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Milena Pogonowska[1], Aneta Guzek[2], Agnieszka Gościńska[1], Agnieszka Rustecka[1], Bolesław Kalicki[1]

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Compensatory epidemic of RSV infections during the COVID-19 pandemic. An analysis of infections in children hospitalised in the Department of Paediatrics, Paediatric Nephrology and Allergology of the Military Medical Institute in Warsaw in 2020–2021

Epidemia wyrównawcza zakażeń RSV podczas pandemii COVID-19. Analiza zakażeń u dzieci hospitalizowanych w Klinice Pediatrii, Nefrologii i Alergologii Dziecięcej Wojskowego Instytutu Medycznego w Warszawie w latach 2020–2021

[1] Department of Paediatrics, Nephrology and Child Allergology, Military Institute of Medicine, Warsaw, Poland
[2] Microbiology Laboratory of the Department of Laboratory Diagnostics, Military Institute of Medicine, Warsaw, Poland
Correspondence: Milena Pogonowska, Department of Paediatrics, Paediatric Nephrology and Allergology, Military Institute of Medicine, Szaserów 128, 04-141 Warsaw, Poland, tel.: +48 261 817 263, e-mail: mpogonowska@wim.mil.pl

ORCID iDs
1. Milena Pogonowska https://orcid.org/0000-0002-7031-8538
2. Aneta Guzek https://orcid.org/0000-0002-6394-8451
3. Agnieszka Gościńska https://orcid.org/0000-0003-4847-8903
4. Bolesław Kalicki https://orcid.org/0000-0003-1606-5100

Abstract

Seasonal outbreaks of respiratory syncytial virus are common among young children and represent an important clinical problem. The infection can affect all floors of the respiratory system. Respiratory syncytial virus is highly infectious and is the most common aetiological agent of bronchiolitis. It is estimated that 90% of children develop respiratory syncytial virus infection by the age of 2 years. In Poland and other countries of the northern hemisphere, these infections usually occur between October and May, with a peak in January–February. During the global COVID-19 pandemic, a significant change was observed in the epidemiology of respiratory syncytial virus infections in Europe and worldwide. The massive use of non-pharmacological interventions, such as closing nurseries, kindergartens, limited interpersonal contact, social distancing, strict hygiene rules and the use of protective masks, resulted in the absence or episodic occurrence of many seasonal infections, including those of respiratory syncytial virus aetiology, in 2020. In 2021, a so-called compensatory epidemic of syncytial virus aetiology was observed, i.e. a significant increase in the incidence associated with the extinction of collective immunity and an increasing proportion of susceptible individuals. The aim of the present study was to retrospectively analyse the incidence of respiratory syncytial virus infections in children hospitalised in the Department of Paediatrics, Paediatric Nephrology and Allergology of the Military Institute of Medicine in Warsaw in the years 2020–2021. We also discussed the prevention and treatment of infections, as well as the association of bronchiolitis with the development of asthma in children.

Keywords: respiratory syncytial epithelial virus, RSV, COVID-19 pandemic, bronchiolitis, asthma

Streszczenie

Sezonowe epidemie syncytialnego wirusa nabłonka oddechowego (*respiratory syncytial virus*, RSV) są powszechne wśród małych dzieci i stanowią istotny problem kliniczny. Zakażenie RSV może dotyczyć wszystkich pięter układu oddechowego. Wirus RSV charakteryzuje się wysoką zakaźnością i jest najczęstszym czynnikiem etiologicznym zapalenia oskrzelików. W związku z rozpowszechnieniem tego wirusa szacuje się, że do ukończenia 2. roku życia 90% dzieci przebywa infekcję RSV. W Polsce i innych państwach półkuli północnej zachorowania spowodowane RSV występują zwykle w okresie od października do maja, ze szczytem w styczniu-lutym. Podczas globalnej pandemii COVID-19 epidemiologia zakażeń RSV uległa znacznej zmianie w Europie i na świecie. Masowe zastosowanie interwencji niefarmakologicznych, takich jak zamknięcie żłobków,

