PORTUGUESE JOURNAL OF PEDIATRICS

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ORIGINAL ARTICLE

Respiratory syncytial virus under 2 years of age: hospitalization trends and risk factors for severe disease – preliminary data from the Portuguese sentinel network

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Abstract

Introduction and Objectives: Respiratory Syncytial Virus (RSV) infection is an important cause of hospitalization in children under five years. A national RSV sentinel network was set up in Portugal in April 2021. We describe the trends in RSV hospitalizations until September 2022 and identify risk factors for severe disease. **Methods:** Acute respiratory infections in hospitalized children under two years were reported and tested for RSV. RSV disease severity was defined by the need for ventilation or admission to an intensive care unit. Risk ratios were used to assess the association between gender, age group, gestational age, birthweight, chronic conditions, RSV subtype and severity of disease. **Results:** We detected two RSV off-season epidemics in June 2021 to February 2022 and May to September 2022. 63.3% of RSV-related hospitalizations occurred in children under six months old and 8.0% had chronic conditions. 11.0% had severe disease. Children under six months and with chronic conditions had, respectively, an 18-fold risk and a 2-fold risk of developing severe illness. **Discussion:** The off-season RSV epidemics were probably triggered by the relaxation of COVID-19 physical distancing measures and immunity debt. In the first epidemic, the proportion of children with severe disease was higher than reported by previous studies, however, this result is probably overestimated due to the high proportion of cases notified by central hospitals. Age < 6 months and chronic conditions predispose to severe disease. As several factors may change the pattern of RSV activity, causing more severe outbreaks at different times, countries should implement year-round RSV surveillance systems.

Keywords: Child. Human. Palivizumab. Respiratory syncytial virus. Respiratory syncytial virus infections/epidemiology. Respiratory syncytial virus infections/prevention and control.

Vírus sincicial respiratório em crianças com menos de 2 anos: tendências nas hospitalizações e fatores de risco para doença grave – dados preliminares da rede de vigilância sentinela Portuguesa

Resumo

Introdução e Objetivos: O vírus sincicial respiratório (VSR) é uma importante causa de hospitalização em crianças com menos de cinco anos de idade. Em abril de 2021, foi implementado um sistema de vigilância sentinela de VSR em Portugal.

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Received: 21-10-2022
Accepted: 10-11-2023
https://pjp.spp.pt

Available online: 07-02-2024
Port J Pediatr. 2024;55(1):4-12
DOI: 10.24875/PJP.M23000129

Neste trabalho, descrevem-se tendências nas hospitalizações de VSR até setembro de 2022 e identificam-se fatores de risco para doença grave. **Métodos:** Foram reportados, e testados para VSR, casos de Infeção respiratória aguda em crianças hospitalizadas com menos de 2 anos de idade. Definiu-se doença grave pela necessidade de ventilação ou de internamento em Unidade de Cuidados Intensivos. Utilizaram-se riscos relativos para avaliar a associação entre sexo, grupo etário, idade gestacional, peso à nascença, comorbilidades, subtipo de VSR e gravidade da doença. **Resultados:** Detetaram-se duas epidemias de RSV fora de época, em junho 2021-fevereiro 2022 e maio-setembro de 2022. 63,3% das hospitalizações por VSR ocorreram em crianças com menos de 6 meses e 8,0% tinha comorbilidades. 11,0% desenvolveu doença grave. Crianças com menos de seis meses e com comorbilidades tiveram, respetivamente, um risco 18 e 2 vezes superior de desenvolver doença grave. **Discussão:** As epidemias de VSR fora de época foram provavelmente desencadeadas pelo relaxamento das medidas de distanciamento social, no âmbito de combate à pandemia de COVID-19, e pela falta de imunidade por ausência de exposição à doença. Na primeira epidemia, a proporção de crianças com doença grave foi superior ao reportado em outros estudos, contudo, este resultado está provavelmente sobrestimado pela proporção elevada de casos notificados por hospitais centrais. Idade inferior a seis meses e comorbilidades predispõem a doença grave. Uma vez que diversos fatores podem afetar a sazonalidade de VSR, causando epidemias mais severas e em diferentes alturas do ano, recomenda-se a implementação de sistemas de vigilância contínua de VSR.

Palavras-chave: Criança. Humano. Infecções por vírus respiratório sincicial/epidemiologia. Infecções por vírus respiratório sincicial/prevenção e controlo. Palivizumab. Vírus sincicial respiratório.

