AMP ACTA MÉDICA PORTUGUESA
A Revista Científica da Ordem dos Médicos

Resurgence of Respiratory Syncytial Virus in Children: An Out-of-Season Epidemic in Portugal

Ressurgimento do Vírus Sincicial Respiratório em Crianças: Atividade Epidémica Fora de Época em Portugal

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Acta Med Port 2023 May;36(5):343-352 ▪ https://doi.org/10.20344/amp.18589

ABSTRACT

Introduction: An out-of-season increase in respiratory syncytial virus (RSV) incidence was observed in Portugal from June 2021 onwards, revealing a continuing surge in cases throughout 2021/2022 autumn/winter. We aimed to describe this out-of-season epidemic and define its epidemic period, by analysing RSV incidence from week 40 of 2020 (2020-W40) to week 18 of 2022 (2022-W18).
Material and Methods: Surveillance data on weekly RSV laboratory confirmed cases, in Portugal, was used to monitor RSV incidence using CUSUM test methodology for count data.
Results: In 2021-W23, the CUSUM score identified a significant increase in the risk of RSV. By that time, the percentage of RSV positive tests rose from 1% in 2021-W22 (3/265) to 6% in 2021-W23 (18/298). Despite a sharp decrease in RSV incidence on 2021-W33 and on 2022-W02, the CUSUM score stayed over the limit up to 2022-W07, indicating that the RSV activity remained at an epidemic level. Distinct peaks of RSV cases were observed between 2021-W30 and 2021-W32 (average of 77 RSV cases per week) and between 2021-W39 and 2021-W41 (average of 79 RSV cases per week) with positivity rates around 60%.
Conclusion: An out-of-season RSV epidemic was identified, with a longer epidemic period compared with previous seasons. Possible reasons include relaxation of COVID-19 physical distancing measures and a greater proportion of population susceptible to disease. As several factors may change the pattern of RSV activity, countries should implement year-round surveillance RSV surveillance systems. These findings might have an impact on public health planning regarding future RSV surges, namely, on the palivizumab prophylaxis period for high-risk infants.
Keywords: Child; Palivizumab; Respiratory Syncytial Virus Infections/epidemiology; Respiratory Syncytial Virus Infections/prevention and control; Respiratory Syncytial Virus, Human

RESUMO

Introdução: A partir de junho de 2021, registou-se um aumento na circulação do vírus sincicial respiratório (VSR) em Portugal, continuando a observar-se um elevado número de casos ao longo do outono/inverno de 2021/2022. O objetivo deste estudo foi descrever esta epidemia fora de época e definir a sua duração, analisando a incidência deste vírus desde a semana 40 de 2020 (2020-40) até à semana 18 de 2022 (2022-18).
Material e Métodos: O número semanal de casos de VSR confirmados laboratorialmente em Portugal foi utilizado para monitorização de incidência, utilizando a metodologia de teste CUSUM para contagens.
Resultados: Na semana 2021-23, foi identificado um aumento significativo no risco de VSR, tendo a proporção de testes positivos aumentado de 1% na semana 2021-22 (3/265) para 6% na semana 2021-23 (18/298). Apesar de ter sido observado um decréscimo acentuado na incidência de VSR nas semanas 2021-33 e 2022-02, o *score* do teste de CUSUM permaneceu acima do limiar epidémico até à semana 2022-07. Foram observados picos distintos na incidência de VSR entre as semanas 2021-30 e 2021-32 (média de 77 casos de VSR por semana) e entre as semanas 2021-39 e 2021-41 (média de 79 casos de VSR por semana), com taxas de positividade em torno de 60%.
Conclusão: Foi identificada uma epidemia de VSR fora de época, com um período epidémico superior ao observado noutras épocas de vigilância. Entre as razões possíveis para esta ocorrência inclui-se o relaxamento de medidas implementadas no âmbito do combate à pandemia de COVID-19 e uma maior proporção de população suscetível à doença. Uma vez que vários fatores podem interferir na sazonalidade do VSR, recomenda-se que os países implementem sistemas de vigilância ao longo de todo o ano. Estes resultados poderão ter impacto no planeamento de medidas de saúde pública em futuros surtos de VSR, nomeadamente, no período de administração de palivizumab para prevenção de infeção em crianças de alto risco.
Palavras-chave: Criança; Infecções por Vírus Respiratório Sincicial/epidemiologia; Infecções por Vírus Respiratório Sincicial/ prevenção e controlo; Palivizumab; Vírus Sincicial Respiratório Humano