przedszkoli, ograniczenie kontaktów międzyludzkich, stosowanie dystansu, przestrzeganie zasad higieny oraz noszenie maseczek ochronnych, spowodowało, że w 2020 roku wielu infekcji sezonowych, w tym o etiologii RSV, nie odnotowano lub pojawiały się one epizodycznie. W 2021 roku zaobserwowano tzw. epidemię wyrównawczą RSV, czyli znaczny wzrost zachorowań związany z wygasaniem odporności zbiorowej i wzrastającym odsetkiem osób podatnych na zakażenie. Celem niniejszej pracy jest retrospektywna analiza występowania zakażeń RSV u dzieci hospitalizowanych w Klinice Pediatrii, Nefrologii i Alergologii Dziecięcej Wojskowego Instytutu Medycznego w Warszawie w latach 2020–2021. Podjęto również dyskusję na temat profilaktyki i leczenia zakażeń RSV, a także związku *bronchiolitis* z rozwojem astmy u dzieci.

Słowa kluczowe: syncytialny wirus nabłonka oddechowego, RSV, pandemia COVID-19, zapalenie oskrzelików, astma

INTRODUCTION

Viruses are the main cause of respiratory tract infections in children. Respiratory syncytial virus (RSV) has a special affinity for airway epithelial cells. Each year, 2.7–3.8 million children under 5 years of age are hospitalised due to RSV infection worldwide, of which nearly 150,000 do not survive[1–3].

RSV infection can involve all floors of the airways. Clinical manifestations depend on age, ranging from mild upper respiratory tract infections (URTIs) to severe lower respiratory tract infections (LRTIs). Acute LRTIs include bronchiolitis and pneumonia, which are characterised by a high risk of severe complications, including respiratory failure, and the need for hospital stay[4]. Bronchiolitis mainly affects children under 2 years of age and presents with expiratory dyspnoea, expiratory wheezing and tachypnoea. Other accompanying symptoms include restlessness, agitation, feeding difficulties, tachycardia, and even cyanosis in some cases[5,6]. Apnoea, i.e. breathing pauses longer than 15–20 seconds, is a typical manifestation of the infection in premature neonates and infants under 3 months of age[7,8].

Other known pathogens causing bronchiolitis include type 1 parainfluenza virus, influenza A virus, rhinoviruses, adenoviruses and coronaviruses. However, RSV is by far the most common etiological agent. It is estimated that 90% of children develop respiratory syncytial virus infection by the age of 2 years[9,10]. The peak incidence is between 2 and 3 months of age, which is related to the decrease in maternal IgG antibodies[11]. A history of infection does not protect against reinfection. It is estimated that 10–20% of children up to the age of 5 years develop several RSV reinfections throughout life. Reinfections are usually mild, but only 1% of children remain asymptomatic. Reinfections in older children are usually milder and have a diverse clinical picture, ranging from upper airway inflammation, otitis media and acute laryngitis to bronchitis[6,12].

Neonates and infants born prematurely with extremely low birth weight (ELBV), bronchopulmonary dysplasia (BPD) and haemodynamically significant heart defects are at the highest risk of severe disease. Infants born prematurely with very low birth weight (VLBW) also have a significantly higher risk than those born at term[13].

Worldwide, the incidence of RSV is seasonal. In Poland and other northern hemisphere countries, RSV infections usually occur from October–November to April–May, with a peak in January–February (about 90% of diagnosed cases of RSV infection in young children), whereas in the southern hemisphere the infections usually occur from May to September, with a peak in May, June or July. In tropical and semi-tropical climates, seasonal outbreaks are usually associated with the rainy season.

