&B Multiplex Real-time PCR Kit are both commercially available tools for detecting SARS-CoV-2, RSV, and influenza virus simultaneously in Korea.¹⁰⁵ In Australia, AusDiagnostics SARS-CoV-2, Influenza and the RSV 8-well assay have also shown efficacy in detecting these viruses at an intermediate concentration, which makes sample pooling a possible issue.¹⁰⁶ Recently, the first non-prescription Labcorp's Seasonal Respiratory Virus RT-PCR DTC test has received EUA approval. Patients can now use a home collection kit to collect nasal swab specimens themselves.¹⁰⁷ The high sensitivity and accuracy of these PCR assays aid in the differentiation and detection of viruses in patients with a viral infection.¹⁰⁸

Treatments for Respiratory Syncytial Virus in COVID-19 Era

In general, respiratory syncytial virus infections are mainly treated with best supportive care. Special consideration should be made in immunocompromised patients, which included hematopoietic cell transplant recipients, lung transplant recipients, other solid organ transplant recipients, and patients with hematologic malignancy.¹⁰⁹ There are three currently available pharmacotherapeutic agents benefit these patients, which includes palivizumab, immune globulin, and ribavirin.¹¹⁰ Ribavirin is the only approved antiviral drug for treating RSV infection by the United States FDA, albeit its effectiveness and expensiveness are major concern. Several small trials showed reduction in days of hospitalization and days of ventilation in infants and young children.¹¹¹ Besides, a retrospective analysis included 23 haematopoietic stem cell transplant recipients with RSV-related respiratory tract infection has demonstrated that oral ribavirin use is associated with reduced morbidity and mortality.¹¹² Similarly, a review on treating RSV infected adult HSCT recipients with ribavirin also revealed a lower mortality rate.¹¹³ However, ribavirin is contraindicated to pregnant females and during the 6 months prior to pregnancy.¹¹⁴ On the other hand, administration of intravenous immunoglobulin (IVIG) might be effective in immunocompromised patients suffered RSV infection.¹¹⁵ Prophylaxis of severe RSV illness with palivizumab, a humanized monoclonal antibody against RSV, is recommended to high-risk patients under 2 years of age.¹¹⁶ The use of palivizumab among adult, especially the elderly and immunocompromised patient, is lack of clinical evidence currently.¹¹⁷ Although the efficacy is uncertain, palivizumab is a well-tolerated and safe option among immunocompromised patients. It might be reasonable to treat immunocompromised patient with palivizumab.^{118,119} Since RSV seasonality has an obvious change after the emergence of SARS-CoV-2, the American Academy of Pediatrics (AAP) supported the administration of palivizumab in those eligible patients. More than 5 consecutive doses of palivizumab should be considered because of the shift in seasonality and the interseasonal spread of RSV.¹²⁰ Individualized consideration should be made especially during the atypical interseason. Besides, the physician should pay attention on RSV epidemiology in the following days.¹²¹

Conclusion

In this narrative review, we collected the most current studies on the epidemiology of RSV in the COVID-19 era as well as data on the RSV resurgence. The importance of RSV infection in those at risk of developing severe disease has attracted attention among experts in this field. It is apparent that RSV remains one of the most common respiratory viruses even after the emergence of SARS-CoV-2. However, to date, there is still no available RSV vaccine.¹²² The development of an RSV reproducible human experimental model could aid further investigations and research on antiviral medication and vaccine.¹²³ Besides quarantine and lockdown, hand washing, mask wearing, and social distancing are all effective at decreasing RSV transmission. Maintaining use of PHSMs could provide a benefit against future outbreaks of those common respiratory viruses. Passive immunization with monoclonal antibody palivizumab should also be considered and administrated in high-risk patients during the RSV season. In addition to future investigations and the development of passive and active immunization, thorough surveillance of RSV variations is also of critical importance as we move into the post-COVID-19 era.

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Disclosure

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