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Seasonality and severity of respiratory syncytial virus during the COVID-19 pandemic: a dynamic cohort study

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ABSTRACT

Objectives: To investigate seasonality, epidemiologic characteristics, and clinical severity variations of respiratory syncytial virus (RSV)-associated hospitalizations following the easing of COVID-19 restrictions in Tuscany, Italy, up to the 2022-2023 season.

Methods: From 2017 to 2023, a dynamic cohort consisting of all resident children aged ≤2 years was followed up in regional registries. The person-time incidence rate of RSV-associated hospitalizations per 1,000 person-years and risk of severe hospitalization (intensive care unit, continuous positive airway pressure, or mechanical ventilation) per 100 RSV hospitalizations were calculated. RSV seasonality was investigated with retrospective methods.

Results: A total of 193,244 children were followed up. After the easing of restrictions, RSV epidemics showed earlier seasonality and shorter duration compared with pre-pandemic (2017 to 2019), with this deviation decreased in 2022-2023. In 2021-2022 and 2022-2023, the incidence rate of RSV-associated hospitalizations significantly increased compared with pre-pandemic (2022-2023 risk ratio 3.6, 95% confidence interval 3.3-4.0), with larger increases among older age groups. Among hospitalized children, only those aged ≥12 months showed an increased risk of severe hospitalization, particularly during 2021-2022 (risk ratio 4.7, 95% confidence interval 1.5-24.3).

Conclusions: Our findings suggest a gradual return of RSV epidemics to the pre-pandemic pattern, although relevant increases in disease incidence persist. Reduced regular RSV exposure among older children may lead to declining immunity and increased severe outcome risks.

Introduction

The respiratory syncytial virus (RSV) is the most common cause of acute lower respiratory tract infections (ALRI) in children younger than 2 years globally [1]. Before the COVID-19 pandemic, RSV circulation followed a generally predictable seasonal pattern each year depending on the latitude; epidemics typically occurred from November to April in the Northern Hemisphere [2]. COVID-19 was first reported in December 2019 and officially declared as a pandemic by the World Health Organization in March 2020 [3]. With the onset of the COVID-19 pandemic and the implementation of numerous non-pharmacologic interventions (NPIs), the circulation of RSV has been disrupted in many regions of the world [4]. In nearly all the European countries, no RSV epidemics were observed during the winter of the 2020/2021 season [5,6]. During the 2021/2022 season, as pandemic measures were eased, many countries saw unusual RSV epidemics, marked by resurgences occurring outside the typical season and high peaks of cases [4,7,8].

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Furthermore, changes in the age distribution of children hospitalized with RSV-associated ALRI were observed, with an increased proportion of cases reported in older children [8,9]. This was probably caused by the absence of viral exposure, which led to an increased pool of children who remained immunologically naïve at older age and of children with waning immunity [10]. The data from the 2022/2023 season suggests that seasonality is returning to the usual pre-pandemic patterns, whereas the shift of cases towards older children seems to persist [8,11]. However, the evidence remains inconclusive due to limited updated population studies.

Studies on the severity of RSV infection during the pandemic are scarce and report conflicting results [7,8,12–16]. Some studies have reported an increase in the need for intensive care admission and mechanical ventilation among children hospitalized for RSV [12–14], whereas others have not shown any difference or have indicated a milder severity [7,8,15,16]. The evidence primarily derives from single-center studies [8,12–14,16] or studies that have considered only the first RSV epidemic (or a portion thereof) occurring during the pandemic [7,14–16]. In addition, limited evidence showed an increased severity in the 2022-2023 season, suggesting the possibility of more virulent strains of RSV as potential contributors, besides waning immunity in children without repeated exposure to RSV [12,13,17].

Understanding perturbations in RSV epidemics has become crucial, especially following the arrival of long-acting monoclonal antibodies and maternal vaccines for preventing RSV infection, which opens the doors to the development of prevention programs for all children [18]. Thus, the aim of this study was to investigate the epidemiologic and seasonality changes of RSV-associated hospitalizations up to the two seasons following the easing of pandemic measures (2021-2022 and 2022-2023), compared with pre-pandemic seasons, in an area-based cohort of children younger than 2 years from Tuscany region (Italy). In addition, the study evaluated clinical severity variations of RSV-associated hospitalizations during both the 2021-2022 and 2022-2023 seasons.