RSV is highly infectious, spreading by the droplet route during cough or sneezing and by direct contact, such as touching contaminated surfaces. Family members are the most common source of infection for infants and young children. The incubation period of the virus (from infection to symptom onset) lasts 2–8 days, and then (after about 8 days) it is excreted from the body. RSV multiplies in the respiratory epithelial cells of the nasopharynx and then migrates to the lower airways. Special cases are newborns, infants and immunocompromised persons, in whom the period of virus shedding, and thus infectivity, can be extended by up to 4 weeks[6]. Infected cells fuse to form characteristic syncytia. The main pathological effect of the virus is due to the involvement of the epithelium lining the airways. The host immune response leads to damage of the infected cells. Necrosis of the bronchial and bronchiolar epithelium results in overproduction of secretions consisting of mucus, fibrils and dead tissue, impairing airway patency and causing bronchial hyperresponsiveness[10].

Syncytial respiratory virus is an enveloped, cytoplasmic, single-stranded RNA virus of 150–300 nm. It belongs to the family *Paramyxoviridae* of the genus *Pneumovirus*. Ten genes encoding viral proteins have been identified in its structure, including transmembrane proteins (G, F, SH), with the G protein responsible for attachment to the host cell surface and the F protein responsible for fusion, as well as capsid proteins (N and P), the L protein that functions as an RNA polymerase, intermediate layer-forming proteins (M1 and M2) and non-structural proteins (NS1 and NS2) that reduce interferon production and apoptosis, thereby promoting RSV replication. Based on variations in antigen composition, nucleotide and amino acid sequence of the G protein, two types of RSV are distinguished: A and B[12,14]. RSV-A is associated with a more severe clinical course of the disease.

For laboratory diagnosis, RSV is difficult to isolate and culture. The presence of the viral genome in infected cells or nasal washings (recommended material) can be confirmed

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Indications for hospitalisation of a child diagnosed with bronchiolitis
Agitation
Apnoea
Tachypnoea 60/min
O_2 saturation <92%
Age under 12 months, particularly under 3 months
Eating or drinking problems
Comorbidities
Prematurity <32 weeks gestation
Poor economic conditions of the family

Tab. 1. Absolute indications for hospitalisation in children diagnosed with bronchiolitis based on the 2016 recommendations for the management of community-acquired respiratory infections

by molecular techniques based on real-time polymerase chain reaction (RT-PCR). Commercial tests for the detection of viral antigen by immunochromatography, immunofluorescence and ELISA are also available[15].

AIM OF THE STUDY

The aim of this study was to analyse RSV infections in children hospitalised in the Department of Paediatrics, Paediatric Nephrology and Allergology at the Military Institute of Medicine in 2020–2021, coinciding with the COVID-19 (coronavirus disease 2019) pandemic.

MATERIALS AND METHODS

Medical records of patients positively tested for RSV infection and hospitalised in the Department of Paediatrics, Paediatric Nephrology and Allergology of the Military Institute of Medicine in 2020–2021 were retrospectively analysed in detail. Children with a diagnosis of bronchiolitis, pneumonia or obstructive bronchitis of RSV aetiology were included in the study. Nasopharyngeal aspirate, usually taken before admission to the ward, was used for virological assessment. The presence of virus in the aspirate was confirmed with a one-step, colorimetric, immunochromatographic Rapid-VIDITEST RSV test[16]. The test and its interpretation were performed according to the manufacturer's instructions. The sensitivity and specificity of the test were 95% and >99%, respectively. During the 2020–2021 infection season, 61 children aged up to 47 months (median: 4 months, interquartile range, IQR: 8 months) were included in the study. Indications for hospitalisation are listed in Tab. 1. The clinical and laboratory status of the patients was assessed both on admission and repeatedly during hospital stay. The following variables were recorded: dyspnoea features, saturation, C-reactive protein (CRP), leucocytosis and the presence of inflammatory changes in the pulmonary parenchyma on chest radiography (X-ray) or ultrasound (US). Furthermore, the treatment process was evaluated, including the percentage of children requiring oxygen therapy, intravenous steroid drugs, inhaled steroid drugs, bronchodilators and antibiotic therapy. The mean duration of hospitalisation was also summarised. The number of cases per month, gender distribution among patients and some risk factors for RSV infection, i.e. low birth weight, prematurity or having many siblings, were also analysed.