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Recebido/*Received*: 19/05/2022 - **Aceite/*Accepted***: 13/10/2022 - **Publicado *Online*/*Published Online***: 27/01/2023 - **Publicado/*Published***: 02/05/2023

INTRODUCTION

Respiratory syncytial virus (RSV) is considered a major pathogen causing severe lower respiratory tract infections, in infants and young children.[1] In 2015, RSV was associated with 33.1 million acute lower respiratory tract infections, 3.2 million hospital admissions, and an overall mortality of 118 200 in children under five years of age worldwide.[1]

With no existing vaccine, prevention methods include passive immunization through the monthly administration of the monoclonal antibody (mAb) palivizumab during the RSV season, in the first year of life in high-risk infants.[2] The IMpact-RSV study, a placebo-controlled trial conducted in the United States, the United Kingdom and Canada, found that palivizumab prophylaxis was associated with a 55% reduction in hospitalization attributable to RSV.[3]

Therefore, for prevention methods to be deployed effectively, an understanding of the seasonality of RSV is required. Previous studies have found that temperate countries in the Northern Hemisphere experience a distinct peak in RSV cases per season, with the start of the RSV season between September and January, in line with colder temperatures.[4–6] In particular, between the 2013-2014 and the 2019-2020 seasons, all RSV epidemics in Portugal that started in December had a median epidemic duration of 10 to 11 weeks, and low or inexistent circulation was registered in summer months.[4,6,7]

However, unlike previous seasons, and similarly to many countries worldwide, an unprecedented low incidence of respiratory viral infections, including RSV, was reported during the 2020-2021 autumn/winter in Portugal.[7] Probable reasons for this low incidence include viral competition and non-pharmaceutical interventions (NPIs) implemented to fight the COVID-19 pandemic, since March 2020.[8–11] As transmission pathways of RSV include aerosols, inhalation of virus-laden liquid droplets, close contact with infected individuals and contact with contaminated surfaces, NPIs affecting daily activities such as stay-at-home mandates, school closures and gathering bans would have a direct impact on reducing infectious social contacts.[12] On the other hand, the high incidence of COVID-19 could induce viral competition between SARS-CoV-2 and RSV through multiple mechanisms, such as antibody-driven cross-immunity and a reduced susceptible pool due to isolation.[13,14] In fact, a change in RSV activity had already been observed during the 2009 pandemic influenza A(H1N1), in France and Hong Kong, thus supporting this hypothesis.[15,16]

From June 2021 onwards, in the setting of relaxed COVID-19 measures in Portugal, an out-of-season increase in RSV incidence was observed, revealing a continuing surge in cases throughout the 2021-2022 autumn/winter. To our knowledge, no study described this epidemic in Portugal, assessed its magnitude, or discussed its implications. RSV surveillance data has the potential to assist informed decision-making in public health by: (1) providing baseline data and a comprehensive assessment of the epidemics; (2) aiding governments in prioritizing healthcare investments and targeting interventions, and considering in particular that RSV protection conferred by monoclonal antibodies or maternal immunization may be short lasting; (3) guiding healthcare services in demand-side planning; (4) aiding the pharmaceutical industry in planning for effective RSV vaccines and new monoclonal antibodies; (5) guiding diagnostic testing and information for parents of vulnerable children.[17–19] Consequently, in this context, we aimed to describe this uncommon RSV epidemic and define its epidemic period by analysing RSV incidence from week 40 of 2020 to week 18 of 2022.

MATERIAL AND METHODS

Setting

The study was implemented in hospitals from the Portuguese Laboratory Network for the Diagnosis of Influenza Infection. The network comprises 20 non-sentinel public hospital-based laboratories, in three mainland regional health administrations (North, Center and Lisbon and Tagus Valley) and the Azores Islands, and is coordinated by the Portuguese Reference Laboratory for Influenza and other Respiratory Virus. Every site reports RSV aggregated data to the Portuguese Reference Laboratory for Influenza and other Respiratory Virus on a weekly basis. The information is collected in a standardized Excel form including the epidemiological week, number of tests performed, number of positive tests and age group. In order to increase data completeness, report timings were adapted according to data availability and to the capacity of paediatricians and laboratories capacity to ensure the reports.

