This is an Accepted Manuscript for Epidemiology & Infection. Subject to change during the editing and production process.
DOI: 10.1017/S0950268824000724

Epidemiology of Respiratory Syncytial Virus in hospitalized children before, during and after the COVID-19 lockdown restriction measures in Greece

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Summary

COVID-19 pandemic modified the epidemiology and the transmission of Respiratory Syncytial Virus (RSV). We collected data on RSV positivity and incidence using a rapid antigen immune chromatography test from children hospitalized in the largest tertiary pediatric hospital in Greece before (2018-20, period A), during (2020-21, period B) and after (2021-23, period C) the COVID-19 lockdown. A total of 9508 children were tested for RSV. The RSV positivity(%) during the whole study period was 14.1% (1337/9508) – 17.6% (552/3134) for period A, 2.1% (13/629) for period B and 13.4% (772/5745) for period C ($p<0.001$). The mean age (±SD) of RSV positive children among the three periods were: A:5.9 (±9.3), B:13.6 (±25.3) and C:16.7 (±28.6) months ($p<0.001$). The peak of RSV epidemiology was shifted from January-March (period A) to October-December (period C). The RSV in-hospital incidence per 1000 hospitalizations in pediatric departments was: A:16.7, B:1.0, C:28.1 ($p<0.001$) and the incidence in ICU was: A:17.3, B:0.6, C:26.6 ($p<0.001$). After the diminished circulation of RSV during the COVID-19 lockdown period, a significant increase in RSV incidence was observed. A change in epidemiological patterns was identified after the end of the lockdown with an earlier seasonal peak and an age shift of increased RSV incidence in older children.

https://doi.org/10.1017/S0950268824000724 Published online by Cambridge University Press

Introduction

Respiratory Syncytial Virus (RSV) is an RNA virus within the Paramyxoviridae family [1]. Although it can cause respiratory infections in all age groups, it is a major cause of bronchitis, bronchiolitis, and pneumonia in children, especially under 5 years of age [2-3]. RSV is transmitted through human-to-human contact via respiratory droplets and can also be spread through dried respiratory secretions, with an incubation period ranging from 2 to 8 days [4].

In 2019, RSV was associated with 33 million cases of respiratory infections worldwide, leading to hospitalization of 3.6 million children aged 0 to 60 months, with nearly 27000 in-hospital fatalities [5]. The burden of RSV is exacerbated by factors such as prematurity, younger age, and low socioeconomic status [5-7].

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) caused a global pandemic with significant morbidity and mortality [8-10]. To contain the transmission of SARS-CoV-2, non-pharmaceutical interventions such as social distancing, mask-wearing, and lockdowns were implemented [11]. These interventions not only reduced the spread of SARS-CoV-2 but also had a notable impact on the transmission of other respiratory viruses, like RSV [12]. Due to the COVID-19 restrictions, off-season RSV epidemics have been observed [13-14].

In Greece, the first COVID-19 patient was detected on February 26th, 2020. The Greek government suspended educational institutions on March 11th, 2020. Stricter measures were implemented, leading to a general lockdown on March 23rd, 2020. After experiencing a second wave of the pandemic, educational institutions were eventually reopened in April 2021 [15].

Before the COVID-19 pandemic and the suspension of educational institutions, RSV transmission in Greece typically followed a seasonal pattern [16]. In Greece only the multiple doses monoclonal antibody (palivizumab) is available for high-risk babies. Given the licensure of the one-dose RSV monoclonal antibodies and RSV vaccines for pregnant women and adults [17], surveillance of data regarding RSV epidemiology could provide valuable guidance for public health decisions.

The objective of this study was to examine the potential change of RSV epidemiology in the period before, during and after the COVID-19 lockdown restriction measures in a large hospitalized pediatric population in Greece.

https://doi.org/10.1017/S0950268824000724 Published online by Cambridge University Press

Materials and Methods

A retrospective observational study was carried out at "Aghia Sophia" Children's Hospital in Athens, from January 1st, 2018, to May 31st, 2023. The research ethical clearance approval letter was obtained from the Research Ethics Committee at the "Aghia Sophia" Hospital, in November 2023 with protocol number: 20818/21.09.2023. "Aghia Sophia" is the largest pediatric hospital in Greece (750 beds), serving approximately 40% of the pediatric population in the Athens metropolitan area.