Keypoints

What is known

– Respiratory Syncytial Virus (RSV) infection is an important cause of hospitalization in children under five years. Seasonal data on RSV detections have been available in Portugal since 2013-2014, however, data on RSV disease burden is sparse.

What is added

– Two RSV off-season epidemics were identified in Portugal. The off-season RSV epidemics were probably triggered by the relaxation of COVID-19 physical distancing measures and immunity debt. In the first epidemic, the proportion of children with severe disease was higher than reported by previous national studies.

Introduction

Respiratory Syncytial Virus (RSV) infection is an important cause of lower respiratory tract infections and hospitalizations worldwide. Infants are the most affected age group, representing 45% of all hospital admissions and deaths from RSV[1]. It is estimated that, in 2015, RSV was responsible for 33.1 million acute lower respiratory tract infections in children younger than five years, resulting in 3.2 million hospitalizations and overall mortality of 118,200[1].

Therefore, reliable data on the burden of RSV infections and the identification of risk factors for severe disease are of utmost importance to aid healthcare professionals and policymakers in informed decision-making and to raise awareness among parents of vulnerable children. Additionally, after an RSV vaccine becomes available in Europe in the coming years, a stable surveillance system will allow to assess vaccine effectiveness and impact on disease burden[2-5]. In 2016, the World Health Organization (WHO) established an RSV surveillance pilot study (2016-2018) based on the Global Influenza Surveillance and Response System (GISRS) in 14 countries[6]. The aim was to standardize RSV surveillance and provide evidence to support Public Health and to inform about the RSV vaccination policy. Based on the key outcomes of the pilot project, several recommendations were proposed, including prioritizing RSV surveillance in children under two years of age and focusing on severe RSV disease that requires hospitalization[6].

Even though seasonal data on RSV detection has been available in Portugal since 2013-2014, data on RSV disease burden is sparse[7-9]. Therefore, following WHO recommendations, a national RSV sentinel network was set up in Portugal to monitor RSV infections in hospitalized children under two years of age. In this work, we describe trends in RSV hospitalizations from the beginning of the surveillance network to most recent data (April 2021 to September 2022). As a secondary objective, we aim to identify risk factors for RSV severe outcomes.

Methods

Setting

The RSV surveillance (VigRSV) network was set up in April 2021 with four hospitals. Until May 2022, it has

gradually expanded to 20 public and private hospitals, from the five mainland regional health administrations (North, Center, Lisbon and Tagus Valley, Alentejo and Algarve) and Madeira Island. The VigRSV network is coordinated by the Portuguese Reference Laboratory for Influenza and other Respiratory Viruses. Detailed information on the participating hospitals is provided in the supplementary material (Table S1).

Case definition

Hospitals reported and tested all acute respiratory infections (ARI) admitted for at least 24 hours. An extended ARI case definition was used for children under two years of age: acute onset of respiratory symptoms (cough, sore throat, shortness of breath or coryza), plus a clinician's judgment that the patient's signs and symptoms are to attributable to a respiratory infection[10]. For children under six months, apnoea and sepsis were also inclusion criteria. Every site reported ARI case-based data using a standardized electronic form. Data collection included the date of symptoms onset, age and gender, clinical history treatment and complications during hospitalization. For this study, we focused on hospitalized ARI cases positive for RSV (RSV-related hospitalizations). All RSV-positive samples were sent to the Portuguese National Reference Laboratory for Influenza and Other Respiratory Virus and genetically characterized. More information on the generic RSV surveillance workflow within the established sentinel surveillance system is presented in supplementary material (Fig. S1).

Study population

The study population comprised children aged 0-2 years living in the geographically defined catchment area of the non-sentinel hospitals (catchment population). The catchment area of the surveillance hospitals is the area that attracts the individuals who usually seek healthcare at the sites when they get sick[11]. To estimate the catchment areas and respective population, we reviewed hospital discharge registries, and for each site, we prepared a hot-spot map based on the place of residency of children aged 0-2 years who were hospitalized due to severe acute respiratory infections (SARI). This map corresponded to a least 85% of SARI cases for each sentinel site in the years between 2018 and 2020. Furthermore, for each selected municipality within the hot spot map, we computed the proportion of SARI in children aged 0-2 years admitted by participating hospitals among all SARI admissions in children aged 0-2 years registered in the muni-cipality. Finally, to estimate the individual contribution of each selected municipality to the catchment population, we applied previously estimated proportions to the most recent resident population estimates for municipalities[12]. This resulted in a total catchment population of 84,547 individuals corresponding to 51.5% of the resident population aged 0-2 years in Portugal. The supplementary material provides detailed information on each sentinel hospital's catchment population (Fig. S2 and Table S1).