Study population

The study population comprised children aged 0 to 4 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 which attracts the individuals who usually seek healthcare at the sites when they get sick.[20] In order to estimate the catchment areas and respective population, we reviewed the hospital discharge registry database that covers all admissions in public hospitals in Portugal, and for each site we prepared a hotspot map based on the residential address of children aged 0 to 4 years who were hospitalized due to severe acute respiratory infections (SARI). This map corresponded to a least of 85% SARI cases in children aged 0 to 4 years hospitalized at each non-sentinel site, in the years between 2018 and 2020. For each selected municipality within the hotspot map we computed the proportion of SARI in children aged 0 to 4 years admitted by participating hospital, among all SARI admissions in children aged 0 to 4 years registered in the municipality. Finally, to estimate the individual contribution of each selected municipality to the catchment population, we applied previously estimated proportions to most recent resident population estimates for municipalities regarding children aged 0 to 4 years.[21] This resulted in a total catchment population of 187 068 individuals which corresponds to 43% of the resident population aged 0 to 4 years in Portugal. Detailed information on the catchment population for each non-sentinel hospital is provided in the supplementary material [Appendix, Fig. 1 and Table 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/18589/15033)].

Study period

All data was updated on the 12th May 2022 and data for the period between week 40 of 2020 (2020-W40) and week 18 of 2022 (2022-W18) (28 September 2020 to 8 May 2022) was used as observation period for our analysis.

Testing strategy

According to the standard 19/2020 issued by the Directorate-General of Health (DGS), all children attended in hospitals and presenting acute respiratory infection symptoms (acute onset of at least one of the following four respiratory symptoms: cough or sore throat or shortness of breath or coryza and a clinician's judgment that illness is due to infection) should be tested for SARS-CoV-2, Influenza and RSV.[22] The study included outpatients and inpatients aged 0 to 4 years tested for RSV. Tests for RSV detection during the analysis period were performed using a multiplex assay, allowing for the simultaneous detection of RSV, influenza and SARS-CoV-2. The most used kit for the detection of RSV was the Allplex™ SARS-CoV-2/FluA/FluB/RSV (ASFR, Seegene Technologies Inc; Seoul, South Korea). According to recent research, the sensitivity of Allplex™ SARS-CoV-2/FluA/FluB/RSV ranges between 92.0% and 98.7%, while the specificity ranges between 99.5% and 100%.[23] Only one laboratory reported using the antigen-based MariPOC® respi test (ArcDia International Ltd; Turku, Finland). The sensitivity and specificity reported by the manufacturer were 88.6% and 100%, respectively.[24] The choice of MariPOC® respiratory test over other rapid detection tests, was made due to the multiplexing feature that allows the simultaneous detection of viruses that have a major impact on healthcare systems.

Outcome measures

The primary outcome of interest was the weekly number of RSV laboratory confirmed cases in paediatric 0-to 4-year-old outpatients and inpatients, in Portugal. Secondary outcomes of interest included the number of RSV tests performed in children aged 0 to 4 years and the distribution per region of RSV laboratory confirmed cases.

Timeline of public health measures

In order to mitigate transmission and severe consequences of SARS-CoV-2 infection, in addition to avoiding the collapse of the healthcare system in Portugal, a coordinated public health response was issued, including NPIs enforced by the government with different stringency levels and duration periods.[25–28] In the second COVID-19 epidemic wave in Portugal (October - December 2020), tiered NPIs based on local epidemic assessment were set. Along with the mandatory use of face masks in outer spaces (mandatory use of masks in inner spaces was already in place since April 2020) and a nationwide curfew between 23.00 pm and 5.00 am, in mainland Portugal, weekend lockdowns were implemented in municipalities classified as extremely high risk (14-day incidence rate of COVID-19 ≥ 240 cases per 100 000 population). In the third epidemic wave (late December 2020 - March 2021), stricter NPIs were issued. Such NPIs included stay-at-home mandates, closure of schools and all non-essential businesses, individual movement restrictions for non-essential activities, international borders closed for non-residents, banning of mass gatherings, visitation restrictions in long-term care facilities and working from home However, the stay-at-home mandates along with the closure of kindergartens and elementary schools were revoked in March 2021, while some NPIs, such as working from home and bans on mass gatherings, were in place until June 2021 (Fig. 1).[28]

Statistical analysis

As we did not have a long series of surveillance historical data (minimum of five years), the method used in this study to specify the epidemic alert thresholds for RSV was chosen taking into account: (1) prospective surveillance methods, based on short-term data[29]; (2) methods tested for respiratory virus surveillance.[30]

