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Comparative analysis of acute respiratory infections of viral etiology in children under 6 months with and without nirsevimab in the Balearic Islands (2022–2023 and 2023–2024)

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ABSTRACT

Introduction: Since 2023, a monoclonal antibody (nirsevimab) specifically directed against the preF form of RSV has been marketed in Spain. The impact of late immunization in the population <6 months as a cause of other respiratory infections requiring a hospital visit has been analyzed.
Material and methods: The viral etiology of acute respiratory infections (ARIs) diagnosed in the 2022–2023 and 2023–2024 seasons has been prospectively compared, and in this last season between recipients and non-recipients of nirsevimab. Global provisional coverage was 77% of the population.
Results: In the 2022–2023 season, 303 < 6 months with an ARI were detected, while in the 2023–2024 season there were 278 minors (19% less). The positivity in the first season was 79.9% compared to 70.5% in the current season. A significant difference has been observed in the detection of RSV between both groups and a decrease of 82.9% of cases in the current season. Of the 278 cases <6 months detected in the 2023–2024 season, 192 (69.1%) received immunization with nirsevimab and 86 (30.9%) did not receive it. The percentage of positivity in those immunized was 69.3%, compared to 73.3% in those not immunized. Significant differences have been observed in the detections of RSV and influenza between both groups.
Conclusions: Immunization at <6 months with nirsevimab has shown a significant reduction in RSV infections compared to the previous season. It does not seem, however, that it can reduce infections by other respiratory viruses.

Análisis comparativo de las infecciones respiratorias agudas de etiología viral en menores de 6 meses con y sin nirsevimab en Baleares (2022-2023 y 2023-2024)

Palabras clave:
Virus respiratorio sincitial
Nirsevimab
Otros virus respiratorios

RESUMEN

Introducción: Desde 2023 se comercializa en España un anticuerpo monoclonal (nirsevimab) dirigido específicamente frente a la forma preF del VRS. Se ha analizado el impacto de la inmunización tardía en la población < 6 meses como causa de otras infecciones respiratorias con necesidad de visita hospitalaria.
Material y métodos: Se ha comparado de forma prospectiva la etiología viral de las infecciones respiratorias agudas diagnosticadas en las temporadas 2022–2023 y 2023–2024, y en esta última temporada entre los receptores y no receptores de nirsevimab. La cobertura provisional global fue del 77% de la población.
Resultados: En la temporada 2022-2023 se detectaron 303 < 6 meses con una infección respiratoria aguda (IRA), mientras que en la temporada 2023–2024 fue de 278 menores (un 19% menos). La positividad en la primera temporada fue del 79,9%, frente al 70,5% de la temporada actual. Se ha observado una diferencia significativa en la detección de VRS entre ambos grupos y una disminución del 82,9% de casos en la

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temporada actual. De los 278 casos de < 6 meses detectados en la temporada 2023–2024, 192 (69,1%) recibieron inmunización con nirsevimab y 86 (30,9%) no la recibieron. El porcentaje de positividad en los inmunizados fue del 69,3%, frente al 73,3% de los no inmunizados. Se han observado diferencias significativas en las detecciones de VRS y gripe entre ambos grupos.

Conclusiones: La inmunización a los < 6 meses con nirsevimab ha mostrado una reducción significativa de infecciones por VRS en comparación con la temporada anterior. No parece, sin embargo, que pueda disminuir las infecciones por otros virus respiratorios.

Introduction

Respiratory syncytial virus (RSV) was discovered in 1955, designated as chimpanzee coryza agent and associated with bronchiolitis in children in 1957.[1,2] It causes acute respiratory diseases (bronchiolitis and pneumonia), which occur mainly in epidemic form during the winter months. Although it can affect the entire population, its pathological impact is much greater in the paediatric population (aged under five years) and in older adults (over-65 s). It is estimated to be responsible for 22% of acute respiratory infections (ARI) in the child population. A 2015 global study estimated that RSV caused 33.1 million ARI per year, resulting in nearly 3.2 million hospitalisations and some 59,000 in-hospital deaths in children under five years of age.[2–4] In children under six months of age, RSV causes around 1.4 million hospitalisations and nearly 27,300 deaths annually.[3]