Methods

Study design, population, and data sources

This is a retrospective cohort study conducted on administrative data from the Tuscany Region Public Health Care System (TRPHCS). Tuscany, located in central Italy, is an administrative region with a population of approximately 3.7 million residents and an area of approximately 23,000 km^2. The TRPHCS ensures universal healthcare coverage, comprising 34 general hospitals and four university hospitals. All acute hospital care for pediatric patients within the region is provided by the TRPHCS.

The study period covered six consecutive RSV seasons from 2017 to 2023. A season was defined from the beginning of the 27th week of a year to the end of the 26th week of the next year.

For each RSV season, a dynamic cohort consisting of all resident children younger than 2 years in Tuscany at the beginning of the season and those born during the season was included in the study. These children were identified from the Regional Population Registry; this registry comprises all residents of Tuscany and records migration events (i.e., departing and new residents), births and deaths in the region. A record-linkage procedure of the Population Registry with the regional Birth Registry and the Hospital Discharge Registry was performed using an anonymous unique identifier. Children with a missing or erroneous unique identifier were excluded from the analysis. In each seasonal cohort, children were followed up until they reached 2 years of age or until they had an RSV illness, the end of the season, death, or migration out from Tuscany region, whichever occurred first.

Study variables

For each cohort, the following children's characteristics were retrieved: sex, age at cohort entry, date of birth, and weeks of gestational age at birth (GA). Hospitalizations for ALRI associated with RSV were identified from the hospital discharge registry using the following International Classification of Diseases Ninth Revision, Clinical Modification (ICD-IX CM) codes in the primary and secondary fields: 079.6, 466.11, and 480.1; data on the laboratory confirmation of the RSV infection were not available in the hospital discharge registry. A subsequent hospitalization within 7 days after the conclusion of the first hospital stay was considered as part of the same unique hospitalization event. For each RSV-associated hospitalization, the following demographic and clinical characteristics were retrieved: age at hospitalization, hospital length of stay, use of continuous positive airway pressure (ICD-IX CM code: 93.90), intensive care unit (ICU) admission, use of mechanical ventilation (ICD-IX CM code: 96.7), and presence of co-infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The information was retrieved on whether infection was present at admission; if present on admission, date of hospital admission was used to identify the date of disease onset; otherwise, the onset date was calculated as the average between admission and discharge dates.

Severe RSV hospitalization was defined as an in-hospital stay in which at least one of the following events occurred: use of continuous positive airway pressure, ICU admission, or mechanical ventilation.

Statistical analysis

Categorical variables were presented as frequencies and percentages, whereas continuous variables were described as median and interquartile range. Children were classified based on GA into the following groups: very preterm (<32 weeks), moderate preterm (32-33 weeks), late preterm (34-36 weeks), and at-term (≥37 weeks).

For all the study period, the weekly counts of RSV-associated hospitalizations in children younger than 2 years were plotted. RSV hospitalization trend was interpreted in the light of the regional context of COVID-19 epidemiology (weekly confirmed COVID-19 new cases in the entire regional population, inclusive of the adults) and key events in terms of NPIs.

For determining the timing of RSV epidemics, methods frequently used in the literature were chosen, considering their data requirements to perform the analysis and the retrospective nature of the analysis [19]. Specifically, the mean detection threshold, wherein the epidemic period is defined by the weeks comprising no <60% of the average weekly number of hospitalizations for each season, was used to characterize RSV seasonality. In addition, a second method, the percentage of detection threshold, was used to further verify the results obtained with the mean detection threshold. In this method, the epidemic period was defined by the weeks during which RSV hospitalizations exceeded 1.2% of the total RSV hospitalizations per season, allowing for 1 week of discontinuity.