The weekly incidence of RSV was monitored using CUSUM test methodology for count data.[31,32] This test computes, for each week n, a score S_n defined by: (1- ascending CUSUM) $S_n = max(0, S_{n-1} + W_n)$ where $S_0 = 0$ and W_n is the log-likelihood ratio sample weight. This weight is a measure of the deviation of the observed count from the target or expected count. For each week, the CUSUM tests the null hypothesis: 'RSV activity is at a baseline level (in control)', against the alternative hypothesis: 'RSV activity is at an epidemic level (out-of-control)' (i.e., $H_0 : \lambda = \lambda_0$ vs $H_1 : \lambda > \lambda_0$, where λ_0 is the mean of the process under in control state).

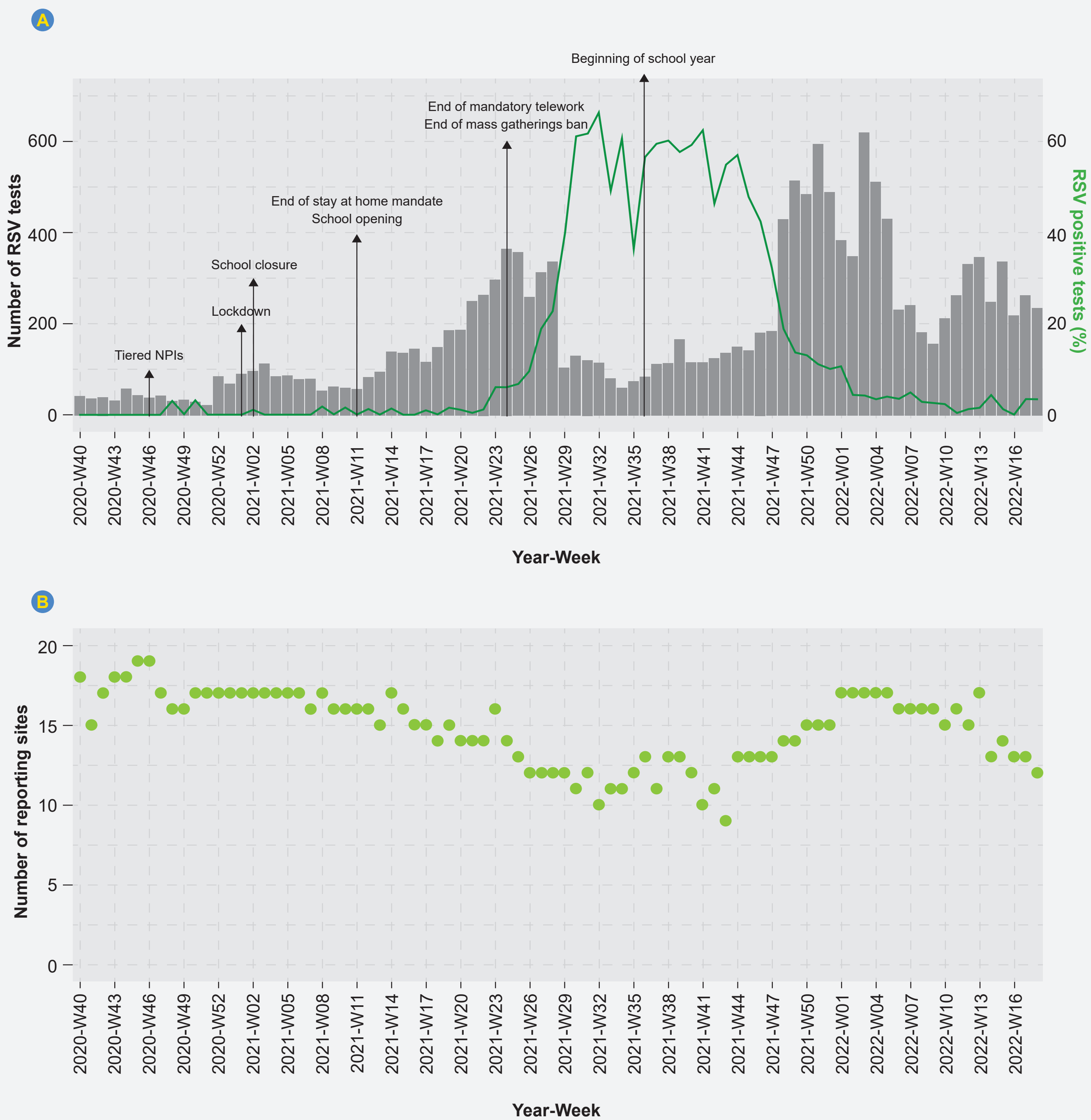

Figure 1 – Weekly number of RSV tests, weekly proportion of RSV positive tests and timeline of NPIs implemented in Portugal (A). Weekly number of reporting non-sentinel sites (B).