Until a year ago, there were no preventive measures available to address RSV infections, so most children became infected naturally.[4] However, in 2023, a monoclonal antibody (nirsevimab) was marketed in Spain that specifically targets the "zero site (Φ)" (highly conserved) of the pre-F form of RSV.[5–7] Different clinical trials have demonstrated an efficacy close to 85% in preventing hospital admission and ICU admission of patients infected by RSV, as well as a significant decrease in the overall disease burden (visits to health centres and hospital accident and emergency [A&E] departments).[8–11]

There are no studies on the viral aetiology of ARI affecting the population immunised with nirsevimab. We therefore decided to analyse the impact of this immunisation on the need for hospital visits (A&E burden) due to ARI in the population under six months of age. We compared the viral aetiology of ARI diagnosed in the 2022–2023 and 2023–2024 seasons, and in the latter season, between recipients and non-recipients of the anti-RSV monoclonal antibody.

Material and methods

In the Balearic Islands, RSV immunisation began late, starting on 27 November 2023 (week 48). Those born from 1 April to that date were immunised in their local health centres, and those born after that date were immunised after birth in the different hospitals.[12,13] The overall provisional coverage was 77% of the target population.

From 27 November 2023 to 31 March 2024, all infants under six months of age who attended the A&E with an ARI (bronchiolitis or similar) were prospectively studied; each one had a nasopharyngeal aspirate sample taken and this was transported straight to the laboratory. The different respiratory viruses were detected using a commercial real-time polymerase chain reaction (RT-PCR) (Allplex Respiratory Assay, Seegen), which simultaneously detects and differentiates 18 different respiratory viruses. In the 2022–2023 season, SARS-CoV-2 was detected using a different technique, separate from the rest of the respiratory viruses, and the positive results have not been included. The results were compared with those obtained in the 2022–2023 season. We only studied the viral aetiology of these infections, not looking at any relationship with possible associated hospital admission.

Results

The epidemiological change over time of RSV detection in the entire paediatric population (<15 years) studied in both seasons is shown in Fig. 1. The 2022–2023 season lasted 16 weeks and the maximum epidemic peak was 58.8 cases/100,000, while the current season lasted 10 weeks and reached a maximum of 44.1 cases/100,000.

During the same study period, in the 2022–2023 season, 303 children under six months of age were detected with an ARI, while in the 2023–2024 season, the figure was 278 children (19% fewer). Detection in the first season was 79.9% compared to 70.5% in the current season. Only one virus was detected per patient (Table 1).

In the 2022–2023 season, the predominant virus was RSV (36.6), followed by rhinovirus (25.7%) and influenza virus (6.2%), with 10 different viruses detected in total. SARS-CoV-2 has not been included this season, as it was performed using another technique and data on this virus were not obtained in this age group. In the current season, the predominant viruses were rhinovirus (17.6%), metapneumovirus (14%), coronavirus OC43 (7.5%), RSV (6.8%) and influenza virus (6.4%), with 11 different viruses detected, including SARS-CoV-2 (5.3%). Of the 242 patients in whom some virus was detected (positive cases) in the 2022–2023 season, RSV accounted for 45.6% and the influenza virus 7.8%, compared to 9.6% and 9.1%, respectively, in the 2023–2024 season (196 cases). A significant difference in RSV detection was observed between the two groups and a decrease of 82.9% in cases in the current season.

Of the 278 cases of children under six months detected in the 2023–2024 season, 192 (69.1%) were immunised with nirsevimab and 86 (30.9%) were not, either due to refusal or not attending the consultation (Table 2). The percentage of positivity in those immunised was 69.3%, compared to 73.3% of those not immunised. The predominant viruses in the immunised group were: rhinovirus (18.2%), influenza virus (5.7%), SARS-CoV-2 (5.2%) and RSV (4.1%), while in the non-immunised group the most commonly detected viruses were: rhinovirus (16.2%), RSV (12.7%), influenza virus (8.1%) and SARS-CoV-2 (5.8%). Significant differences between the two groups were found in the detection of RSV and influenza. The eight cases of RSV in immunised children corresponded to two RSV-A (25%) and six RSV-B (75%), while in the 11 cases of RSV in non-immunised children, four were RSV-A (36.4%) and seven RSV-B (63.6%).