Seasonal incidence rate (IR) (person-time) of RSV-associated hospitalizations and severe hospitalizations were calculated per 1,000 population per year. The 95% confidence intervals (CIs) were obtained by means of the Poisson distribution [20]. Incidence rate ratios (IRR) for the RSV-associated hospitalizations and severe hospitalizations for the 2021/2022 and 2022/2023 seasons were calculated by comparing IRs of these seasons with the mean IR in the pre-pandemic seasons (2017-2018 and 2018-2019 seasons), the exact binomial method was used to estimate 95% CI. The 2019-2020 season was not considered for these comparisons as SARS-CoV-

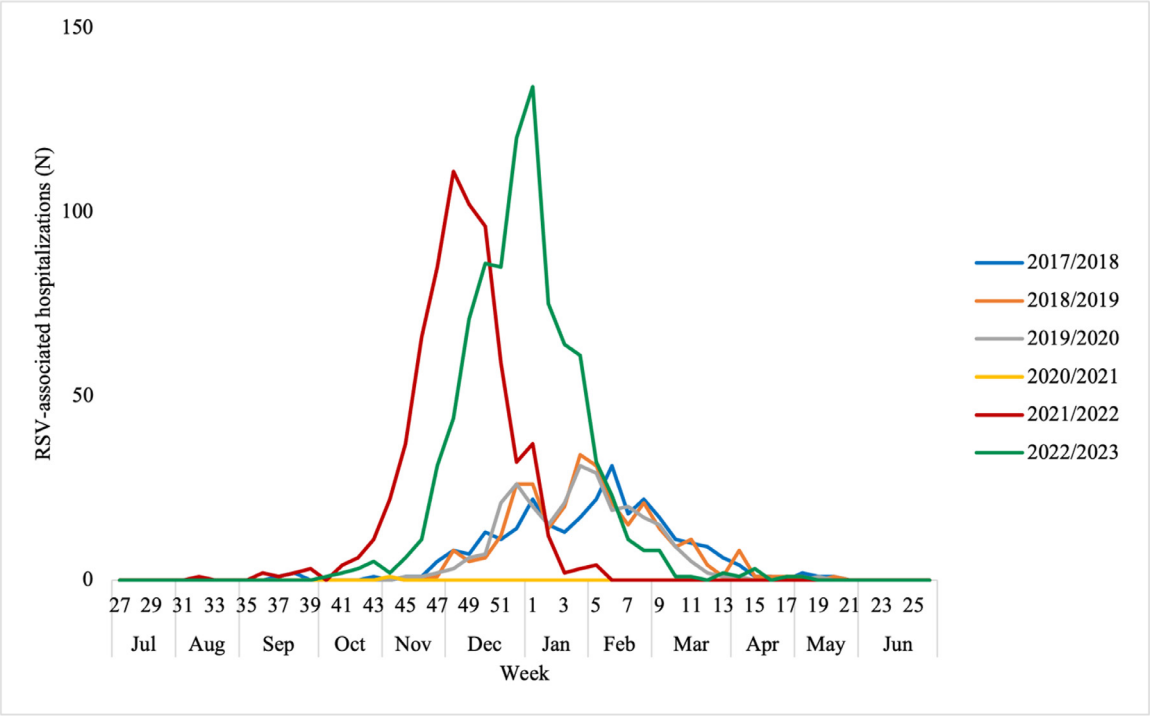

Figure 1. RSV epidemic seasonality characteristics in Tuscan children younger than 2 years (60% mean detection threshold retrospective method).

2 was already circulating during part of this season. Risks of severe hospitalization, ICU admission, and receiving mechanical ventilation were also calculated as proportion per 100 RSV-associated hospitalizations, with the 95% CI obtained by means of the Poisson distribution. Risk ratios (RR) for severe hospitalizations, ICU admission, and mechanical ventilation were calculated for the 2021/2022 and 2022/2023 seasons by comparing risks of these seasons with the mean risks in the pre-pandemic seasons (2017-2018 and 2018-2019 seasons), using the exact binomial method to estimate 95% CI.

Data analysis was performed using Stata 15SE (StataCorp LP, College Station, Texas).

Results

Study population

A total of 196,409 children younger than 2 years resided in Tuscany region during the study period. Of these, 3,165 (1.6%) children had a missing or erroneous unique identifier and were excluded from the analysis. In total, 193,244 (98.4%) children were included in the study, of whom 99,355 (51.42%) were male. Supplementary Table 1 presents the demographic characteristics of the cohorts, along with median follow-up duration and reasons for cohort exit. The number of children born during the study period declined from 25,598 in the 2017/2018 season to 21,580 in the 2022/2023 season. The age and sex distributions, as well as the proportion of children with a history of prematurity in the cohorts, were relatively constant over the study period (Supplementary Table 1).

