Introduction of nirsevimab in Catalonia, Spain: description of bronchiolitis and the Respiratory Syncytial Virus incidence in the 2023/24 season

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Abstract

Purpose

Respiratory Syncytial Virus (RSV) causes most of the bronchiolitis and thousands of deaths annually, particularly in infants less than 6 months. In Catalonia (Spain), infants born between April 2023 and March 2024 aged 0–6 months during their first RSV season have been candidates to receive nirsevimab, the novel monoclonal antibody against RSV, since October 2023. We aimed to analyse the dynamics of all-causes bronchiolitis diagnoses and RSV community infections in the current season and compare them to pre-nirsevimab epidemics.

Methods

We collected epidemiological data from the Information System for Surveillance of Infections (SIVIC) in Catalonia on daily all-causes bronchiolitis clinical diagnoses and RSV-confirmed cases provided by rapid antigen tests in Primary Care Practices. We calculated the rate ratio (RR) for the incidence of all-causes bronchiolitis for children aged 0-11m-old concerning 12-35m-old between September 2014 and January 2024. We analysed the RR of the incidence of RSV-confirmed infection for 0-11m-old and 12-35m-old concerning the > 35m-old, from January 2021 to January 2024. We then computed the relative difference of the RR, named percentage of reduction of risk, between season 2023/24 and former epidemics.

Results

With a global coverage rate for nirsevimab of 82.2% in January 2024, the age-specific 0-11m-old RR (95%CI) of RSV infection incidence regarding > 35m-old was 1.7 (1.5-2.0) in last season 2023/24. The RR (95%CI) had been 7.4 (5.6–9.9), 8.8 (6.9–11.3), and 7.1 (5.7–8.9) in 2020/21, 2021/22 and 2022/23 seasons. Regarding the incidence of all-causes bronchiolitis for 0-11m-old group compared to the 12-35m-old, the pre-pandemic (2014/15-2019/20) and 2022/23 RR (95%CI) were 9.4 (9.2–9.6) and 6.0 (5.7–6.2) respectively, significantly higher than the RR of 3.6 (3.4–3.8) for the last season 2023/24.

Conclusions

Coinciding with the introduction of nirsevimab, the risk of RSV infection for infants aged 0-11m-old regarding > 35m-old has been reduced by 75.6% (73.4–77.5) from last season, and the risk for all-cause bronchiolitis regarding 12-35m-old by 61.9% (60.9–62.9) from the pre-pandemic period and by 39.8% (39.3–40.2) from 2022/23 epidemic, despite a high RSV community transmission, especially in older infants.

Summary

What is known:

- RSV is responsible for approximately 70% of bronchiolitis and causes severe disease, particularly in infants <6 months.
- Nirsevimab effectiveness against RSV-associated disease, particularly hospitalisations, was expected to be around 80%.
- Other Spanish regions, such as Galicia and Valencia, and European countries like Luxembourg and Germany, have already reported good results on implementing nirsevimab to prevent RSV-associated hospitalisations and PICUs.

What is new:

- We provide insight on the community incidence of RSV and all-causes bronchiolitis this season 2023/24 when nirsevimab has been introduced to the Catalan population.
- This study is conducted with primary healthcare data, which enables us to assess the burden of RSV infections and bronchiolitis in the commonly seasonally saturated Primary Healthcare.
- Our study reveals that the risk of all-causes bronchiolitis for infants aged 0-11 m-old regarding older infants has been reduced by 40% compared to the previous season and 62% compared to pre-pandemic standards, and for RSV infection has been reduced by 76%.

1 Introduction

The Respiratory Syncytial Virus (RSV) causes most of the bronchiolitis (60–80%) and thousands of deaths annually, particularly in infants < 6 months old (1)(2). The RSV epidemic is expected every year between October and March in tempered North-Hemisphere areas. Although the COVID-19 pandemic altered the circulation of RSV and its seasonal pattern, an epidemic pattern similar to the pre-pandemic has been observed again in the 2021/22 and 2022/23 seasons, causing severe disease and hospitalisation in infants, especially among the youngest.

On the other hand, the European Medicines Agency (EMA) recommended in September 2022 a marketing authorisation of nirsevimab, the novel monoclonal antibody against RSV, to prevent first seasonal episodes of RSV-associated lower respiratory tract disease (LRTI) in infants. Nirsevimab is expected to avoid RSV-associated severe disease by 80% (3). However, only a few European countries started the campaign for this preventive measure during the 2023/24 RSV season and countries like France (4, 5), and the United States (6) reported difficulties in distributing it due to a limited supply.