Discussion

From an epidemiological point of view, the current RSV season has been quantitatively lower than the 2022–2023 season, not only in terms of duration but also in community intensity; 501 cases of RSV infection were detected during that season, compared to 280 this season (44.2% fewer cases). These initial data seem to point to a first impact of universal immunisation with nirsevimab, despite

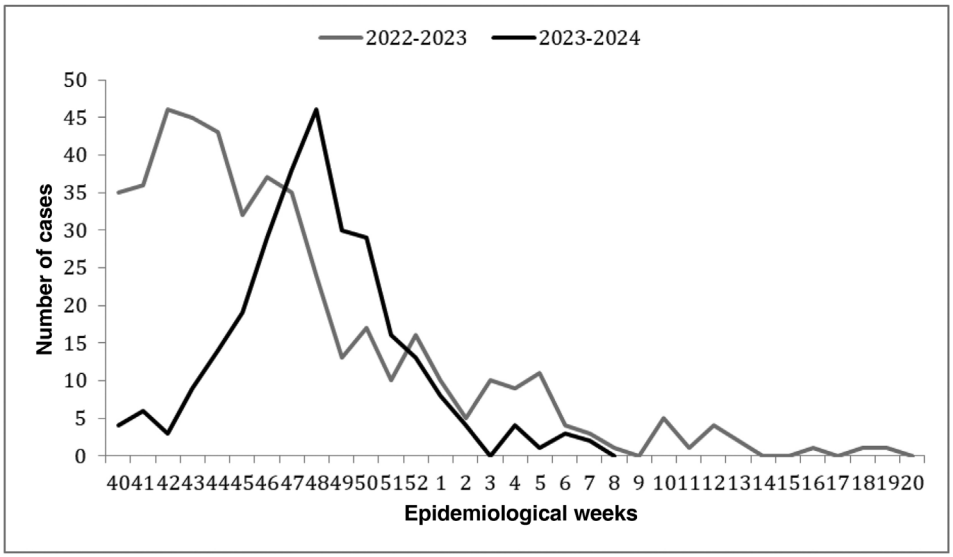

Fig. 1. Epidemiological change over time of RSV detections in the total paediatric population (<15 years) in the 2022–2023 and 2023–2024 seasons.

Table 1
Comparison between viruses detected in children under six months of age with acute respiratory infection.

	2022–2023 (n = 303)	2023–2024 (n = 278)
Rhinovirus	78 (25.7)	49 (17.6)
Metapneumovirus	11 (3.6)	39 (14.0)
Coronavirus OC43	2 (0.6)	21 (7.5)
RSV	111 (36.6)	19 (6.8)
Influenza virus	19 (6.2)	18 (6.4)
SARS-CoV-2	0	15 (5.3)
Parainfluenzavirus 3	1 (0.3)	13 (4.6)
Adenovirus	9 (2.9)	10 (3.5)
Bocavirus	2 (0.6)	6 (2.1)
Enterovirus	7 (2.3)	4 (1.4)
Parainfluenzavirus 4	2 (0.6)	2 (0.7)
Negative	61 (20.1)	82 (29.5)
Positive	242 (79.9)	196 (70.5)

Number of patients (%). There was only one virus per patient.
In the 2022–2023 season, positive cases of SARS-CoV-2 could not be included.

Table 2
Detection of respiratory viruses in patients under six months of age with acute respiratory infection (2023–2024).

	With nirsevimab (n = 192)	Without nirsevimab (n = 86)
Rhinovirus	35 (18.2)	14 (16.2)
Metapneumovirus	29 (15.1)	10 (11.6)
Coronavirus OC43	16 (8.3)	5 (5.8)
Influenza virus	11 (5.7)	7 (8.1)
SARS-CoV-2	10 (5.2)	5 (5.8)
Parainfluenzavirus 3	10 (5.2)	3
RSV	8 (4.1)	11 (12.7)
Adenovirus	6	4
Bocavirus	4	2
Enterovirus	3	1
Parainfluenzavirus 4	1	1
Negative	59 (30.7)	23 (26.7)
Positive	133 (69.3)	63 (73.3)

Number of patients (%). There was only one virus per patient.

the very late start, already at the peak of the epidemic, and with a vaccination coverage of 77%, well below the national average of 91.9% (range between 85.7% and 96.7%).[14] However, in the previous season, it was predominantly the RSV-A serotype that circulated (70.2%), while this season it was RSV-B (82.4%); the RSV-B subtype has been shown to affect the older paediatric population.[15] It is therefore difficult to assess this comparative overall decline in cases.