RSV seasonality and seasonal incidence rates

In Tuscany, the first lockdown started on March 9th, 2020, when RSV hospitalizations in the 2019-2020 season had already declined sharply (Supplementary Figure 1). Figure 1 shows the RSV epidemic seasonality estimated with the 60% mean detection threshold method. Seasonality in the 2019-2020 season was comparable to the pre-pandemic seasons (2017-2018 and 2018-2019), with a slightly earlier conclusion. In these three seasons, the RSV epidemic typically began around the end of November or the beginning of December, peaked at the end of January or the beginning of February, and concluded by the middle of March or the beginning of April (Figure 1).

In the 2020-2021 season, two RSV-associated hospitalizations were observed; during this season, the traditional RSV epidemic period (November-April) coincided with the regional lockdown, which lasted until the end of April (Supplementary Figure 1). In the following season (2021-2022), the RSV epidemic started earlier (in the 43rd week), experienced an earlier peak of cases (48th week, 2021), and had a shorter duration (12 weeks), ending in February (in the second week), compared with the pre-

Table 1
Cumulative number and incidence rates of respiratory syncytial virus-associated hospitalizations and severe hospitalizations in Tuscan children younger than 2 years (season 2017-2018 to season 2022-2023).

	2017/2018 n (%)	2018/2019 n (%)	2019/2020 n (%)	2020/2021 n (%)	2021/2022 n (%)	2022/2023 n (%)
Respiratory syncytial virus-associated hospitalizations	287	293	274	2	698	893
Hospitalizations at peak week	31 (10.8)	34 (11.6)	31 (11.3)	-	111 (15.9)	134 (15.0)
Severe hospitalizations	64 (22.3)	58 (19.8)	62 (22.6)	0	170 (24.3)	179 (20.0)
Hospitalization incidence rate[a] (95% confidence interval)	5.3 (5.1-6.0)	5.7 (5.5-6.4)	5.6 (5.3-6.3)	0.04 (0.02-0.14)	15.3 (14.9-16.4)	19.9 (19.5-21.2)
Severe hospitalization incidence rate[a] (95% confidence interval)	1.2 (1.1-1.5)	1.1 (1.0-1.4)	1.3 (1.1-1.6)	0 (0-0.05)	3.7 (3.5-4.3)	4.0 (3.8-4.6)

[a] Per 1,000 person-years.

pandemic seasons (Figure 1). Furthermore, the peak number of RSV-associated hospitalizations increased significantly compared with the pre-pandemic seasons (Table 1). Similarly to the 2021-2022 season, the 2022-2023 season showed an anticipated seasonality pattern and a decreased duration compared with pre-pandemic seasons, albeit with a lesser deviation (Figure 1). Similar findings on seasonality were found using the 1.2% percentage of detection threshold method (Supplementary Table 2).

The overall IR of RSV-associated hospitalizations was relatively similar between the 2019-2020 season and the pre-pandemic seasons (Table 1). After the near-total absence of cases in the 2020-2021 season, the IR of RSV-associated hospitalizations almost tripled (15.3, 95% CI 14.9-16.4 per 1,000 person-years) in the 2021-2022 season or quadrupled (19.9, 95% CI 19.5-21.2, per 1,000 person-years) in the 2022-2023 season, compared with the pre-pandemic seasons. In the 2021-2022 and 2022-2023 seasons, the IR of severe hospitalizations showed increases of similar magnitude (Table 1).

Comparison of the respiratory syncytial virus-associated hospitalization characteristics between the pre- and pandemic seasons

Compared with the pre-pandemic average (2017-2018 and 2018-2019 seasons), the IR of RSV-associated hospitalization showed larger increases with age in both the 2021-2022 and 2022-2023 seasons, with the highest increase observed in children aged 18-23 months (IRR 5.1, 95% CI 3.0-8.7 and IRR 5.5, 95% CI 3.3-9.4 in the 2021-2022 and 2022-2023 seasons, respectively) (Table 2). Furthermore, IR of RSV-associated hospitalization stratified by GA showed the largest increases in late preterm and at-term children in both the 2021-2022 and 2022-2023 seasons (2022-2023 season: IRR 3.5, 95% CI 2.3-5.2 and IRR 3.8, 95% CI 3.4-4.2 for late-preterm and at-term children, respectively) (Table 2). In both the 2021-2022 and 2022-2023 seasons, the IR of severe hospitalizations showed a similar age trend to the IR of RSV-associated hospitalization, with a markedly more pronounced increase in children aged 12 months or older (Supplementary Table 3).