The null hypothesis is rejected when the CUSUM score crosses a decision limit h.

The sample weight was computed as: (2) $W_n = X_n - \{(\lambda_1 - \lambda_0) : [(log\ (\lambda_1) - log\ (\lambda_0))]\}$ where X_n is the RSV count for week n, and λ_0 is the mean weekly numbers of RSV cases expected if the incidence is in control and and λ_1 is smallest out-of-control mean of RSV cases we want to detect. We estimated the baseline level of RSV activity, λ_0, as the average of weekly RSV counts recorded when the RSV positivity rates were below 10%. The 10% threshold was set according to Centre for Disease Control (CDC) guidelines.[33] We designed the CUSUM test to detect a four-fold increase in RSV incidence (relative risk of 4).

Based on these values, we determined the decision limit h that controls type I error rate. The analogous of type I rate for a CUSUM test is the average run length (ARL) under the null hypothesis, i.e., the expected number of weeks until the CUSUM test detects an out-of-control level of RSV given that the incidence is in control. The limit h was set to 2, to ensure an ARL about 400 weeks if the process is in-control. For this purpose, ARL was first approximated using existing tables and then a more precise determination of h was estimated using computer software.[31,34]

Determining the period when a process returns to its in-control state can be difficult if the recorded deviation was significantly high, either from a long out-of-control period or the presence of a particularly large epidemic. These situations cause the CUSUM statistic to rise steeply, and it may take some time after the end of an epidemic for the CUSUM statistic to return to previous levels.[35]

Therefore, if the CUSUM test detected an epidemic level for the RSV activity, the hypotheses were reversed, and we tested for a decrease in the monthly incidence from the out-of-control situation (λ_1) to the in-control situation (λ_0). In this case, the score S_n test was defined by:

(3 – descending CUSUM) $S_n = min(0, S_{n-1} - W_n)$

All analyses were performed using 4.1.2 statistical software.[36] For computing the decision interval (h) for CUSUM test, we used the 'CUSUMdesign' package.[34]

Ethics statement

The aggregated data used within this study were anonymised and collected in the scope of epidemiological surveillance for which submission to an ethics committee was not required.

RESULTS

Between 2020-W40 and 2022-W18, among a population of 187 068 individuals aged 0 to 4 years under surveillance, 15 614 RSV tests were performed, resulting in 1986 laboratory confirmed cases of RSV [Fig.1 and Table 2 of the Appendix (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/18589/15033)]. Almost 90% of the laboratory confirmed RSV cases were detected in the North (52.0%) and Lisbon and Tagus Valley (36.6%) regions. Only 9.1% and 2.4% of RSV cases were from the Center region and the Azores islands.

Although, the number of RSV tests varied during the analysis period, the number of weekly reporting sites was fairly constant: on average 14 hospitals per week (minimum of nine hospitals on week 43 of 2021 and maximum of 19 hospitals on weeks 46 and 47 of 2021) reported data [Fig.1 and Table 2 of the Appendix (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/18589/15033)].

CUSUM analysis showed no significant deviation from the expected weekly number of RSV cases between 2020-W40 and 2021-W22 (Fig. 2). In 2021-W23, the CUSUM score crossed the decision limit, i.e., identified a significant increase in the risk of RSV. By that time, the percentage of RSV positive tests rose from 1% in 2021-W22 (3/265) to 6% in 2021-W23 (18/298), coinciding with the end of the mass gatherings ban and mandatory working from home) (Fig. 1).

Despite a sharp decrease in RSV incidence on 2021-W33 (followed by a steep rise in 2021-W36 aligned with the beginning of the school year) and on 2022-W02, the CUSUM score stayed over the limit up to 2022-W07, indicating that the RSV activity remained at an epidemic level. A significant decrease was identified in 2022-W08. From 2022-W08 onwards, no significant increase in RSV cases was identified, thus supporting the hypothesis of a return to the baseline situation (Fig. 2).