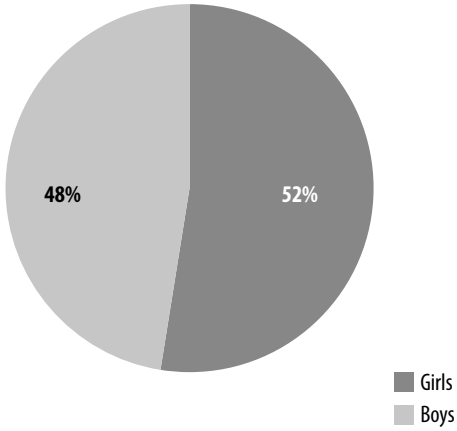

Fig. 1. Distribution of RSV infections in the period July–October 2021 by gender (number of patients)

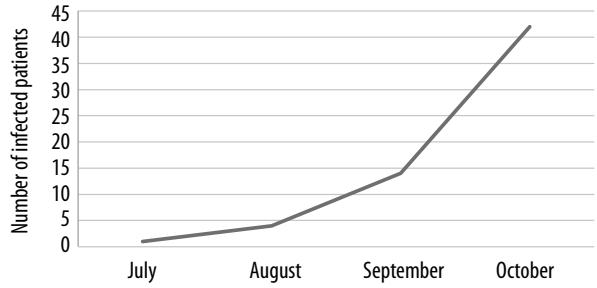

Fig. 2. Distribution of RSV infections by month in 2021

RESULTS

In 2020–2021, 61 (27%) out of 218 patients were tested positive for RSV infection (52% girls and 48% boys).

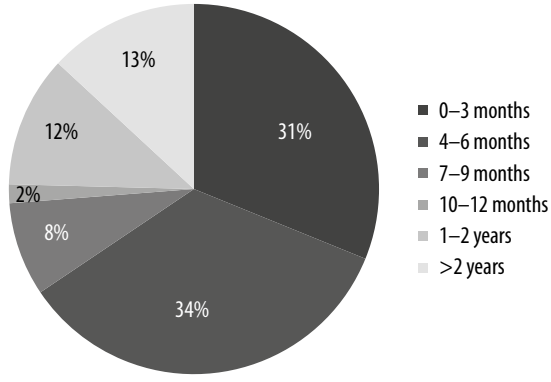

Fig. 3. Distribution of RSV infections in July–October 2021 by age

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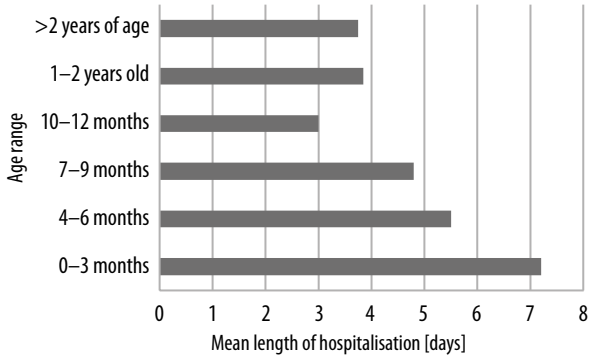

Fig. 4. Average length of hospitalisation for RSV infection by age in 2021

The distribution of infections by gender is shown in Fig. 1. From October 2020 to June 2021, there were no hospitalisations due to RSV infection in the Department of Paediatrics, Paediatric Nephrology and Allergology. The first cases appeared in July 2021 and gradually increased in number, reaching a peak in October of the same year, when 42 patients were hospitalised (69% of the cases of disease). The total number of infections by month is shown in Fig. 2. Of the children hospitalised, 65% were under 6 months of age. The distribution of infections by age is presented in Fig. 3. The length of hospital stay depended on the child's age, clinical course of the disease and co-occurrence of complications. The mean length of hospitalisation was 5.5 days with a decreasing tendency in older children (Fig. 4). In laboratory tests, elevated CRP levels were noted in 11 (18%) children and the mean number of white blood cells in 1 μL of peripheral blood was 10,500. In relation to age norms, leucocytosis was found in only 6 (9.84%) children, of whom 4 (6.56%) had coexisting elevated CRP levels. Oxygen therapy was needed in 75.41% of children due to clinical dyspnoea and/or abnormal saturation measurements (<92%). Bronchodilators were used in 55 (90.16%) and inhaled corticosteroids in 52 (85.2%) patients. Intravenous corticosteroids were used in more than half (55.74%) of children hospitalised for RSV infection.