Study period

All data was updated on September 16th 2022, and data from the beginning of the RSV surveillance network to the most recent data period between week 14 of 2021 (2021-W14) and week 36 of 2022 (2022-W36) (April 5th 2021 to September 11th 2022) was used as an observation period.

RSV molecular detection and subtyping

Molecular detection of RSV was performed in each participating hospital. Positive RSV samples were sent to the Portuguese National Reference Laboratory for Influenza and other respiratory viruses to be sub-typed as RSV A or RSV B, using a commercial real-time Reverse Transcription Polymerase Chain Reaction (rRT-PCR) kit[13]. The subtype was also confirmed in all RSV-positive samples with cycle threshold (Ct) values < 25, by partial sequencing of the G gene, using a protocol adapted from that described by Trento et al.[14].

Outcome measures

The primary outcomes of interest were the incidence of RSV-related hospitalizations in children aged 0-2 years and the number of hospitalized children aged 0-2 years with severe RSV infection, assessed by the need for ventilation or admission to an intensive care unit (ICU).

Exposure variables

Risk factors for RSV severe disease included gender (male/female), age group (< 6 months/6-23 months), gestational age category (pre-term/term), birthweight category (low weight/normal weight), presence of chronic conditions (at least one of the following: congenital heart disease, chronic obstructive pulmonary disease, trisomy 21 or immunodeficiency; yes/no) and RSV virus subtype (A/B). Pre-term was defined as a

patient born at gestational age < 37 weeks. Low birthweight was defined as < 2500 g.

Statistical analysis

Weekly incidence of RSV-related hospitalizations, by date of symptoms onset, were used to plot epidemic curves. Demographic and epidemiological characteristics were described using proportions. Crude risk ratios (RR) and 95% confidence intervals (CI) were used to assess the association between gender, age group, gestational age category, birthweight category, chronic diseases, and severity of RSV disease. Comparison of frequency data was performed by the chi-square test or by Fisher's exact test in case of expected frequencies less than five. A p-value < 0.05 was considered evidence of statistical significance. All analyses were performed using R 4.1.2 statistical software[15].

Ethical statement

This study received ethical approval from the Ethical Committee of the Portuguese National Health Institute Doutor Ricardo Jorge. Legal representatives of study participants provided written informed consent. All questionnaires and samples were pseudonymized and the identification key is in possession of the attending physician who performed the data collection.

Results

Trends in RSV-related hospitalizations

Between 2021-W14 and 2022-W36, among a population under surveillance of 84,547 individuals aged 0-2 years, 300 RSV-related hospitalizations were reported. We identified a first surge of RSV-related hospitalizations in June 2021. Following a period with inexistent RSV infections, we observed an increasing trend in RSV-related hospitalizations incidence rate since 2021-W23, peaking in 2021-W31 with a weekly incidence rate of 87.7 per 100,000 population. The RSV-related hospitalizations incidence rate subsided after 2021-W31, however, an increase was registered again in 2021-W37 (incidence rate of 57.5 per 100,000 population) resulting in an elevated incidence rate until 2022-W05. After a period with low RSV detections, a second surge of RSV infections was observed in May 2022, peaking in 2022-W26 with an RSV-related hospitalizations incidence rate of 58.7 per 100,000 population (Fig. 1).

The number of weekly reporting sites increased until 2022-W19, in line with an increasing number of participants in the RSV surveillance network. However, we registered a decrease in the number of reporting sites since the beginning of summer (Fig. 1).

Characteristics of RSV-related hospitalizations

We observed that 63.3% of RSV-related hospitalizations occurred in children under six months old, 16.8% in pre-term children, and 8.0% in children with at least one chronic condition. Severe RSV disease, defined by admission to an ICU unit or ventilation, was observed in 11.0% of children (11.0% were admitted to ICU and 9.7% needed ventilation). More RSV A (64.4%) than RSV B (35.6%) infections were detected (Table 1).

We also analyzed the characteristics of RSV-related hospitalizations in two separate periods: 2021-W23 to 2022-W05 (first epidemic) and 2022-W19 to 2022-W36 (second epidemic) (Fig. 1). We observed that the proportion of children under six months old, children with chronic diseases, and children with complications during the hospitalization (admitted to ICU or needing ventilation) was higher in the period 2021-W23 to 2022-W05 than in the period 2022-W19 to 2022-W36 (Table 1). Although, we have a small number of RSV sub-typed samples in the period 2022-W19 to 2022-W36, we detected more RSV B than RSV A infections, in opposition to those observed in the 2022-W19 to 2022-W36 period (Table 1).