In Catalonia (Spain), all infants born between April 2023 and March 2024 (one-year cohort), aged 0 to 6 months during their first RSV season, and high-risk infants during the second season were eligible to receive nirsevimab (7). This immunisation has been broadly administered in Primary Care Practices (PCP) and Public and Private Hospitals. Coverage is publicly reported (8).

Besides, since the end of 2020, rapid antigen tests (RAT) have been available for paediatricians working at PCP to be potentially used for testing for Influenza A, Influenza B, Adenovirus, and RSV. These RATs have been performed on children with respiratory viral infection symptoms. Data on both RSV-confirmed infections with RAT and daily all-causes bronchiolitis clinical diagnoses from patients who attended PHC are publicly available in the Information System for Surveillance of Infections in Catalonia (SIVIC) database (9). PCP is free and universal in Catalonia.

We aimed to analyse the dynamics of all-causes bronchiolitis diagnoses and RSV-confirmed community infections in the current season once nirsevimab has been introduced.

2 Materials and methods

2.1 Data acquisition

The open-access SIVIC database was used to extract daily all-causes bronchiolitis clinical diagnoses (September 2014 - January 2024) and daily RSV-confirmed cases with RAT (January 2021 - January 2024) in Paediatric PCP (9). These electronic medical records are classified by age group (0–11 months old, 12–35 months old, > 35 months old). SIVIC extracts this data from the Primary Care Clinical History (PCCH). All public PCPs in Catalonia use the same PCCH.

We collected data on bronchiolitis diagnoses, including the International Classification of Diseases 10th version (ICD-10) codes J21, J21.0, J21.1, J21.8 and J21.9. This disease should be exclusively reported for infants ≤ 24 months, but the data source does not have this resolution. Hence, for this analysis, bronchiolitis for infants up to 35 months have been considered, knowing that the most burden of the disease affects infants ≤ 24 months. On another note, the protocol for performing RATs is available in the **Supplementary Material**. RATs are mostly recommended for children ≤ 24 months with viral respiratory infection suspicion but are not restricted to infants.

Reference populations per year and by age group have also been obtained from the SIVIC database. Access to the PCP system is universal and free in Catalonia.

2.2 Statistical analysis

We computed daily incidences of all-causes bronchiolitis disease or RSV infection as reported cases per 100,000 inhabitants. The average pre-pandemic season for description of all-causes bronchiolitis was created as the mean of the epidemics from 2014/15 to 2019/20, considering the whole period from September to August. Previous alignment was unnecessary due to the regularity of the bronchiolitis epidemic seasonality in Catalonia. The average 95% confidence interval (CI) was also provided.

For further analysis, we defined a bronchiolitis or RSV season as the period of three months containing the months before, during, and after the epidemic peak, i.e., November to January for all years except 2020/21, which was delayed to May 2021 - July 2021. For 2021/22 and 2022/23, it was anticipated from October to December.

Besides, we comprehensively depicted weekly RSV-infections incidence, RAT incidence named diagnostic effort, and positivity rates, i.e., the percentage of RSV-positive tests regarding the number of tests performed across the different age groups and study periods. A Mann-Whitney U test was employed to compare the most recent season, 2023/24, and prior seasons, 2020/21, 2021/22, and 2022/23. To account for multiplicity, the Bonferroni correction was implemented. We also analysed the percentage of RSV-confirmed infections for each paediatric age group (0-11m-old, 12-35m-old, > 35m-old), computing the percentage of weekly (7-days accumulated) infections corresponding to each age group based on the total number of weekly RSV cases.

In addition, we calculated the incidence rate ratios (RR) and associated 95% CIs for the incidence of all-causes bronchiolitis in 0-11m-old from seasons 2014/15 to 2023/24. We selected the 12-35m-old group as a baseline reference. Similarly, the RRs (95%CI) for the incidence of RSV infection in 0-11m-old and 12-35m-old from 2021/22 to 2023/24 were obtained, with the > 35m-old group as the baseline reference.