Two distinct peaks of RSV cases were observed during the analysis period: between 2021-W30 and 2021-W32 (average of 77 RSV cases per week) and between 2021-W39 and 2021-W41 (average of 79 RSV cases per week) with positivity rates around 60% (Figs.1 and 2).

DISCUSSION

We reported an out-of-season RSV epidemic in Portugal, with a longer epidemic period comparing to previous seasons, after easing of COVID-19 restrictions.

During the 2020–2021 autumn/winter season in Portugal, the RSV epidemic (which usually starts in December)[4,6,7] remained at baseline levels while an out-of-season epidemic starting in June 2021 (2021-W23) was observed. This surge was coincident with the relaxation of COVID-19 NPIs and may have been facilitated by increased levels of travel due to the start of the summer holidays, along with a decrease in COVID-19 risk perception and lesser use of protective measures.[37] Similar out-of-season epidemics and on a different scale to previous trends, after easing of COVID-19 physical distancing measures, were also experienced in several countries worldwide.[8,9,38–42] As socioeconomic activity and movement were re-established, the overall risk for respiratory infections in all population, but specially in infants and young children who had less chance to have a previous contact with common respiratory viruses, increased as a consequence.

Contrary to previous years, two distinct peaks of RSV cases were observed during the analysis period: between 2021-W30 and 2021-W32 and between 2021-W39 and 2021-W41 with positivity rates around 60%.[4,6,7] A sharp decrease in RSV cases was registered in 2021-W33, followed by a steep rise in 2021-W36. Even though the number of tests performed during these three weeks (average of 73