Regarding the clinical characteristics of RSV-associated hospitalizations, the median length of stay in each age in the admission group did not differ between the pre-pandemic seasons and both the 2021-2022 and 2022-2023 seasons (Supplementary Table 4). Furthermore, only 0.29% (2/669) and 1.36% (12/881) of the RSV-associated hospitalizations had a documented SARS-CoV-2 co-infection during the 2021-2022 and 2022-2023 seasons, respectively.

Among children younger than 2 years who experienced an RSV-associated hospitalization, the overall risks of severe hospitalization, ICU admission, and requiring mechanical ventilation were similar in the pre-pandemic seasons and in the 2021-2022 and 2022-2023 seasons (Table 3). Risk of severe hospitalization, stratified by age, revealed similar values within the age groups of 0-2 months and 3-11 months between the pre-pandemic seasons and both the 2021-2022 and 2022-2023 seasons. Among children aged 12 months or older, the risk of severe hospitalization significantly increased more than 4.7 times during the 2021-2022 seasons compared with the pre-pandemic seasons (5.6 cases [95% CI 1.1-16.2] and 26.2 cases [95% CI 17.3-38.1], per 100 RSV hospital admissions; RR 4.7 [95% CI 1.5-24.3]; $P = 0.003$). In the 2022-2023 season, the risk of severe hospitalization in this age group was positioned halfway between the values observed in the 2021-2022 season and those of the pre-pandemic seasons (13.0 cases [95% CI 7.4-21.1] per 100 RSV hospital admissions; RR 2.3 [95% CI 0.7-12.5], $P = 0.165$). The risk of ICU admission and requiring mechanical ventilation appear to follow a similar age pattern, although the small number of events in the 12-month or older age group does not allow

Table 2
Incidence rates and incidence rate ratios for respiratory syncytial virus-associated hospitalization in Tuscan children younger than 2 years by age group and gestational age at birth.

	Respiratory syncytial virus-associated hospitalization (N)			Incidence rate per 1,000 person-years (95% confidence interval)			Incidence rate ratio vs pre-pandemic[b] (95% confidence interval)			
	Pre-pandemic[a]	2021/2022	2022/2023	Pre-pandemic[b]	2021/2022	2022/2023	2021/ 2022	*P*-value	2022/ 2023	*P*-value
Total	580	698	893	5.5 (5.4-6.0)	15.3 (14.9-16.4)	19.9 (19.5-21.2)	2.8 (2.5-3.1)	<0.0001	3.6 (3.3-4.0)	<0.0001
Age (months)										
0-2	332	338	399	26.3 (25.3-29.3)	59.8 (57.6-66.5)	72.9 (70.4-80.3)	2.3 (1.9-2.7)	<0.0001	2.8 (2.4-3.2)	<0.0001
3-5	122	162	231	9.6 (9.0-11.4)	28.6 (27.1-33.3)	42.4 (40.5-48.1)	3.0 (2.3-3.8)	<0.0001	4.4 (3.5-5.6)	<0.0001
6-11	72	95	140	2.8 (2.5-3.4)	8.5 (7.9-10.3	12.5 (11.8-14.7)	3.1 (2.2-4.2)	<0.0001	4.6 (3.4-6.1)	<0.0001
12-17	31	52	70	1.2 (1.0-1.6)	4.6 (4.1-5.9)	6.1 (5.6-7.7)	3.9 (2.5-6.4)	<0.0001	5.3 (3.4-8.4)	<0.0001
18-23	23	51	53	0.9 (0.7-1.2)	4.3 (3.9-5.6)	4.7 (4.2-6.1)	5.1 (3.0-8.7)	<0.0001	5.5 (3.3-9.4)	<0.0001
Gestational age (weeks)										
<32	13	7	11	13.2 (10.6-22.0)	20.6 (15.0-40.5)	33.9 (26.6-58.7)	1.6 (0.5-4.2)	0.35	2.6 (1.0-6.2)	0.03
32-33	25	14	12	23.9 (20.6-34.8)	37.9 (30.6-61.8)	34.4 (27.3-58.3)	1.6 (0.8-3.2)	0.18	1.4 (0.7-3.0)	0.37
34-36	47	63	62	7.6 (6.8-10.0)	26.8 (24.4-34.0)	26.2 (23.9-33.4)	3.5 (2.4-5.3)	<0.0001	3.5 (2.3-5.2)	<0.0001
≥37	495	614	805	5.1 (4.9-5.6)	14.4 (14.0-15.6)	19.3 (18.8-20.6)	2.8 (2.5-3.2)	<0.0001	3.8 (3.4-4.2)	<0.0001

[a] Cumulative number from 2017-2018 season to 2018-2019 season.
[b] Seasonal mean from 2017-2018 season to 2018-2019 season.