The study population consisted of all children from birth until 16 years of age who had been hospitalized during the study period. Children, who were hospitalized with lower respiratory symptoms, had been tested for RSV via a rapid antigen immune chromatography test in nasopharyngeal wash specimens (RSV Respi-Strip, Coris-Bioconcept). Data were retrieved from the microbiology laboratory archive. Children over 16 years, children with inadequate samples for testing or with duplicate tests within a month were excluded from the study. Additional data about the overall number of hospitalizations during the total study period from pediatric clinics and intensive care units (ICU) were retrieved from the Hospital's Statistical Department.

The overall study period was divided in three subperiods concerning the COVID-19 lockdown restrictions measures; before (January 2018 – February 2020, period A), during (March 2020 – June 2021, period B) and after (July 2021 – May 2023, period C) the COVID-19 lockdown.

For each period RSV positivity rate (%) was calculated by dividing the total number of RSV-positive samples by the total number of samples examined in the laboratory during the respective time period. RSV in-hospital incidence per 1000 hospitalizations was also calculated for each period by dividing RSV-positive samples by the total number of hospitalizations during the respective time period.

Subsequently data of each period was divided into four subperiods: January-March (I), April-June (II), July-September (III) and October-December (IV). The corresponding positivity rate and incidence of RSV for each period were calculated and compared with each other. The data were also analyzed for each age group separately to examine the possible effect of the age in the observed differences between the subperiods the comparisons of the positivity rates.

For the statistical analysis, initially, Pearson's chi-squared test or Fisher's exact test were used to compare data among study subperiods. ANOVA test was conducted to compare the mean age between

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the three periods. Logistic regression was also performed to estimate the possible effect of children's age and each subperiod to the RSV positivity rate.

Statistical significance was set at 0.05. Statistical analysis was conducted using SAS statistical analysis software (SAS v9.4).

Results

During the study period a total of 10647 children were tested for RSV. From them, 1139 children were excluded due to inadequate sample for testing or duplicate tests within a month. Finally, 9508 children, with a mean (±SD) age of 21.7 (±33.6) months, were included in the analysis. Among them, 826 (8.7%) were newborns (<1 month), 4851 (51.0%) were infants (1 month to 1 year), 2058 (21.6%) were toddlers (>1 year to 3 years), 1023 (10.8%) were at preschool age (>3 years to 6 years), 490 (5.2%) were at school age (>6 years to 11 years), and 260 (2.7%) were adolescents (>11 years to 16 years). The age distribution between the three periods was: A: 3134 children with a mean (±SD) age of 10.6 (±20.3) months, B: 629 children with a mean (±SD) age of 13.8 (±24.4) months and C: 5745 children with a mean (±SD) age of 28.6 (±38.3) months ($p<0.001$). The observed increment of the age between the three periods was also confirmed through logistic analysis where it was found that for one year more in the age the risk to be in a later period was more than 50% (OR=1.69, [95% CI=1.47-1.95], p-value=0.0001).

The RSV positivity (%) during the total study period was 14.06% (1337/9508) and 741 (55%) were male. RSV positivity (%) during the three study periods were: A: 17.6% (552/3134), B: 2.1% (13/629) and C: 13.4% (772/5745) ($p<0.001$). The mean (±SD) age of RSV positive children among the three study periods were: A: 5.90 (±9.30), B: 13.55(±25.26) and C: 16.71 (±28.58) months ($p<0.001$).

The specific RSV positivity (%) per age group is presented in Table 1 and Figure 1. Comparing the three study periods for each age group statistically significant differences were detected for ages 0-1month; A: 21.0%, B: 2.8%, C: 30.1% ($p<0.001$), 1month-1year; A: 9.5%, B: 2.1%, C: 17.1% ($p<0.001$) and 1year-3years; A: 11.7%, B: 0.9%, C: 9.5% ($p<0.001$). No statistically significant differences regarding RSV positivity were detected for age groups >3 years (3-6years, 6-11years, 11-16years).