Severity of RSV disease

Children under six months and those suffering from chronic conditions had, respectively, an 18-fold risk (RR: 18.53; 95% CI: 2.57-133.71) and a 2-fold risk (RR: 2.56; 95% CI: 1.17-5.58) of having severe illness compared to children aged 6-23 months and those without chronic conditions (16.8% in children under six months vs. 0.9% in children aged 6-23 months; 25.0% in children with chronic diseases vs. 9.8% in children without chronic conditions) (Table 2).

Discussion

We report two RSV off-season epidemics in June 2021-February 2022 and May-September 2022. We observed an increasing trend in RSV-related hospitalizations since June 2021, coinciding with the easing of non-pharmaceutical interventions (NPI) implemented in Portugal to fight the COVID-19 pandemic, namely, the end of mandatory teleworking and the ban on mass

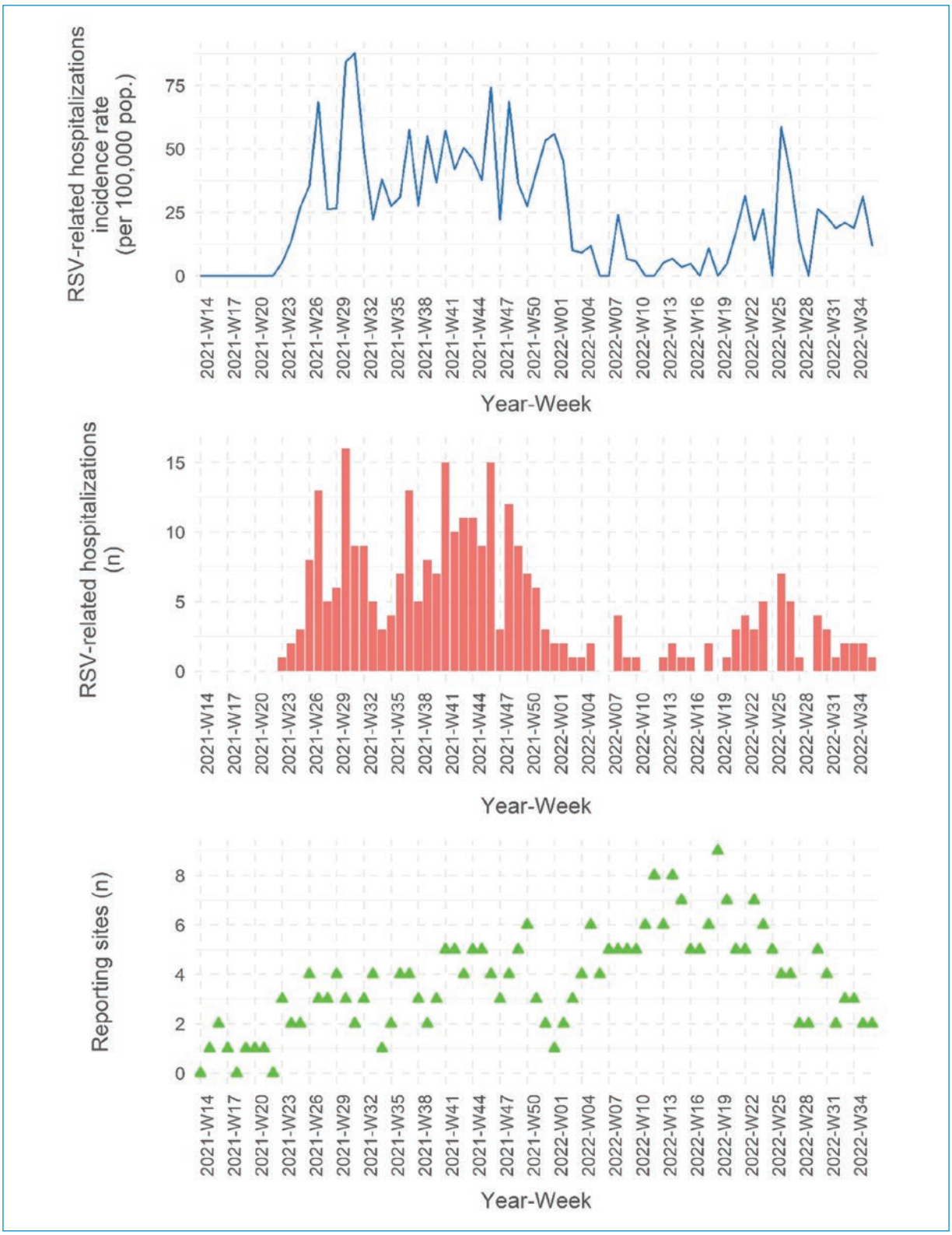

Figure 1. Weekly incidence rate of RSV-related hospitalizations (per 100,000 population) in children aged 0-2 years, number of RSV-related hospitalizations in children aged 0-2 years, and number of reporting sites, Portugal, 2021-W14 to 2022-W36 (April 5th 2021 to September 11th 2022).
RSV: respiratory syncytial virus.

Table 1. Characteristics of RSV-related hospitalizations in children aged 0-2 years, Portugal, 2021-W14 to 2022-W36 (April 5th 2021 to September 11th 2022)

	Analysis period 2021-W14 to 2022-W36	First epidemic 2021-W23 to 2022-W05	Second epidemic 2022-W19 to 2022-W36
	n (%)	n (%)	n (%)
Overall	300	243	44
Gender			
Male	155 (51.7)	128 (52.7)	21 (47.7)
Female	145 (48.3)	115 (47.3)	23 (52.3)
Age group			
< 6 months	190 (63.3)	164 (67.5)	18 (40.9)
6-23 months	110 (36.7)	79 (32.5)	26 (59.1)
Gestational age category			
Pre-term	50 (16.8)	38 (15.8)	8 (18.2)
Term	248 (83.2)	203 (84.2)	36 (81.8)
Birthweight category			
Low weight	43 (14.6)	33 (13.9)	7 (15.9)
Normal weight	252 (85.4)	205 (86.1)	37 (84.1)
Chronic conditions			
Yes	24 (8.0)	21 (8.6)	3 (6.8)
No	276 (92.0)	222 (91.4)	41 (93.2)
RSV subtype			
A	85 (64.4)	79 (67.5)	4 (40.0)
B	47 (35.6)	38 (32.5)	6 (60.0)
Severe RSV disease			
Yes	33 (11.0)	30 (12.3)	3 (6.8)
No	267 (89.0)	213 (87.7)	41 (93.2)

RSV: respiratory syncytial virus.

Table 2. Risk factors for severe RSV-related hospitalizations, Portugal, 2021-W14 to 2022-W36 (April 5th 2021 to September 11th 2022)

	n (%)	RR (95% CI)	p-value
Gender			
Masculine	19 (12.3)	0.79 (0.41-1.51)	0.472
Feminine	14 (9.7)		
Age group			
< 6 months	32 (16.8)	18.53 (2.57-133.71)	< 0.001
6-23 months	1 (0.9)		
Gestational age category			
Pre-term	9 (18.0)	1.86 (0.92-3.76)	0.134