Table 3
Risks for severe hospitalization, intensive care unit admission, and mechanical ventilation among children that experienced a respiratory syncytial virus-associated hospitalization by age group and gestational age at birth.

	N	N	N	Risk per 100 respiratory syncytial virus hospital admissions (95% confidence interval)			Risk ratio (95% confidence interval)			
	Pre-pandemic seasons[a]	2021/2022	2022/2023	Pre-pandemic seasons[b]	2021/2022	2022/2023	2021/2022 vs pre-pandemic[b]	*P*-value	2022/2023 vs pre-pandemic[b]	*P*-value
Severe hospitalization	122	170	179	21.0 (17.5-25.1)	24.4 (20.8-28.3)	20.0 (17.2-23.2)	1.1 (0.9-1.5)	0.217	1.0 (0.8-1.2)	0.680
Age										
0-2 months	93	104	125	28.0 (22.6-34.3)	30.8 (25.1-37.3)	31.3 (26.1-37.3)	1.1 (0.8-1.5)	0.512	1.1 (0.8-1.5)	0.415
3-11 months	26	39	38	13.4 (8.8-19.6)	15.2 (10.8-20.7)	10.2 (7.2-14.1)	1.1 (0.7-1.9)	0.630	0.8 (0.5-1.3)	0.294
≥12 months	3	27	16	5.6 (1.1-16.2)	26.2 (17.3-38.1)	13.0 (7.4-21.1)	4.7 (1.5-24.3)	0.003	2.3 (0.7-12.5)	0.165
Gestational age at birth										
<32 weeks	6	4	2	46.2 (16.9-100)	57.1 (15.6-100)	18.2 (2.2-65.6)	1.2 (0.3-5.2)	0.735	0.4 (0.04-2.2)	0.264
≥32 & <37 weeks	18	24	17	25.0 (14.8-39.5)	31.2 (20.0-46.4)	23.0 (13.4-36.8)	1.2 (0.6-2.4)	0.485	0.9 (0.4-1.9)	0.805
≥37 weeks	98	142	159	19.8 (16.1-24.1)	23.1 (19.5-27.3)	19.8 (16.8-23.1)	1.2 (0.9-1.5)	0.237	1.0 (0.8-1.3)	0.981
Intensive care unit admission	*74*	*93*	*107*	12.8 (10.0-16.0)	13.3 (10.8-16.3)	12.0 (9.8-14.5)	1.0 (0.8-1.4)	0.783	0.9 (0.7-1.3)	0.676
Age										
0-2 months	64	67	83	19.3 (14.8-24.6)	19.8 (15.4-25.2)	20.8 (16.6-25.8)	1.0 (0.7-1.5)	0.437	1.0 (0.8-1.5)	0.650
3-11 months	9	15	17	4.6 (2.1-8.8)	5.8 (3.3-9.6)	4.6 (2.7-7.3)	1.3 (0.5-3.3)	0.599	1.0 (0.4-2.5)	0.960
≥12 months	1	11	7	1.9 (0.0-10.3)	10.7 (5.3-19.1)	5.7 (2.3-11.7)	5.8 (0.8-48.2)	0.053	3.1 (0.4-38.5)	0.300
Gestational age at birth										
<37 weeks	17	15	14	20.0 (11.7-32.0)	17.9 (10.0-29.5)	16.5 (9.0-27.6)	0.9 (0.4-1.9)	0.753	0.8 (0.4-1.8)	0.597
≥37 weeks	57	78	92	11.5 (8.7-14.9)	12.7 (10.0-15.9)	11.4 (9.2-14.0)	1.1 (0.8-1.6)	0.576	1.0 (0.7-1.4)	0.959
Mechanical ventilation	20	25	41	3.4 (2.1-5.3)	3.6 (2.3-5.3)	4.6 (3.3-6.2)	1.0 (0.6-2.0)	0.904	1.3 (0.8-2.4)	0.296
Age										
0-2 months	15	13	25	4.5 (2.5-7.5)	3.8 (2.0-6.6)	6.3 (4.1-9.2)	0.9 (0.4-1.9)	0.676	1.4 (0.7-2.8)	0.321
3-11 months	5	6	9	2.6 (0.8-6.0)	2.3 (0.9-5.1)	2.4 (1.1-4.6)	0.9 (0.2-3.8)	0.867	0.9 (0.3-3.6)	0.896
≥12 months	0	6	7	0 (0-6.8)	5.8 (2.1-12.7)	5.7 (2.3-11.7)	6.3 (0.8-55.4)	0.297	6.1 (0.4-51.1)	0.300
Gestational age at birth										
<37 weeks	7	5	5	8.2 (3.3-17.0)	5.9 (1.9-13.9)	5.9 (1.9-13.7)	0.7 (0.2-2.6)	0.595	0.9 (0.2-3.0)	0.791
≥37 weeks	13	20	35	2.6 (1.4-4.5)	3.3 (2.0-5.0)	4.3 (3.0-6.0)	1.2 (0.6-2.7)	0.554	1.7 (0.9-3.4)	0.116

