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ORIGINAL PAPER

COVID-19 restrictions' impact on epidemiology of respiratory syncytial virus in south-eastern Poland

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ABSTRACT

Introduction: Respiratory syncytial virus (RSV) is a serious healthcare problem in Poland and one of the most common causes of lower respiratory tract infections in young children. During the pandemic, coronavirus disease 2019 significantly reduced the number of RSV cases due to restrictive measures to reduce social contact. The coronavirus disease 2019 pandemic led to widespread changes in health and social functioning, including restricted access to medical services and the closure of schools and workplaces. Non-pharmaceutical interventions significantly altered the seasonality and epidemiology of RSV. Recent years have shown a shift in the dynamics of RSV infections in children in the south-eastern region of Poland. The observed changes, particularly in the number of infections and related hospitalizations during autumn and winter, provide an opportunity to better understand RSV transmission patterns.

Material and methods: Analyses were conducted in R 4.3.2. (R Core Team, 2024). Descriptive statistics were used, and temporal trends were assessed with line-point plots based on absolute and relative monthly counts, adjusted for calendar days and leap years (lubridate package).

Results: This study included 1804 RSV cases with a median age of 5 months (interquartile range – IQR: 2–14, range 1–117). Males predominated (n = 1010, 55.9%). The median hospital stay was 6 days (IQR 4–8). Among hospitalized patients (n = 1466, 81.3%), diagnostic lag was most often zero (n = 1211, 82.6%), with only 55 cases (3.8%) exceeding 7 days (range 30–81).

Conclusions: These findings may support changes in the timing and criteria for immunoprophylaxis. Based on our results and similar data from other countries, we propose revising prophylactic recommendations to better protect children in the post-pandemic era.

KEY WORDS:
children, epidemiology, prophylaxis, COVID-19, respiratory syncytial virus.

INTRODUCTION

Respiratory syncytial virus (RSV) is a significant and major problem in acute lower respiratory tract infections in the pediatric population. Each year, RSV is responsible for almost 34 million cases worldwide in children under five years of age, 3.4 million (10%) hospitalizations and 66,000–199,000 deaths [1]. Morbidity and mortality risk is particularly pronounced in infants under six months of age, with this group accounting for 39% of RSV lower respiratory tract infection hospitalizations and over 50% of in-hospital deaths among children aged 0–60 months [2].

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Although RSV paralyses the pediatric wards' work system every year, there are no licensed vaccines available for children [1]. Before coronavirus disease 2019 (COVID-19), RSV season lasted from November to March, peaking in January and February in the Northern Hemisphere, while in the Southern Hemisphere from June to September [3].

During the pandemic, COVID-19 significantly reduced the number of RSV cases due to restrictive measures to reduce social contact [3]. Reports from Italy, Finland, Belgium, the UK, and the USA showed a sudden and earlier end of the RSV epidemic season starting from March 2020, compared to the previous years and almost no cases were detected in the following months [4–7]. That situation gave rise to the question of where the virus has gone and what impact it would have on the next RSV seasons. With the easing of restrictions in the world, emerging cases of RSV were observed in the following months, with the peaks out of regular seasons. The Australian study showed a significant increase in the incidence of RSV from September 2020 in Western Australia, which was greater than epidemic data of average cases from 2012 to 2019 [8]. Out-of-season waves of RSV cases were also observed in studies from the United Kingdom, South Africa and France [9–11]. The study from France reported a 3-month delayed RSV epidemic and a shift in the age of onset. On the other hand, the study showed a decrease in morbidity in the age group under six months and also lower rates in adult cases [11].

The aim of our study was to show how COVID-19 restrictions related to contact limits among children influence the epidemiology of RSV infection and hospitalization. We created the survey based on data (between 2018 and 2022) from four pediatric departments in south-eastern Poland.

MATERIAL AND METHODS

In order to assess the occurrence of RSV in children, we performed a detailed retrospective analysis of the medical records of pediatric patients with a positive test for RSV in the years 2018–2022. The study was conducted in 4 health centers in the south-eastern part of Poland: St. Louis Regional Specialised Children's Hospital in Cracow, St. Queen Jadwiga Clinical Provincial Hospital No. 2 in Rzeszow, Edward Szczeklik Specialist Hospital in Tarnow and the Health Care Center Hospital in Debica.