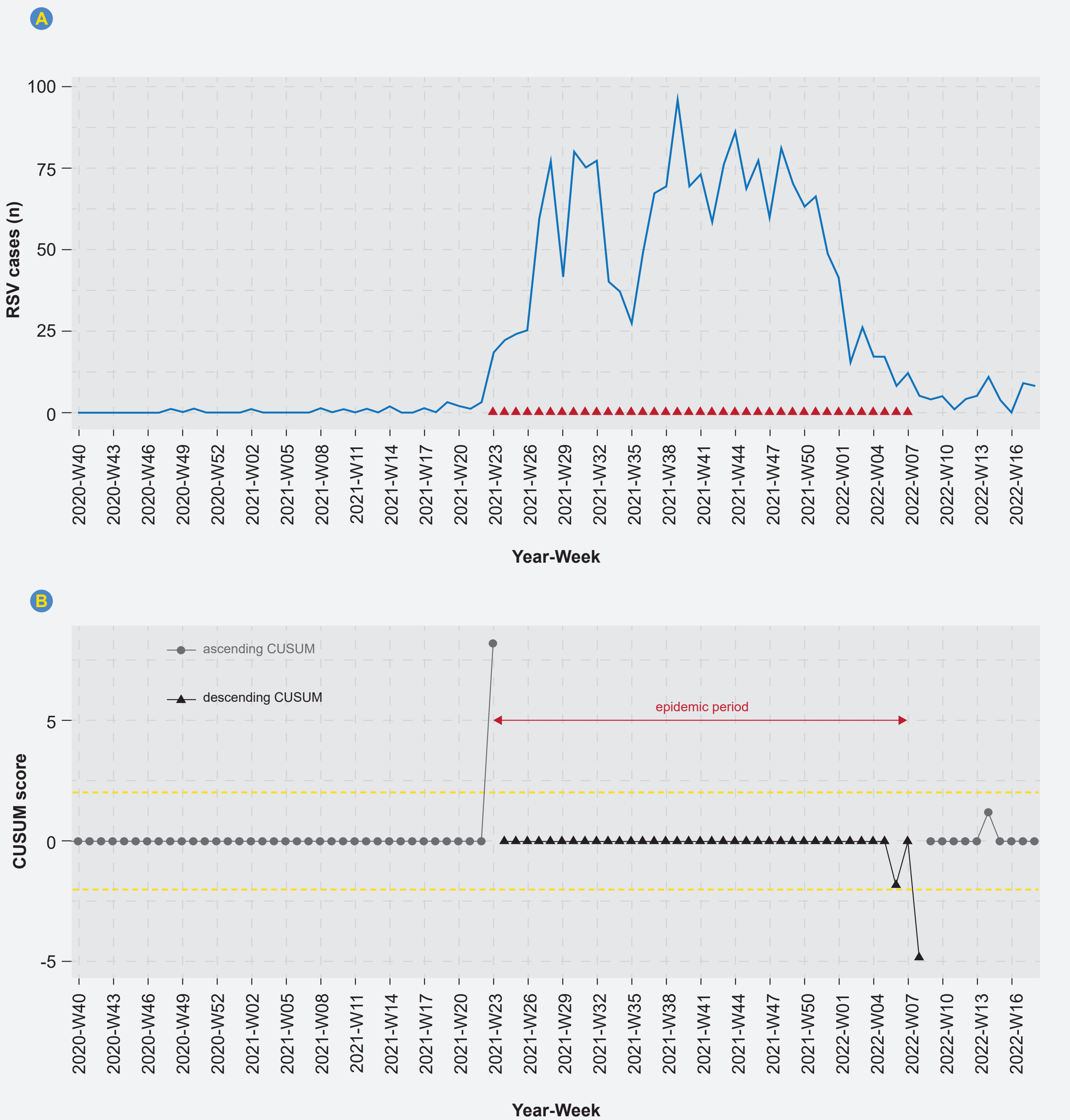

Figure 2 – Distribution over time of RSV cases between 2020-W40 and 2022-W18. Weekly report of RSV cases (A). Red triangles denote incidence is out-of-control. Cumulative sums (CUSUM). Horizontal yellow dashed lines represent the test limits (B).

tests per week) was lower than in the previous three weeks (average of 123 tests per week), the number of reporting sites remained the same (average of 11 reporting sites per week). Therefore, although we cannot exclude the influence of testing capacity in the number of RSV positive samples detected, we postulate that this decrease was mainly due a disruption in RSV transmission because of the summer holidays, as it was a period that coincided with an increase in mobility in parks, retail and recreation.[43] The increase in RSV cases in 2021-W36 was time aligned with the end of the summer holidays and the restart of school activities for children. We postulate that primary school and day care facilities had an important impact on this RSV transmission, which is in line with other studies.[38,44] Additionally, we note that the main RSV transmission routes are aerosols, droplets (generated during coughing, sneezing or talking), direct contact (from an infected person to a susceptible individual) or indirect contact (fomite transmission).[12] As wearing masks was mandatory in schools for children over 10 years of age, but these social distancing measures did not apply to infants and young children, the latter were at higher risk of RSV infections.

RSV incidence remained at epidemic levels from 2021-W23 until 2022-W07, in a total of 37 weeks. This epidemic period was considerably longer than in previous years, considering a median epidemic duration of 10-11 weeks from 2013-14 to 2018-2019.[4] In light of these results, some public health implications should be emphasised. In Portugal, five doses of palivizumab, in the period between October 15th and February 15th, are recommended for young children with congenital heart disease, pulmonary comorbidities, or with T-cell immunodeficiency, as well as for premature infants or infants with pulmonary comorbidities.[45] In 2021, due to the exceptional circulation of RSV in the summer, the Directorate General of Health in Portugal decided to anticipate the administration of palivizumab to September 15th.[46] This recommendation also stated that monitoring of the RSV epidemic (with the support of the Portuguese Laboratory Network for the Diagnosis of Influenza Infection) would be required to determine the timing of the administration of the last dose of palivizumab. As a result, following a sharp decrease in RSV circulation in January 2022, the timing of the last dose of palivizumab was set to February 15th.[47]

Therefore, our findings suggest that climate characteristics cannot be used as a definitive predictor for the timing of RSV epidemics and highlight the need to take into account the country's surveillance data when defining the prophylaxis period for palivizumab, as the COVID-19 pandemic might have an effect on RSV activity in the following seasons. Several modelling studies analysed how the build-up of immunity debt due to COVID-19 NPIs could result in earlier and larger outbreaks of RSV and possibly affect seasonality for some years to come.[48,49] Moreover, a study conducted in the setting of a delayed surge of RSV in the USA showed a more severe disease course, explained by decreased immunity from lack of previous exposure.[50] Nonetheless, even in countries where an increase in seriousness of disease was not observed, the burden on the healthcare system was substantial: surveillance data from New Zealand, for children aged 0 to 4 years showed that, in 2021, the RSV-associated hospitalization and ICU incidence rates were, respectively, 3 times and 2.8 times higher than the average of peaks between 2015 and 2019.[40] Similar trends were observed in Italy and Germany in 2021, where the out-of-season RSV epidemics were characterized by an extraordinary burden on paediatric hospitals.[41,42] On the other hand, a Canadian study had already demonstrated the added value of prospective surveillance data in aiding decision-making regarding prophylaxis periods: compared to using a predetermined date for the palivizumab prophylaxis period onset, the prospective method involved the administration of less five palivizumab doses, thus minimizing excess healthcare expenditure.[51]