[a] Cumulative number from 2017-2018 season to 2018-2019 season.
[b] Seasonal mean from 2017-2018 season to 2018-2019 season.

for a proper comparison of risks. Pre-pandemic seasons and both pandemic seasons showed similar risks of severe hospitalization, ICU admission, and mechanical ventilation within preterm and full-term children, except very premature children hospitalized in the 2022/2023 season, who showed a marked but not significant decrease in the risk of severe hospitalization ($P = 0.264$).

Discussion

In Tuscany, the onset of the pandemic and the related implementation of the NPIs occurred towards the tail end of the RSV epidemic, likely without significant impact in the 2019-2020 season. In the 2020-2021 season, only two RSV-associated hospitalizations were registered, as the regional lockdown and school closures almost entirely overlapped with the traditional RSV epidemic period. The subsequent season (2021-2022) showed a resurgence of the RSV epidemic, which started, peaked, and concluded earlier than usual and had a reduced duration of about 1 and a half months. In the most recent season under study (2022-2023), the seasonality characteristics of the RSV epidemic still showed these deviations, albeit to a lesser extent than what was observed in the 2021-2022 season. The shifts in the 2021-2022 seasonal patterns align with observations made in other European countries and elsewhere in the Northern Hemisphere [5,6]. As for the 2022-2023 RSV seasonality, our data suggest a gradual, at least partially, return to seasonal patterns resembling those observed in the pre-pandemic years. Currently, there is limited updated population-based evidence in the literature regarding the seasonal trends of RSV epidemics; a gradual return towards the usual seasonality has been described in the United States [11]. However, at present, our data indicate that the RSV seasonality continues to differ from pre-pandemic years, and it is hard to predict if and when there will be a return to a typical seasonality; in this regard, the ongoing presence of SARS-CoV-2 could potentially cause viral interference with unpredictable repercussions on RSV activity [21].

Compared with pre-pandemic years, the incidence of RSV-associated hospitalizations increased approximately three-fold in the 2021-2022 and 2022-2023 seasons. These data are consistent with previous studies indicating that a reduced exposure to RSV during the period of stricter containment measures has led to an increase in the pool of immunologically vulnerable children, ultimately leading to larger RSV epidemics when such measures were eased [7,22–25].

Interestingly, the incidence of RSV-associated hospitalization remained high also in the second season after the easing of NPIs (2022/2023), even in children aged 12 to 23 months who experienced the first RSV surge in the 2021/2022 season. Factors related to the circulating RSV subtypes and cross-immunity between them may have played a role in this unexpected RSV epidemiology. Studies conducted in regions bordering Tuscany revealed that RSV subtype A was predominant in the 2021-2022 season, whereas RSV subtype B dominated the 2022-2023 season; moreover, the RSV-B post-pandemic strains were characterized by a higher genetic divergence [17,26]. Given the geographical proximity, it is likely that this occurred in Tuscany as well; if this was the case, it is conceivable — in line with the hypothesis of an increase in the pool of immunologically vulnerable children — that the higher number of cases recorded in the last epidemic season was driven by RSV-B, as the immunity debt was paid only for RSV-A in the previous season. Furthermore, the RSV-B genetic divergence may have contributed to immune escape. However, it is also important to consider that, starting in 2020, in Tuscany, a project (NET-VAC) evaluating the incidence and burden of several infectious diseases preventable through immunization in pediatric populations younger than 18 years was implemented [27]. This could have increased disease awareness, case detection, and notification even in children younger than 2 years whose clinical attention for RSV is higher.