To compare last season, 2023/24, to pre-nirsevimab epidemics, we calculated the mean pre-nirsevimab RR with its 95% CIs. For bronchiolitis, seasons 2020/21 and 2021/22 were excluded, and 2022/23 was compared separately because of the alterations suffered due to the pandemic. The percentage of change in risk for RSV infection or all-causes bronchiolitis was assessed by computing the relative difference of the 2023/24 RR concerning pre-nirsevimab RRs. To rigorously evaluate the variation in RSV or bronchiolitis incidences between the different seasons, a Mann-Whitney U test was performed in Python 3.11.9 (10).

The entire code and process, including libraries used and variable names, is available for further reference and replication at https://github.com/BIOCOM-SC/cloud-of-codes/tree/main/Aida_Perramon-Malavez/Nirsevimab.

3 Results

3.1 All-causes bronchiolitis description

3.1.1 Comparison of pre-pandemic and post-pandemic all-causes bronchiolitis epidemics with 2023/24

We depicted the incidence of all-causes bronchiolitis across infants 0-11m-old, 12-35m-old, and the combined group (all of them, ≤ 35 months), comparing the average incidence from pre-pandemic seasons (95%CI) with the last three epidemics (Fig. 1). In the 2023/24 season, bronchiolitis incidence notably decreased compared to pre-pandemic years among 0-11m-old. Conversely, incidence increased among children 12-35m-old, aligning with the ongoing post-pandemic trend. Analysis of the epidemic's overall impact on the combined ≤ 35m-old age group revealed a pattern consistent with that observed in the 0-11m-old, as anticipated due to the higher disease burden in this cohort. This analysis indicated an

overall reduction in bronchiolitis incidence during the 2023/24 season, with seasonality closely resembling the pre-pandemic average.

Figure 1. Daily bronchiolitis clinical diagnoses data per 100,000 inhabitants for **(A)** 0-11m-old, **(B)** 12-35m-old, **(C)** ≤ 35m-old. The grey line represents the average pre-pandemic season (2014/15 to 2019/20) with 95% CI. The yellow, blue, and red lines correspond to seasons 2021/22, 2022/23 and 2023/24, respectively.

3.1.2 Associated risk of all-causes bronchiolitis by age and per season

For the 0-11m-old group compared to the 12-35m-old, the pre-pandemic and 2022/23 RRs (95%CI) were 9.4 (9.2–9.6) and 6.0 (5.7–6.2), respectively, significantly higher than the RR of 3.6 (3.4–3.8) for the last season 2023/24. Significance results from the Mann-Whitney U test comparing incidences of the aforementioned periods also showed $p < 0.001$. (**Supplementary Material**)

Hence, in 2023/24, the risk for all-causes bronchiolitis in infants 0-11m-old compared to 12-35m-old has been reduced by 61.9% (60.9–62.9) from the pre-pandemic period and by 39.8% (39.3–40.2) from the 2022/23 epidemic.

3.2 RSV infections description

3.2.1 Comparison of 2021/22 and 2022/23 RSV epidemics with 2023/24 by age group

We analysed the percentage of confirmed RSV infections for each age group (Fig. 2). A significant increase in RSV cases in the last season 2023/24 may be due to a higher diagnostic effort for age groups ≥ 12m-old.

Figure 2. Percentage of weekly RSV infections (left axis) corresponding to 0-11m-old (blue), 12-35m-old (green), > 35m-old (magenta) concerning total number of RSV infections (black, right axis).

However, positivity rates for all age groups were similar to the season 2020/21 (summer 2021) (Fig. 3), the first during the COVID-19 pandemic, when there was a larger susceptible cohort not previously exposed to RSV and therefore naïve to the infection. This hypothesis, named immunity debt, justified the higher proportion of RSV infections in the 12-35m-old group in that season (11). Conversely, during the peak of season 2023/24, 30% of the RSV infections were in children > 35m-old, compared to 20% in 0-11m-old or 50% in 12-35m-old. Hence, regardless of the diagnostic effort, findings suggest a significantly increased community transmission of RSV in children ≥ 12m-old ($p < 0.001$).

3.2.2 Associated risk of RSV infection to age, per season

For the 0-11m-old group, the RRs (95%CI) before 2023/24 were 7.4 (5.6–9.9), 8.8 (6.9–11.3), and 7.1 (5.7–8.9) in 2020/21, 2021/22 and 2022/23 seasons, significantly higher than the RR (95%CI) of 1.7 (1.5-2.0) in last season 2023/24. (Fig. 4) Significance results from the Mann-Whitney U test comparing incidences of the periods mentioned above also showed $p < 0.001$.