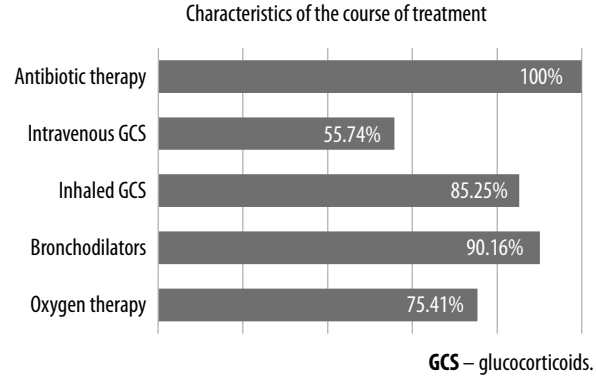

Fig. 5. Treatment in children hospitalised for RSV infection in the 2020–2021 infection season

A severe clinical course and the need for further treatment in the Intensive Care Unit was reported in 1 (1.64%) male child aged 3 months, burdened with additional risk factors, including a heart defect. Among children with bronchiolitis, complications in the form of pneumonia confirmed by X-ray or ultrasound were observed in up to 55 (90.16%) patients. Children without complications were initially treated only symptomatically, but treatment outcomes were unsatisfactory in each case, as a result of which antibiotic therapy was used in all children. The applied treatment is presented in Fig. 5. Features of atopy (bronchial asthma, inhalatory allergy, food allergy) were described in anamnesis in 10 (16.4%) children, while a positive family history of allergic diseases was found in 12 (19.67%) children. Of the hospitalised children, 49 (80.33%) had siblings and 9 (14.75%) patients were born before 37 weeks gestation.

DISCUSSION

Respiratory syncytial epithelial virus is a seasonal virus. The peak of RSV infections occurs in the autumn and winter months[12,17]. A significant decrease in respiratory viral illnesses other than severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was most likely due to the widespread requirement to use masks and social distancing, was an unexpected outcome of the COVID-19 pandemic[18,19]. In 2020, reports from around the world showed a 98% decrease in RSV infections[20]. In a study published in December 2020, Baker et al. predicted altered RSV epidemiology after a long period of non-pharmacological interventions among the public (isolation, social distancing, use of personal protective equipment). This analysis indicated that the cumulative number of susceptible individuals after the missed RSV season could lead to an unusually high incidence in the upcoming 2021/2022 season[21]. These data coincide with observations at the Department of Paediatrics, Paediatric Nephrology and Allergology of the Military Institute of Medicine, according to which there has been a shift in the season of RSV infections. In 2020, one patient was hospitalised due to RSV bronchiolitis, while in the following year, the first case was recorded in July. In September and October, a total of 56 hospitalisations due to RSV infection were registered, which resulted in full occupancy of the ward and difficulties in providing all patients with access to oxygen therapy. For the purpose of this article, patients hospitalised until the end of October 2021 were included in the study group. It is likely that this month represented the peak incidence of the described infectious season and that the total number of cases will ultimately be higher than in previous years, but continued follow-up is needed to draw definitive conclusions.