In the study, we assessed age, gender, length of hospitalization and the type of test confirming infection in children. The results of patients from 1 month to 10 years of age diagnosed with pneumonia, acute bronchiolitis and acute bronchitis caused by the RSV were included in the analysis. Epidemiological data, the period between the easing of COVID-19 restrictions, the time shift of RSV prevalence, and the nature of healthcare related to the limits were analyzed.

The analysis was carried out in R 4.3.2 (R Core Team, 2024). Descriptive statistics are provided for continuous and categorical variables, and expressed as mean (standard deviation), median (interquartile range – IQR), range or count and proportion (*n*, %).

Temporal trends were analyzed with visual examination based on line-point plots. Two different approaches were utilized: absolute counts in a given month per year, and relative monthly counts per year. The relative annual proportion was also adjusted for differences in the number of days per month and leap year functions from the lubridate package. We first calculated the absolute number of cases per month and year, and expressed the count relative to the number of days at a specific calendar date ("days_in_month" function), with subsequent calculation of the adjusted, relative number of RSV cases per year.

Despite the large number of analyzed cases and the use of data from several clinical centers, the study has certain limitations. The analysis included only hospitalized children, which may overestimate the clinical severity and does not reflect the full spectrum of RSV infections in the general population. The data originate from south-eastern Poland, which limits the generalizability of the findings on a national scale. During the COVID-19 pandemic, the availability of RSV testing was limited, and diagnostic procedures were implemented unevenly, which could have led to an underestimation of the actual number of cases. Comorbidities, infection severity, and information on immunoprophylaxis were not taken into account, making it difficult to assess individual risk factors. Furthermore, co-infections with other respiratory viruses, which could have influenced the frequency and severity of hospitalizations, were not analyzed. Additionally, the observed shift in RSV seasonality is still ongoing, so caution is warranted when interpreting the results as established trends.

RESULTS

This study involved 1804 RSV cases with a median (IQR) age of 5 (2–14) months and a range 1–117 months. Male (n = 1010, 55.98%) patients were more prevalent in this cohort.

Median duration of hospitalization was 6 (4–8) days. Diagnostic lag defined as time from the diagnostic test to hospital admission calculated for patients who required hospital admission (n = 1466, 81.26%) was zero (n = 1211, 82.60%). The range for the diagnostic lag was between –30 and 81, with only a total 55 (3.75%) individuals recorded with a lag of over 7 days.

Monthly case distribution across the study period is summarized in Table 1 and visualized in Figure 1. Overall, RSV activity showed a clear seasonal pattern in the pre-pandemic years (2018–2019), with peaks typically occurring in December–February. This pattern was disrupted in 2020, when a sharp reduction in RSV circula-

tion was observed. In contrast, 2021–2022 demonstrated an atypical resurgence with unusually early and intense activity, particularly between September and November 2021 and again in late 2022.

We divided patients into age groups of clinical interest: newborns (0–1 month; n = 159, 8.81%), infants (1–12 months; n = 1142, 63.30%), younger (12–36 months; n = 414, 22.95%) and older children (36–120 months; n = 89; 4.93%).

Overall, when comparing changes in the total number of RSV infections across different ages, infants appear to be at greatest risk, irrespective of the time of year (Figure 2). Despite the sample size of this study, there were certain months (spring–summer) in which a null or very low event count was recorded.

To address the potential bias associated with difficulty in reliable estimation of population proportions due to a low event count, we also examined the relative changes in incident RSV across groups only including time periods with at least 50 cases (Figure 3). Within these high-incidence months, infants remained the dominant affected population.

A temporal comparison of reported RSV case counts by patients' sex (Figure 4) indicates relatively comparable trends over time. Both sexes demonstrated the same temporal peaks and troughs, with no evidence of sex-specific shifts in seasonality or magnitude of outbreaks.