Term	24 (9.7)		
Birthweight category			
Low weight	7 (16.3)	1.58 (0.73-3.41)	0.270
Normal weight	26 (10.3)		
Chronic conditions			
Yes	6 (25.0)	2.56 (1.17-5.58)	0.044
No	27 (9.8)		
RSV subtype			
A	14 (16.5)	0.65 (0.25-1.68)	0.444
B	5 (10.6)		

RSV: respiratory syncytial virus.

gatherings[16]. As transmission pathways of RSV include aerosols, inhalation of virus-laden liquid droplets, close contact with infected individuals, and contact with contaminated surfaces, activities such as mass gatherings had a plausible direct impact on increasing infectious social contacts[17]. On the other hand, the end of mandatory teleworking with more parents resorting to childcare providers and increasing mobility has the potential to accelerate RSV transmission in the community. After easing COVID-19 NPIs, similar out-of-season epidemics were also experienced in several countries worldwide[18-24]. The incidence rate of RSV-related hospitalizations subsided as the summer progressed, in temporal association with increased in mobility in parks, retail, and recreation[25]. Therefore, we postulate that summer holidays and the consequent absence of school activities were responsible for the disruption in RSV transmission and decreased RSV-related hospitalizations. However, the incidence of RSV-related hospitalizations increased again following the re-opening of the schools, this time with a continuous surge of cases throughout the autumn/winter, until February 2022. We registered a new period of anomalous RSV activity, from May 2022 onwards, although, with lower intensity than the June 2021-February 2022 epidemic. This RSV epidemic followed the end of the mask mandate in Portugal on April 22nd 2022[16]. Considering RSV transmission pathways, we hypothesize, that lifting the mask mandate facilitated RSV transmission in Portugal. However, the impact of mask mandates may go beyond the direct impact on RSV incidence. It may be an indirect consequence of changes in the population´s daily activities, supported by an increase in mobility trends for transit stations and a decrease in residential places in Portugal after lifting the mask mandate, or an indirect consequence of altered risk perception, which was found to be associated with restrictions imposed to mitigate the pandemic in a Portuguese study[26,27]. Given that the COVID-19 pandemic had an impact on the circulation of RSV and the risk of infection or pressures in the healthcare systems may occur at different times, year-round RSV surveillance systems are recommended in order to monitor RSV activity throughout the year.