Hence, in 2023/24, the risk for RSV infection in infants 0-11m-old regarding > 35m-old has been reduced by 76.7% (73.0-79.9), 80.3% (78.0-82.5) and 75.6% (73.4–77.5) from 2020/21, 2021/22 and 2022/23 epidemics, respectively.

4 Discussion

Since October 2023, in Catalonia, nirsevimab has been recommended, financed with public funds, and administered in all PCPs and hospitals as a preventive measure to protect children against RSV in their first season and high-risk children in their second RSV season. It was expected to reduce severe disease by 80% (12). Our findings suggest that the risk of RSV infection for infants aged 0-11m-old regarding > 35m-old has been reduced by 75.6% (73.4–77.5) from last season, and the risk for all-cause bronchiolitis regarding 12-35m-old by 61.9% (60.9–62.9) from the pre-pandemic period and by 39.8% (39.3–40.2) from 2022/23 epidemic, despite a high RSV community transmission, especially among children aged ≥ 12 months. Remarkably, the reduction in RR for bronchiolitis diagnoses would be more significant if only RSV-bronchiolitis were considered, but these data are not publicly available at the primary care level.

The coverage rate for nirsevimab for those born between April and September 2023 has been 88%, and the global coverage rate for children under 1 year of age, estimated until the end of January 2024, is 82.2%. Note that there is a delay in data registration; therefore, these percentages might be even higher than reported.

Unlike other previously published studies about reducing RSV-associated hospitalisation with nirsevimab (13, 14), our study used PCP data, which contains the greatest health care burden as it is the primary health care and because of its universality and gratuity, hence with a larger sample size and study period from September 1, 2014, to January 31, 2024. Besides, we provide the RR of incidence of RSV infection and all-causes bronchiolitis diagnosis of infants eligible for nirsevimab concerning non-eligible cohorts, allowing for quantifying the consequences of the immunisation on the RSV epidemics and potentially related severe disease (bronchiolitis).

Similarly, concerning the last outbreak, we found a substantial reduction in all-causes bronchiolitis for 0-11m-old. Additionally, there were fewer cases of RSV infection in this age group. Nonetheless, we observed more all-causes bronchiolitis cases and a higher incidence of RSV infection in older infants, particularly 12-35m-old, pointing to a high-circulation epidemiological context in the absence of immunisation. Previously published studies mentioned an increased mean age of hospital-admitted children but did not provide a comprehensive age-specific analysis (13, 14).

Comparable findings have been observed in Galicia, another autonomous community of Spain that introduced nirsevimab in the autumn of 2023 (15). They also noted an increased community transmission of RSV, although lower 0-11m-old incidences of bronchiolitis and RSV infections.

Interestingly, RSV positivity for 0-4y-old infants in Germany in 2023/24 was similar to the previous year (16), even after the implementation of the immunisation. After introducing the immunisation in France, bronchiolitis in children < 35m-old reached pre-pandemic incidences during season 2023/24, slightly lower than in 2022/23 (17). These differences would be attributed to the divergent immunisation protocols and coverage rates and the reported irregularities in nirsevimab supplies (5).

As for limitations, we must consider that compliance with the protocol for testing children with a RAT is not necessarily homogeneous among PCP paediatricians despite its availability; therefore, data about community incidence cannot be deduced from RSV-confirmed cases. Nevertheless, we assume there have not been significant changes in time in each particular PCP, so the season-to-season compatibility is still feasible. Also, aggregated epidemiological data do not incorporate relevant confounders like those related to socioeconomic factors, which could bias the results. Nevertheless, the magnitude of the measured impact is consistent with other results, thus pointing to a minor effect of these confounders. Moreover, when calculating the RR, a historically consistent baseline group should be used to provide robustness when comparing between periods. For that reason, the > 35m-old was used as the control group to assess the divergence in the incidence of RSV infections among epidemics since, in every epidemic, the number of infected > 35m-old was similar. However, for all-causes bronchiolitis, we are limited by the diagnosis criteria and the age resolution of the reported data. Thus, we used 12-35m-olds as the control group, which may have biased our results.