We also calculated relative changes in the annual rate of RSV cases after accounting for calendar-specific dif-

TABLE 1. Number of respiratory syncytial virus cases per month in a given year

Month	2018	2019	2020	2021	2022
January	97	84	77	4	19
February	89	90	95	3	3
March	68	55	42	2	6
April	27	19	3	3	4
May	3	3	0	3	2
June	1	2	0	4	4
July	0	0	0	8	5
August	0	0	0	52	5
September	0	0	0	119	3
October	0	2	0	220	27
November	14	5	3	130	145
December	51	30	0	41	132

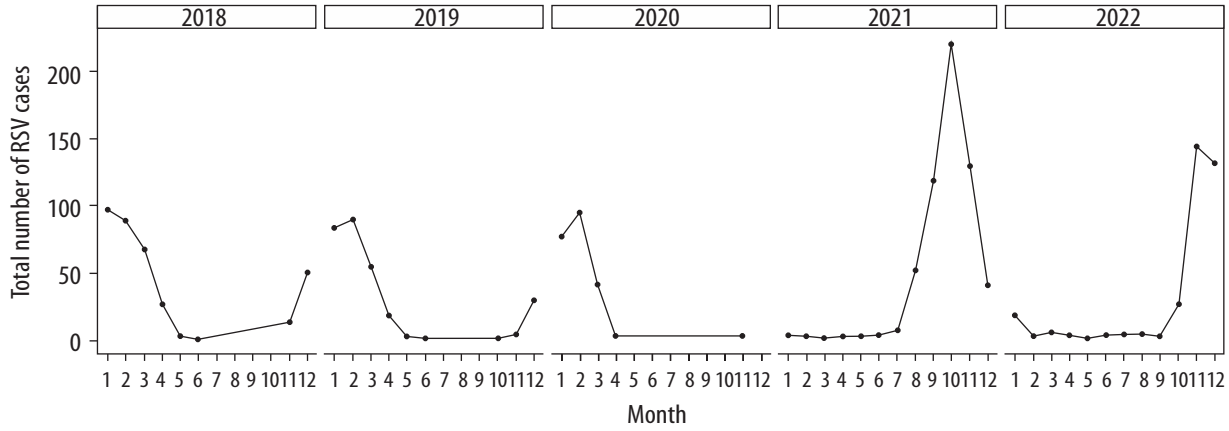

FIGURE 1. Incident cases of respiratory syncytial virus infection compared on a monthly time frame between 2018 and 2022
RSV – respiratory syncytial virus

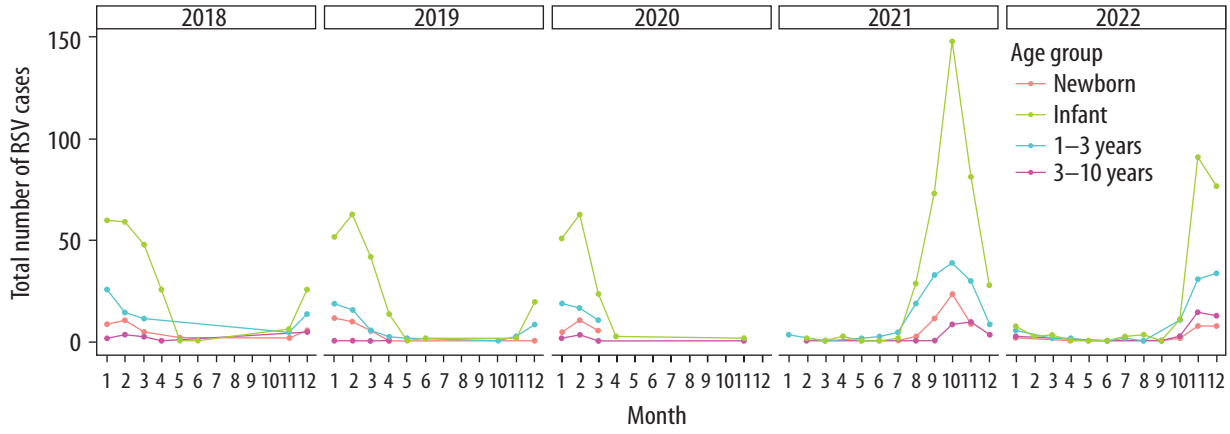

FIGURE 2. Incident cases of respiratory syncytial virus infection stratified by age group and compared on a monthly time frame between 2018 and 2022
RSV – respiratory syncytial virus