This trend differs significantly from the expected seasonal pattern, according to which the peak of RSV infections in the northern European climatic zone is in January and February[12,17]. This was also confirmed by observations in the Department of Paediatrics, Paediatric Nephrology and

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Allergology in previous years[22,23]. The shift in the infection season and the significant increase in cases in 2021 can be considered as a compensatory epidemic, i.e. occurrence of a higher number of cases than expected against the previous low number of cases at a certain time and in a certain region. This is associated with the extinction of collective immunity and an increasing proportion of susceptible individuals[24]. The results presented are in line with observations from Western Australia, the United States, Japan and Switzerland[18,20,25,26]. As in the cited publications, the data obtained by the authors indicate a more severe course of the disease in younger infants, as well as an increased incidence in the older age group (mainly 2–3-year-olds) compared to previous seasons. Reduced immunity due to lack of exposure to RSV in the earlier season may be considered as one of the likely causes. The closure of kindergartens, nurseries and distance learning may have resulted in a lower spread of the disease among older children[26]. Based on the early results presented in this publication, we are not able to predict the exact height of the RSV peak or the duration of the disease, but we can infer the need to plan in advance for the number of paediatric beds in hospitals with access to oxygen.

Additionally, it is worth considering extending monthly prophylaxis with palivizumab in infants at risk of severe RSV disease to provide continued protection during this unexpected increase in incidence[18]. Palivizumab is a humanised monoclonal IgG antibody, showing potent virus neutralising and fusion inhibitory activity for both RS virus subtypes (A and B). It is administered intramuscularly at a dose of 15 mg/kg monthly during the time of an increased risk of disease, which, according to the Summary of Product Characteristics, is from 1 October to 30 April. In Poland, palivizumab prophylaxis, due to its high cost, is used within the reimbursed drug programme in newborns and infants born up to 33 weeks of gestation, including all children with diagnosed bronchopulmonary dysplasia[27]. According to the recommendations of scientific societies, it would be additionally worthwhile to extend the prophylaxis to include infants with congenital, haemodynamically significant heart diseases, but reimbursement is still awaited in Poland[28].

Currently, there is no causal treatment for RSV infections, but preliminary reports of phase III clinical trials on vaccines sound very promising. There are currently two trials in Poland, which include individuals over 60 years of age, with the main aim of assessing the safety and efficacy of vaccination in the prevention of moderate-to-severe lower respiratory tract disease caused by RSV[29,30]. This is important in the context of preventing the spread of infection in the population and gives hope for the registration of a vaccine for a younger age group in the future.

The treatment of RSV infections remains a major clinical challenge. According to the available guidelines of the National Programme for the Protection of Antibiotics, symptomatic treatment is recommended, with proven efficacy shown only for oxygen therapy, mechanical ventilation and fluid therapy[28,31]. The clinical course of bronchiolitis resembles asthma exacerbation, hence bronchodilators, as well as inhaled and intravenous corticosteroids are often used off-label. Antibiotics are not routinely recommended for bronchiolitis unless there is concern for complications such as secondary bacterial pneumonia or respiratory failure, but are nevertheless often used[32]. In our group of patients, antibiotic therapy was used in all children with confirmed inflammatory lesions in the lung parenchyma or poor general condition and lack of response to symptomatic treatment. The most common lesions seen on X-ray were consolidations, peribronchial thickening and/or interstitial infiltration. Ultrasonographic features of pneumonia included subpleural consolidations and B-line artefacts[33]. According to the literature, antibiotics are used in 34–99% of RSV infections in children, mainly for the prevention of bacterial superinfection[34].

Acute bronchiolitis in early childhood is associated with an increased risk of asthma, which may persist into early adulthood. There is an ongoing debate as to whether bronchiolitis is the cause of airway damage that results in subsequent episodes of wheezing and the development of asthma, or whether it is related to individual susceptibility. It seems that the first episode of severe bronchiolitis in children under 2 years of age is an early prognostic factor of susceptibility to asthma and may therefore motivate the development of preventive strategies for this disease[35,36].

CONCLUSIONS

1. The shift in the season of RSV infections from 2020 to 2021 is most likely related to the use of non-pharmacological methods of prevention, such as increasing social distance, the use of masks, and the closure of nurseries, kindergartens and schools.
2. The number of RSV infections has increased not only in infants but also in nursery and preschool children.
3. The course of RSV infections in the 2020–2021 season was more severe than that observed in previous years. Pneumonia was the most common complication.

Conflict of interest

The authors declare no financial or personal relationships with other persons or organisations that could adversely affect the content of the publication and claim rights to this publication.

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