Comparing the viral aetiology of children under six months of age between the two seasons, we found that in the 2022–2023 season, a respiratory virus was detected in 79.9% of these patients, compared to 70.5% of the current group, without identifying any statistical differences. It is worth noting that in the previous season, without immunisation, RSV was the most predominant virus, with 111 cases (36.6%), compared to 19 cases (6.8%) in the current season, which is a statistically significant difference. RSV accounted for 45.8% of all viruses detected in the 2022–2023 season, compared to 9.6% in the current season. The high prevalence of RSV in the previous season barely allowed the circulation of other respiratory viruses, and in the current season the ecological niche left by RSV has been occupied by other viruses, mainly metapneumovirus.[16]

Analysing the group of children aged under six months – the target of immunisation – between the two seasons, we found that 278 cases were detected overall this season, which represents a decrease of only 19.1%. These data refer only to this age group, as a 41% increase in cases was observed in the two-to-five age group; that is, there was a shift of RSV infection to older ages, in which the virus does not have the same morbidity as in children under six months of age.[4]

Nirsevimab is a highly-specific monoclonal antibody against the RSV pre-F protein; its administration would not therefore be expected to lead to a decrease or an effect on other respiratory viruses and, as a consequence, on acute respiratory disease.[6,7] We found that some respiratory virus (including RSV) could be detected in 69.3% of immunised children, compared to 73.3% of non-immunised children, which seems to indicate that immunisation does not prevent or avoid respiratory infection by viruses other than RSV. In their phase 3b HARMONIE study, Drysdale et al.[11] reported a 58% reduction in the incidence of hospital admissions for lower respiratory tract disease from any cause, including other respiratory viruses. Our study is only aetiological and was carried out with patients who came to the Accident and Emergency department with ARI, without analysing whether or not their hospital admission was determined by other viral respiratory infections.

The respiratory viruses that infected both groups are practically the same, that is, those that circulated in the absence of RSV. Rhinovirus and metapneumovirus were the viruses most frequently detected in both groups. The influenza A virus appears to have

infected somewhat more non-immunised patients (8.1% compared to 5.7%), but not significantly. The greatest impact, as expected, was the detection of RSV and, although the difference between the two groups was only three cases, the percentages of detection (4.1% versus 12.7%) do show statistical significance. In the immunised group, nirsevimab would have a vaccine effectiveness of 95.9%. Of all the positive cases detected in the immunised group, RSV accounted for only 6% (8/133), compared to 17.4% (11/63) in the non-immunised group. That is to say, late immunisation has led to a significant reduction in the number of cases in that group and also overall since this preventive process began.

The eight cases of children immunised with nirsevimab who developed RSV infection could probably be explained by vaccination failures (viral load cycle threshold [CT] <26), by the fact that the effectiveness of the monoclonal does not exceed 85%,[5–7] or by escape mutants resistant to it. However, studies carried out on these mutants, mainly RSV-B, have shown a circulation below 1% of the total, and that does not appear to have changed in recent seasons.[17] This is logical, as until now RSV circulated freely without any human immunological pressure; therefore, from now on, the molecular characteristics of RSV detected in the immunised population should be monitored.[18]

Despite its late implementation, universal immunisation with nirsevimab in children under six months of age in the Balearic Islands has shown a significant reduction in RSV infections compared to the 2022–2023 season. It does not appear, however, that it can reduce infections by other respiratory viruses, especially by metapneumovirus, which seems to be able to occupy the ecological niche left by RSV after its drastic elimination, and which could be prevented by common immunisation with RSV.[19] In subsequent seasons, it will be necessary to evaluate whether the new respiratory viruses that are occupying the RSV niche led to hospital admission rates similar to or lower than this virus. In our study, nirsevimab only reduced A&E visits by 19%, since patients came in for other viral aetiologies. To determine the real impact of nirsevimab in the infant population under six months of age, it is very important to continue monitoring subsequent RSV epidemic seasons with complete universal immunisation both epidemiologically and virologically.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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