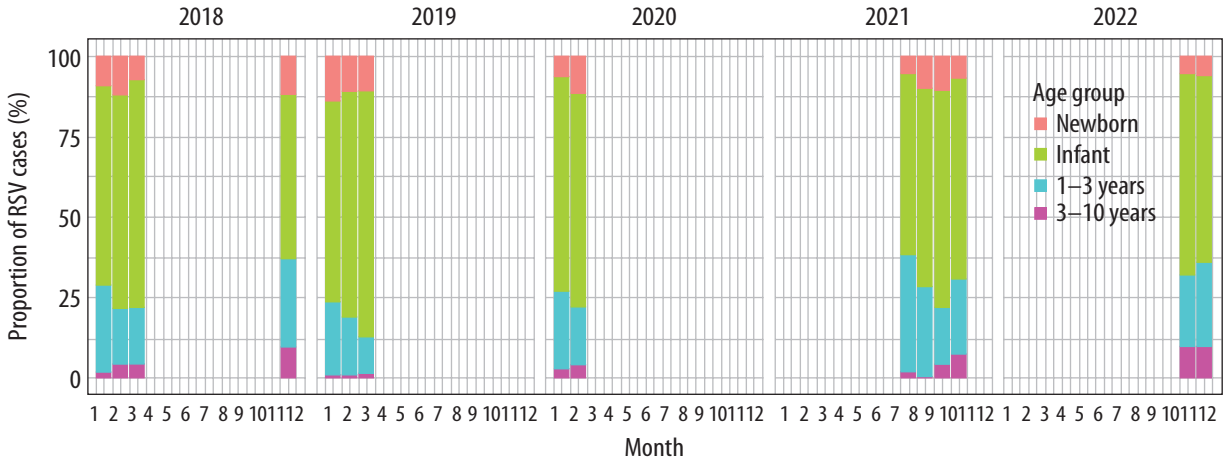

FIGURE 3. Relative number of cases of respiratory syncytial virus infections in specific age groups compared on a monthly time between 2018 and 2022 after exclusion of time points with < 50 cases

RSV – respiratory syncytial virus

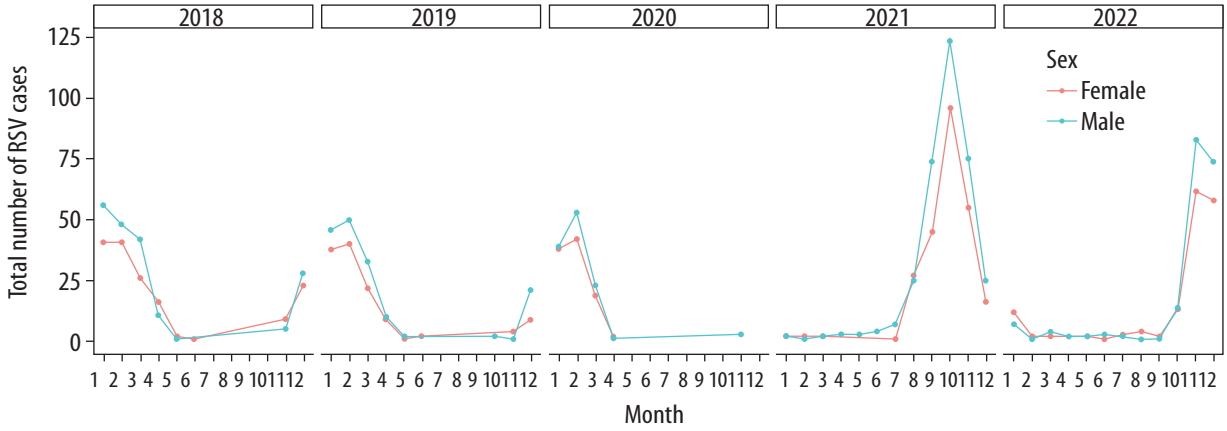

FIGURE 4. Incident cases of respiratory syncytial virus infection stratified by patients sex' and compared on a monthly time frame between 2018 and 2022