Despite this, our study also has several strengths. Using primary care data, we account for all children attending PCP in Catalonia, potentially 1.5 million children (18) since healthcare is universal and free. Moreover, while most previous studies have only reviewed hospitalisation data, we have provided a depiction of the changes in primary school outcomes since the introduction of nirsevimab, which we have not found in any previous literature. Therefore, this work provides epidemiological context for this 2023/24 RSV season in Catalonia, which can be used for other related studies willing to estimate the effectiveness of nirsevimab. Finally, the quality and completeness of the SIVIC database is to be highlighted, being used for surveillance of respiratory infections in Catalonia and served in numerous studies (19–21).

5 Conclusion

This season 2023/24 has had a significantly lower comparative risk of RSV infection incidence (by 75.6% (73.4–77.5)) and all-cause bronchiolitis incidence (by 39.8% (39.3–40.2)) from last season, in infants 0-11m-old, even in a high RSV season community burden in Catalonia. Children 12-35m-old carried the main burden of community RSV infection in season 2023/24. During the latter, there have been significantly higher all-causes bronchiolitis and RSV infection incidences in children ≥ 12m-old. These

differences from previous seasons might be attributed to the introduction of the immunisation campaign with nirsevimab.

Declarations

Author Contribution

A.P-M., C.P. and A.S-A. wrote the main manuscript text, A.P-M. prepared figures 1-4, statistical analyses and the supplementary material. E.H. assisted the statistical analyses. A.P-M., C.P., A.S-A., E.C. and E.H. participated in the methodology description and interpreted the results. All authors participated in the discussion and reviewed the manuscript.

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Data Availability

Data is provided within the manuscript or supplementary information files.

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Figures

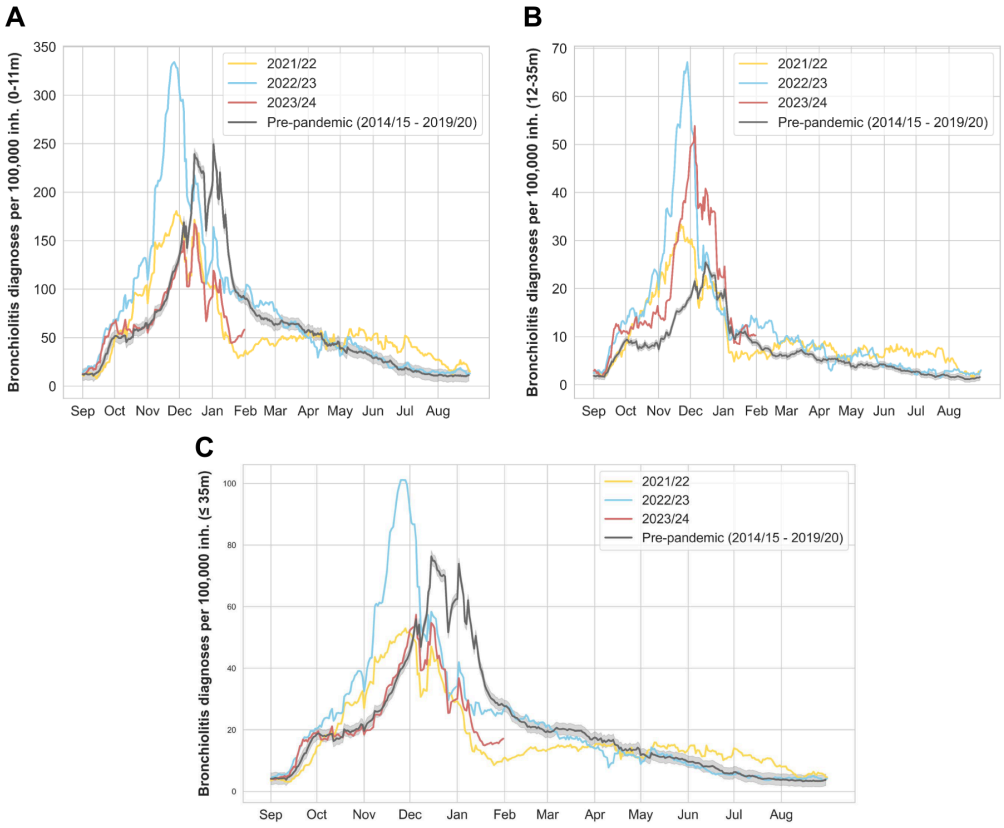

Figure 1

Daily bronchiolitis clinical diagnoses data per 100,000 inhabitants for **(A)** 0-11m-old, **(B)** 12-35m-old, **(C)** ≤35m-old. The grey line represents the average pre-pandemic season (2014/15 to 2019/20) with 95% CI. The yellow, blue, and red lines correspond to seasons 2021/22, 2022/23 and 2023/24, respectively.