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The RSV positivity (%) for the three study periods for each subperiod and for each age group is presented in Table 1. Before COVID-19 lockdown (period A) the peak of RSV was observed during January-March, with a positivity (%) of 25.7%, followed by April-June 7.8%. During the lockdown period (B), the positivity (%) from October-March was 0% and the highest peak was detected from April-June (4.7%). Finally, after the COVID-19 lockdown (period C), the peak of RSV positivity was observed during October-December (23.7%).

Logistic analysis (Table 2) confirms the above findings. Specifically, during the pre-lockdown period, the primary peak in RSV positivity and associated excess of the virus, as compared to the lockdown period, occurred in the well-established timeframe of January to March (OR=16.31, 95%CI=9.32-28.56, p-value=0.0001), followed by April-June and September-December (OR=3.27 95%CI=1.97-7.23, p-value=0.0001, OR=2.34 95%CI=1.22-4.50, p-value=0.01 respectively). However, in the post-lockdown period, the highest peak of RSV occurred during October-December (OR=17.82 95%CI=10.17-31.21, p-value=0.0001) followed by January-March (OR=8.51 95%CI=4.82-15.02, p-value=0.0001).

The RSV in-hospital incidence per 1000 hospitalizations for each month throughout the study period is presented in Figure 2 and supplementary Figure 1 (available on the Cambridge Core website). The RSV in-hospital incidence for the total study period was 18.1/1000 hospitalizations. A statistically significant difference in the in-hospital RSV incidence per 1000 hospitalizations was detected among the three study periods: A: 16.7 (552/33131), B: 1.0 (13/13079) and C: 28.1 (772/27509) (p<0.001).

The peak of RSV in-hospital incidence before COVID-19 lockdown (period A) occurred during January-March at a rate of 41.3/1000 hospitalizations, followed by April-June at 4.9/1000 hospitalizations. During COVID-19 lockdown (period B) the RSV in-hospital incidence from October-March was 0% (p<0.001) and a low peak was detected during April-June (2.2/1000 hospitalizations). After the COVID-19 lockdown the peak of RSV in-hospital incidence was observed during October-December (61.9/1000 hospitalizations) (p<0.001). The RSV in-hospital incidence for the three periods is presented in supplementary Table 1 (available on the Cambridge Core website).

Among RSV positive children, 151/1337 (11.29%) required admission in neonatal (NICU) or pediatric intensive care unit (PICU) and 56% were males (84/151). RSV infection incidence per 1000

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hospitalizations in general pediatric department and neonatal or pediatric intensive care unit ICU (%) is shown in Figure 3. Among them 133 (88%) children were 0-1m, 13 (8.6%) were 1m-1y, 4 (2.6%) were 1y-3y and 1 child (0.6%) was above 3 years of age. The distribution of children who were admitted to ICU due to RSV infection among the three study periods was: A: 70/3134 (2.23%) children, B: 1/629 (0.16%) child and C: 80/5745 (1.4%) children ($p<0.001$). Their mean (±SD) age for the three study periods was A: 2.0 (± 6.5) months, B: 0.2 (N/A) months and C: 1.3 (±4.1) months ($p=0.7$). Among ICU admissions, RSV positivity (%) for children hospitalized within the ICU during the three study periods was: A: 18.0% (70/389), B: 1.6% (1/61) and C: 25.5% (80/314) ($p<0.001$), whereas the RSV incidence per 1000 hospitalizations in ICU was: A: 17.3, B: 0.6 and C: 26.6 ($p<0.001$).

Discussion

In the present study, we described the epidemiology of RSV before, during and after COVID-19 lockdown restriction measures in a large sample of children hospitalized in the largest pediatric hospital of Athens in Greece. After the reduced RSV circulation during the COVID-19 lockdown period, a significant increase in RSV incidence was observed, whereas a shift was detected in RSV epidemiology involving mostly older children and an earlier peak than on usual periods.

Similar reports from Finland, Italy, the UK and the USA indicate a significant decline of the RSV incidence during the Sars-CoV-2 restriction measures, compared to previous years [18-22]. In Western Australia a decline up to 98% was also detected in RSV epidemiology during the winter of 2020 [23]. The RSV reduction could most probably be attributed to the total lockdown combined with non-pharmaceutical interventions, such as hand hygiene and the use of face masks [9]. After the reduced circulation of RSV, an increased incidence and positivity was noted worldwide [22,24-25]. This could be attributed to the increased circulation of the virus after the end of restriction measures or to the absence of immunity to the virus, which could make children more vulnerable [14,26].