RSV – respiratory syncytial virus

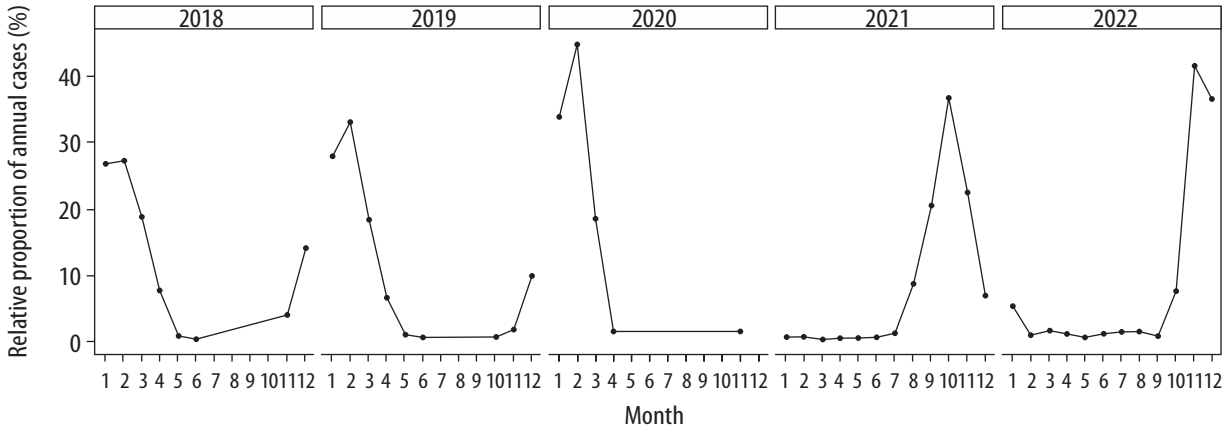

FIGURE 5. Temporal trends of respiratory syncytial virus infection based on annual calendar-weighted counts

Adjusted case counts for each month are represented by points. If no event was recorded at a given time (per month, per year), it was replaced with a conservative count of zero and no black point was illustrated.

ferences in days per month in a given year (e.g. days in February, leap year, *etc.*). This approach is considered as a theoretical adjustment of variable time of exposure to potential RSV infection. Of interest, in the years preceding the pandemic, February appears to be a month of particular susceptibility (Figure 5).

DISCUSSION

The first case of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in Poland was detected on March 4th, 2020, which resulted in the introduction of a nationwide lockdown on March 20th, 2020.

Restrictions consisted of limiting leaving the house and wearing masks. Also, schools and most public places were closed until the end of June 2020. Restrictions have been lifted for the summer holiday and the start of the next school year. However, after a drastic increase in COVID-19 cases, the country was divided into zones, and the restrictions depended on the number of cases in a given region. The second total lockdown was announced on March 27th, 2021 and lasted until the end of August 2021, but restrictions were rarely followed during the summer holiday period. All these non-pharmaceutical activities, which were implemented to flatten the number of COVID-19 hospitalizations, have also impacted the annual seasonality of RSV epidemiology [12].

The respiratory syncytial virus epidemic generally lasts from November to April in the Northern Hemisphere, where Poland is located [13]. Still, the seasonality must be divided into two periods: before and after implementing COVID-19 restrictions. According to the previous publication, a significant impact of COVID-19 on RSV epidemiology has been observed [7], as it was found in our research work.

Based on the data we gathered, we have noted a significant shift in the RSV season. In the years 2018/2019 (before the COVID-19 pandemic), the peak of RSV infections lasted from November to April. After the outbreak of the COVID-19 pandemic, an increased incidence of RSV cases was observed in the 2021/2022 years during the period from October to December. In addition, a significant reduction in the number of RSV cases during the pandemic was observed. According to the literature, this unexpected decrease in cases related to viruses other than SARS-CoV-2 during the COVID-19 pandemic was probably caused by the use of protective measures in the form of masks or protective gloves, as well as isolation, thus limiting the transmission of the virus [14].