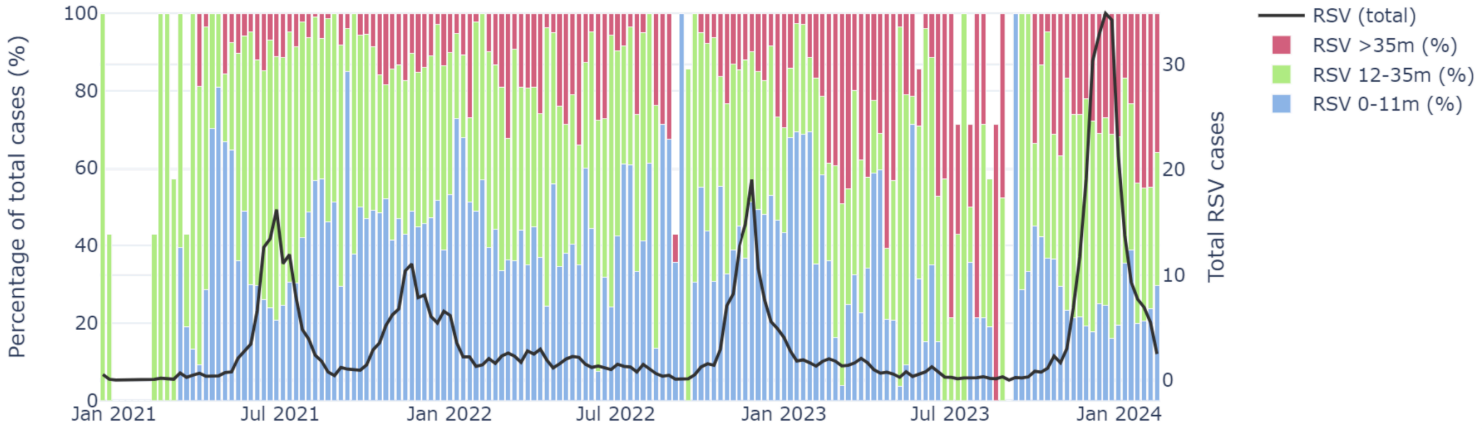

Figure 2

Percentage of weekly RSV infections (left axis) corresponding to 0-11m-old (blue), 12-35m-old (green), >35m-old (magenta) concerning total number of RSV infections (black, right axis).