Additionally, there was a shift in RSV seasonal patterns. A multicenter analysis across 11 countries reported a consistent delay in RSV peak, ranging from 13 weeks in France to 88 weeks in Brazil, with an average delay of 39 weeks. These delayed seasons were characterized by high RSV activity outside

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the normal period; summer instead of winter in South Africa, the Netherlands, Israel, and the United States and 13 weeks later in winter instead of late autumn in France [27-28]. A very recent study at 2 large Austrian Pediatric Departments also noticed an earlier RSV peak; in the first center during November and in the second one in October [29]. This shifted epidemiology could be due to a viral interference effect and the ongoing use of face masks and other non-pharmaceutical interventions. A similar effect was detected during the 2009 H1N1 influenza pandemic, where RSV peak and seasonality was delayed up to 2.5 months [25].

When we compared the mean age of RSV positive children among the three periods of our study, an age shift to older children was observed, even though the majority of RSV positive children remained under 3-years-old. In most studies RSV posed a greater risk and necessitated hospitalization in infants, while older children typically exhibited milder symptoms [6]. A study, carried out across 7 different hospitals in the USA, reported that 87% of RSV-positive children were under 2-years-old [30]. Nevertheless, data from Iceland indicated that an age shift in RSV positive children also occurred during the pandemic and the median age of RSV-positive cases increased from 5.7 months to 16 months in 2020–2021 [31].

After the COVID-19 restriction measures, a significant increase in RSV positive children requiring admission to the Pediatric Intensive Care Unit (PICU) was noted. A study conducted in British Columbia, Canada, from September 1st, 2017 to May 15th, 2023, also showed a considerable increase in children up to 6 months old after COVID-19. The severity of RSV infection was increased due to more children requiring supplemental oxygen after the restriction measures. Although the proportion of children who required mechanical ventilation and the number of deaths did not change [32]. Another study among 4 different Italian hospitals describes an increased admission rate to ICU after COVID-19 period from 18 to 29% (p=0.013) [20]. However, in contrast to these findings, data from two Austrian hospitals indicate that, although there was an increased number of RSV infected children, no significant change in admission rate to PICU or in the mortality rate was detected [29].

Results from this study are based on a large sample of children hospitalized in the largest tertiary pediatric hospital in Athens, Greece. However, as they are a single center data, cannot generalized to the whole population of children. The incidence that was calculated, represents the in-hospital

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incidence, which indicates the RSV hospital burden, however it is an underestimation of the population burden. In addition, data regarding the duration of hospitalizations, the possible nosocomial transmission or therapeutic interventions needed were not available from the electronic records in order to have additional criteria for the evaluation of clinical severity.

Data presented in the current study indicate a significant increase in incidence of RSV infection after the Sars-CoV-2 restriction measures with more ICU admissions and shifted epidemiological patterns in this study samples. Given the recent availability of RSV vaccines and one-dose RSV monoclonal antibodies, surveillance of data regarding RSV epidemiology is important and could provide valuable data that could guide the decisions of public policy makers and authorities. It would be intriguing to conduct further research to observe whether the seasonal epidemiology of RSV will return to its previous patterns in the upcoming years.

Author Contributions

MB, AM and ND designed the study. ND performed the statistical analysis. EP, EK, LZ, and VB gathered and prepared the datasets. AM, TS and VB drafted the first version of the manuscript. All authors read, revised and approved the final version.

Financial Support

This research received no external funding.

Conflict of Interest

None.

Data Availability Statement

The data presented in this study are available on request from the corresponding author. The data are not publicly available due to anonymity and confidentiality.

Institutional Review Board Statement

https://doi.org/10.1017/S0950268824000724 Published online by Cambridge University Press

Research ethical issues including anonymity, and confidentiality, were addressed carefully during the study process. The research ethical clearance approval letter was obtained from the Research Ethics Committee at the "Aghia Sophia" Hospital, Athens, Greece, in November 2023.

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