We have also noted an increase in the number of RSV cases in all groups of age after the pandemic. However, the highest increase in the number of RSV infections was observed among children over 24 months of age. Similar data were obtained in studies conducted in Japan, Portugal and the United States [15, 16]. It is believed that reduced immunity to RSV among children may be due to a lack of exposure to RSV in the previous season. Moreover, the closure of kindergartens, nurseries and schools, as well as the introduction of remote learning, may have reduced the transmission of RSV, especially among older children [17]. Our data also coincide with data described in another publication from Poland (Warsaw), which shows non-RSV hospitalizations from October 2020 to June 2021 and earlier onset of the RSV epidemic, with the observation of first cases in July 2021 and peak in October 2021. Additionally, the authors observed a much more severe course of infections compared to the years before COVID-19 [18]. Similar data on postponing the RSV epidemic can be found in publications from Australia, the UK, and France [8, 9, 11]. The study from France reported a 3-month delayed RSV epidemic and also showed a shift in the age of onset. More children aged 6–11 months were infected compared to the previous outbreaks. Earlier research suggested that after a missed RSV season, the accumulation of the number of people susceptible to infection could lead to a high incidence in the upcoming 2021/2022 season [19].

Our research particularly shows the development of a compensatory epidemic, i.e., a phenomenon that consists of an increase in the number of cases at a particular time and in a certain area in a more significant number than expected, compared to the previous lower number of cases. It might be related to the increased number of people susceptible to infection and the expiry of herd immunity [20]. In our study, we observed that during October 2021, significantly more infections than in any month of the previous years (2018, 2019, 2020) were noted. The situation repeated itself in November 2022. Ultimately, the most common symptoms in children with RSV infection are cough, fever, labored breathing and wheezing [21]. Acute bronchiolitis in early childhood is associated with an increased risk of asthma, which can persist into early adulthood [22]. Additionally, children hospitalized with RSV infection in the first two years of life require more health care because of respiratory problems at the age of 2–4 years and, as reported by parents, have a poorer health-related quality of life [22].

The use of non-pharmaceutical methods to prevent infection is not possible in the long term. Currently, we have the possibility to implement immunoprophylaxis with palivizumab, and recently, a new monoclonal antibody – nirsevimab – has been approved in Europe. Palivizumab is indicated for the prevention of severe lower respiratory tract disease caused by RSV, requiring hospitalization in children at high risk of the disease caused by RSV, i.e., in children born at or before 35 weeks of gestation and less than six months of age, in children under two years of age, requiring treatment for bronchopulmonary dysplasia in the previous six months and children under two years of age with hemodynamically significant congenital heart disease [23]. The recommended intramuscular dose of palivizumab is 15 mg/kg, administered every month during the period of increased risk of disease, which in Poland, according to the summary of product characteristics, falls between October 1 and April 30. Moreover, high-risk children should receive subsequent doses monthly until the end of the RSV season. Our study showed a shift in the RSV season; therefore, a change in palivizumab use may be considered in order to prevent infections as effectively as possible, especially among children most at risk of the severe course.

In January 2023, the European Medicines Agency's Committee for Medicinal Products for Human Use issued a positive opinion on nirsevimab, recommending its approval for the prevention of RSV infection in infants and

young children at high risk of severe disease [24]. This opinion was based on the results of two phase III clinical trials, which demonstrated that nirsevimab effectively prevented RSV infections in this population [25]. Nirsevimab belongs to a group of drugs called monoclonal antibodies and targets the F protein of RSV, which is crucial for its ability to infect cells [26]. According to clinical trial results, nirsevimab has shown potent antiviral activity and has been well-tolerated in both healthy children and children with respiratory illnesses [26, 27]. The suggested administration of nirsevimab is a single injection of 50 mg through an intramuscular route for infants with a body weight of less than 5 kg and a single injection of 100 mg through an intramuscular route for infants with a body weight of 5 kg or more [28]. It is recommended that nirsevimab be given before the commencement of the RSV season or from birth for infants born during the RSV season [28]. According to the currently implemented infection prevention program for RSV in Poland, prophylaxis is recommended for children up to 1 year of age who were born before the 28th week of gestation or have been diagnosed with bronchopulmonary dysplasia, as well as for children up to 6 months of age born in the 29th to 32nd week of gestation [29]. Recently, an expert group recommended prophylaxis for children under 24 months of age with the following conditions: bronchopulmonary dysplasia, significant congenital heart disease, cystic fibrosis and neuromuscular disorders [29].