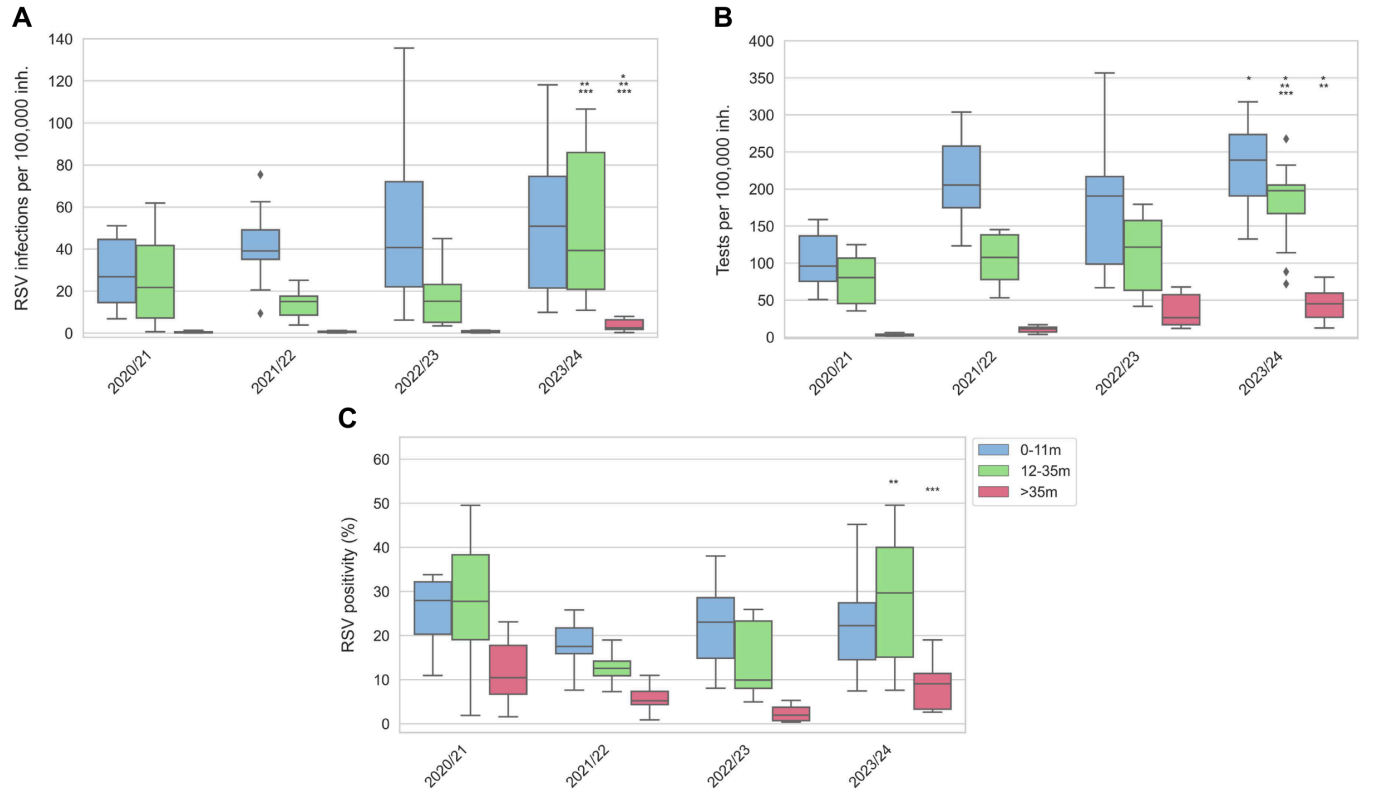

Figure 3

(A) Weekly RSV incidence, **(B)** diagnostic effort and **(C)** positivity for 0-11m-old (blue), 12-35m-old (green) and >35m-old (magenta) children and the RSV epidemics from 2020/21 to 2023/24. A Mann-Whitney U test was performed to compare medians between seasons 2023/24 and 2020/21 (* if p <0.05), 2021/22 (** if p <0.05) and 2022/23 (*** if p <0.05). P-values were corrected using the Bonferroni correction.

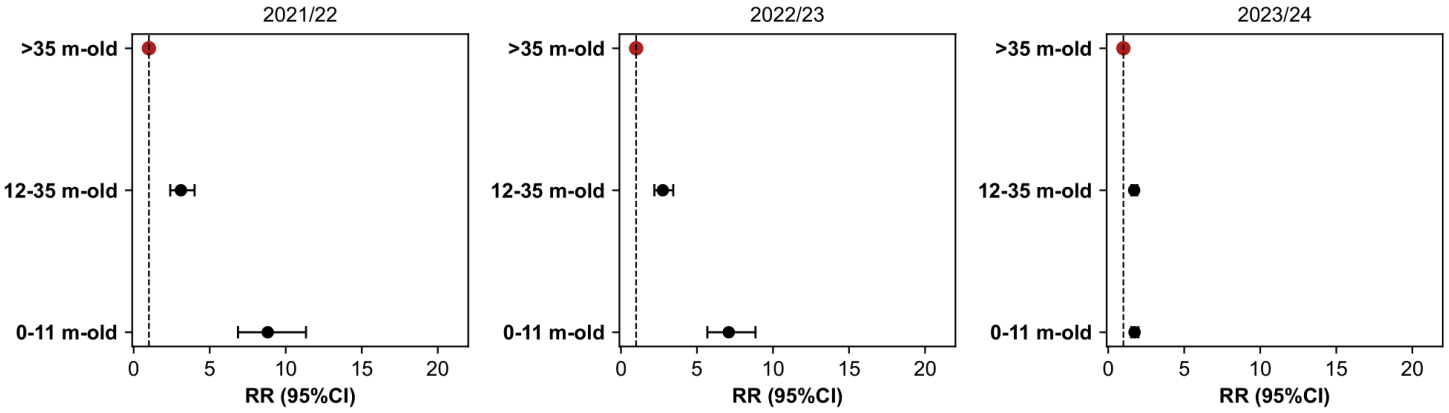

Figure 4

Rate Ratio (RR) of RSV infection for age groups 0-11m-old and 12-35m-old, regarding >35m-old, for seasons 2021/22, 2022/23 and 2023/24.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryMaterial.docx