As COVID-19 NPIs are relaxed, it is necessary to adapt currently existing surveillance systems, in order to guarantee the identification of new threats, increase in epidemic activity or the emergence of serious forms of disease, with the proportional use of resources, and without increasing pressure on healthcare services. Systematic RSV surveillance data will allow targeted intervention strategies for better management of infections and prevention of severe illness, and will save costs, thus allowing maximum benefit from prophylaxis and ultimately, will protect children lives.[17–19]

This study has several limitations. As we assessed RSV activity using CUSUM test methodology for count data our results have the potential to be biased if testing strategies change. However, according to the DGS guideline 19/2020, testing strategies remained stable in the period under analysis and included RSV testing for every children with an acute respiratory infection.[22] Even though the number of RSV tests varied within the analysis period, as the number of reporting sites remained relatively stable, we postulate that testing differences were mainly due to the COVID-19 epidemiological situation in Portugal: as RSV tests were performed in multiplex with SARS-CoV-2 and influenza, periods with a higher incidence of COVID-19 should have a positive effect in RSV testing and vice-versa.[52] Nevertheless, we cannot exclude the possibility that, according to epidemiological context and clinical situation, individual testing might differ from this standard. Before 2020-W40, testing strategies differed and therefore, previous periods could not be used for direct comparison.

Additionally, underreporting of RSV cases could cause the algorithm to miss an epidemic. The number of reporting sites was constant during the analysis period, apart from a decrease on 2022-W43 due to the start of the autumn/winter season and consequent re-organization of healthcare services in hospitals. Nonetheless, as the CUSUM score crossed the decision limit in 2021-W23 and stayed over the limit up to 2022-W07, the potential underreporting on 2022-W43 does not have an impact in the epidemic detection for this period. We cannot exclude, however, the possibility that the true number of RSV detected cases might be of higher magnitude, especially during epidemic peaks, as healthcare professionals who participate in the surveillance might see data reporting as time-consuming during times of increased workload.[53,54] We surveyed the focal points of each non-sentinel site on their willingness to participate in the surveillance system and on the simplicity of data reporting. All answers perceived the public health relevance of RSV disease and emphasized the importance of participation and inclusion in a national epidemiological study. However, 38% of sites reported difficulties in filling the surveillance Excel form. Keeping this in mind, and in order to improve the feasibility of the surveillance system, from October 2022 onwards, reporting will be made through an online platform, which we expect to improve reporting timeliness and data completeness. Furthermore, an attempt should be made to engage in the surveillance system hospitals from the regions of Algarve, Alentejo and Madeira islands. However, our surveillance system has the advantage of including a large study population, corresponding to 43% of the Portuguese children aged 0 to 4 years, and therefore, it provides useful information on RSV epidemiology.

Finally, we lacked clinical data regarding the severity of RSV reported cases (e.g., need for intensive care, mechanically assisted ventilation, or death) and, therefore, we cannot conclude if this out-of-season epidemic has an increased severity compared with previous epidemics. However, we are currently working on a paediatric RSV sentinel surveillance system in hospitals, with the aim to provide disease incidence estimates, identify associated risk factors and assess RSV-related illness severity. Previous studies showed RSV subtype A to be associated with a more severe disease compared with subtype B.[55] Among cases reported within the paediatric RSV sentinel surveillance system, between June 2021 and February 2022, more RSV subtype A (67%) than RSV subtype B (33%) virus were detected. As such, more research is needed on whether viral characteristics in interaction with host susceptibility factors increased severe illness in the 2021-2022 RSV epidemic.[56]

CONCLUSION

An out-of-season RSV epidemic was identified, with a longer epidemic period compared with previous seasons. Possible reasons include relaxation of COVID-19 physical distancing measures and a greater proportion of population susceptible to disease, arising from an extended period of low exposure to RSV. As several factors may change the pattern of RSV activity, and risk of infection or pressures on the healthcare systems may occur at different times, countries should implement year-round surveillance RSV surveillance systems in order to be prepared for uncertain times. These findings might have an impact on public health planning regarding future RSV surges, namely, on the palivizumab prophylaxis period for high-risk infants.

AUTHOR CONTRIBUTIONS

All authors contributed equally to this manuscript.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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