Moreover, clinical studies confirm promising results of RSV vaccines in both adults and children. It has been observed that the vaccine prevents lower respiratory tract diseases and acute respiratory illnesses associated with RSV in adults aged 60 years and older without raising significant safety concerns [30]. However, further research is necessary to fully understand the long-term effectiveness and safety of the RSV vaccine. Specifically, analysis of adverse effects and monitoring of long-term protective effects should be conducted to obtain a comprehensive assessment of the vaccine's value. Optimal dosing and vaccination schedules for RSV are also crucial in optimizing protection against the virus in children. Studies on optimal vaccination strategies can contribute to establishing best practices and guidelines in this regard [31]. The introduction of an RSV vaccine can have a significant impact on public health, particularly among the most susceptible groups, such as children at risk of severe complications. Research, effectiveness monitoring, and widespread implementation of vaccinations can significantly reduce the burden of RSV infections in the pediatric population. In this context, maternal vaccination against RSV during pregnancy elicits an effective immune response, leading to the production of neutralizing antibodies in maternal serum. These antibodies are efficiently transferred through the placenta, suggesting protective potential against RSV-associated lower respiratory tract diseases in infants [31]. These findings underscore the importance of RSV vaccination in protecting the population against viral infections. Studies on long-term effectiveness, safety, optimal dosing, and impact on public health are necessary for a comprehensive understanding of the value and potential of this vaccine in reducing the burden of RSV in the pediatric and older adult populations.

Last but not least, our study showed a shift in the seasonality of RSV cases and an increase in the number of cases, especially in the age group over 24 months, due to the outbreak of the COVID-19 epidemic. The lack of exposure to RSV in the earlier season due to COVID-19 infection prevention measures such as the use of masks, isolation and school closures can be considered as probable reasons for this phenomenon. Therefore, there is a need to extend the inclusion criteria and increase the accessibility and frequency of administration of the aforementioned monoclonal antibodies – palivizumab and nirsevimab. It is worth considering extending the monthly prophylaxis with palivizumab to infants at risk of developing RSV to prevent RSV infections due to the increase in cases after the COVID-19 epidemic. Moreover, taking into account our research findings and publications from other countries confirming the shift in RSV infection age after lifting COVID-19 restrictions, we propose discussing the extension of palivizumab administration to 24 months of age and the earlier use of the drug than it was currently recommended (from October 1st to the end of April).

An important issue affecting the correct analysis of the test is the time in which the proper diagnosis of RSV infections had to be faced. At all study sites, RSV infection was diagnosed by antigen or polymerase chain reaction RSV testing. It should be noted that the availability of the above diagnostic methods was limited. This was due to the increase in the burden of diagnostic techniques of hospitals towards the spreading COVID-19 pandemic than RSV. Such circumstances resulted in partial diagnostics, overlooking potential patients with the infection discussed in this paper. The data concern several cities (Cracow, Tarnow, Debica, Rzeszow) in the south-eastern part of Poland, including some pediatric patients with confirmed RSV infection from this region. The epidemiological shift curve is still active, which is also a barrier to correct statistics. Nevertheless, we believe that a large number of patients hospitalized in major treatment centers dedicated to RSV infection, supplemented with a proper statistical analysis in a well-chosen period, outweighs the aspects limiting the study.

CONCLUSIONS

Taking everything into account, the emerging possibilities for RSV prevention, such as maternal vaccination providing immunity to infants in their early months of life, nirsevimab offering protection against infection with a single dose, and potential future vaccines, con-

stitute a range of actions that can significantly limit the spread of the RSV virus. This would greatly reduce the number of hospitalizations and complications later in life. We suggest the continued need to monitor the epidemiological situation so that recommendations for preventing RSV infections can be developed based on the new prophylaxis possibilities.

DISCLOSURES

1. Institutional review board statement: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Bioethics Committee of the University of Rzeszów (protocol code No. 2022/104, of 07/12/2022).
2. Assistance with the article: None.
3. Financial support and sponsorship: None.
4. Conflicts of interest: None.

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