The proportion of RSV-related hospitalizations with severe disease in June 2021-February 2022, was higher than that reported by previous national studies[8,9]. We postulate that this result may be overestimated due to the high number of cases reported by central hospitals. Nonetheless, we could not undertake a sensitivity analysis excluding cases reported by central hospitals due to the small number of hospitals reporting in the beginning of the surveillance network. However, we also hypothesize that the absence of RSV circulation during the first COVID-19 pandemic year may be associated with diminished immunity in young children and, consequently, an increased risk of developing severe disease[28]. This hypothesis is in line with a study conducted in the setting of a delayed surge of RSV in the USA which showed a more severe disease course[29]. Additionally, surveillance data from New Zealand, for children aged 0-4 years, show that, in 2021, the RSV-related ICU incidence rate was 2-8 times higher than the average peaks between 2015 and 2019[22].

We found that children under six months old and children with chronic conditions had an increased risk of severe illness. These results are consistent with a systematic literature review on the risk factors for severe RSV in young children[30]. Additionally, the lower proportion of children under 6 months and with chronic conditions hospitalized due to RSV in May-September 2022, compared to the June 2021-February 2022 period, may be associated with the lower proportion of severe RSV cases observed. However, we still have to consider that: (1) immunity debt in May-September 2022 was expected to be lower than in June 2021-February 2022 and, hence, we expected to observe a decreased proportion of severe cases; (2) although, no association was found between RSV subtype and severity of disease, previous studies showed RSV subtype A to be associated with a more severe disease compared with subtype B[31]. Consequently, the lower proportion of RSV severe cases in the second epidemic wave may also be related to dominance of the RSV subtype B, even if statistical significance was not reached because of the small sample size. In the long term, we aim to compute adjusted risk-ratios with a larger sample size and test these hypotheses.

We detected more RSV A than RSV B infections in June 2021-February 2022. However, we have a small number of sub-typed samples in May-September 2022 and more RSV B samples were detected. Evidence in the related literature shows that following an RSV infection, individuals gain transient immunity with an average duration of 2 years[32]. As this immunity is partial in its efficacy, and greater for the homologous challenge (60%) than heterologous (16%), the A/B dominance patterns observed in June 2021-February 2022 and May-September 2022 are expected[32].

This study has several limitations. Firstly, the number of reporting sites varied during our analysis period, specifically, with a higher proportion of central hospitals reporting during the first RSV epidemic wave and a decreasing participation rate during the second RSV

epidemic wave, coincident with the beginning of summer. We expect that participation rates will increase at the beginning of the influenza and other respiratory virus surveillance seasons, in week 40 of 2022, even though, an attempt should be made to engage hospitals in year-round surveillance. Also, the Azores islands were not yet included in the surveillance network and thus, an attempt should be made to engage the local hospitals of the region in order to cover all the Portuguese territory. Nevertheless, our surveillance network has the advantage of including a large study population, corresponding to 51.5% of Portuguese children aged 0-2 years, and thereby, it provides useful information on RSV epidemiology. Finally, as this surveillance network was implemented in 2021, we lack baseline data regarding RSV-related hospitalizations from previous seasons and, therefore, we cannot make a comprehensive assessment of the epidemics, or set thresholds to assess the impact of disease in the population.

Acknowledgments

The authors warmly thank Dr. David Lito for critical reviewing this work.

Supplementary data

Supplementary data are available at DOI: 10.24875/PJP.M23000129. These data are provided by the corresponding author and published online for the benefit of the reader. The contents of supplementary data are the sole responsibility of the authors.

Funding

None.

Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. Right to privacy and informed consent. The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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