As far as the continued higher increase in RSV incidence in the 2022/2023 in children aged 12-23 months, it should also be considered that a significant proportion of them were already born in the 2020/2021 season when there was no RSV circulation. For this reason, many of these children in the 2022/2023 season may still have had less immune protection than those of the same age group in the pre-pandemic era, as they had fewer opportunities to get re-infected and thus boost their immune response.

The low prevalence of co-infection with SARS-CoV-2 in children hospitalized for RSV, as observed in both our study and previous research [4,28], does not appear to support the hypothesis of an additive interaction between SARS-CoV-2 and RSV contributing to the excess of hospitalizations [21].

The highest increases in hospitalization risk from pre-pandemic were observed in children belonging to the older age groups (12 to 23 months) in both the 2021-2022 and 2022-2023 seasons. A global analysis of the changes in RSV epidemiology and other regional studies in young children support these findings [8,9]. Furthermore, among children hospitalized, an increase in the risk of severe clinical outcomes from pre-pandemic years was observed only for older children, particularly during the first season after the easing of NPIs (2021-2022). These findings likely reflect the reduced exposure to RSV experienced by older age groups more than others and suggest that regular exposure to RSV in older children is crucial for maintaining immunity at a level that protects against hospitalization and more severe clinical outcomes [10].

During the 2021-2022 and 2022-2023 seasons, the risks of severe clinical outcomes during hospitalization were similar to those observed in pre-pandemic years in age groups younger than 12 months, in preterm and at-term children. Currently, there are conflicting findings in the literature regarding potential changes in the clinical severity of RSV infections during pandemic seasons. As for the first RSV surge after the pandemic, some studies have shown a disproportionate increase in the need for intensive care and mechanical ventilation among hospitalized RSV patients compared with pre-pandemic seasons [14], whereas others found risks similar to pre-pandemic years in all the age groups [7,24,29]. Furthermore, other studies have indicated an increase in the clinical severity of cases only in the subsequent epidemic season of 2022-2023, attributing this to a waned population immunity but also to the possibility of a heightened virulence in the circulating RSV strains during the latter season [12,13,17]. In this regard, our findings, indicating increased disease severity only in older children, do not support the hypothesis of an increased virulence of RSV or the hypothesis of an additive interaction with SARS-CoV-2; the prevalence of co-infections in our study was too low for the latter. Instead, they suggest a role for reduced immunity due to lack of regular viral exposure in older age groups.

Collectively, our findings raise important considerations for developing prevention programs targeting healthy children with recently approved long-acting monoclonal RSV antibodies and maternal vaccines [30–33]. RSV seasonality shifts may impact the optimal timing for providing protection to children. Furthermore, if such prevention programs delay the first RSV infection in the infant population, the risk of primary infection at an older age might increase. Our findings suggest that this delayed primary infection could result in an increased number of hospitalizations and ICU admissions in older children. This should be taken into account in cost-effectiveness analyses for tailoring RSV-prevention programs, especially for defining the eligible population age groups. However, it should be pointed out that the available evidence seems to indicate that prophylaxis with long-acting monoclonal antibodies to protect against RSV disease in the first season does not shift the

burden of disease to the second season, as they do not inhibit an immune response to natural RSV infection [34,35].

The present study has several limitations. First, RSV-associated hospitalizations were identified using ICD-IX CM RSV-specific codes due to the unavailability of data on laboratory-confirmed RSV tests in regional registries. This limitation could have resulted in underestimating the true burden of RSV-associated hospitalizations. Second, during the study period, there have been changes in testing practices for RSV. Specifically, prior to the pandemic, RSV alone was mainly tested by polymerase chain reaction on nasopharyngeal swabs; after the pandemic onset, an expanded polymerase chain reaction panel for several respiratory pathogens causing influenza-like illness was introduced. Furthermore, some hospitals of the TRPHCS transitioned to more universal testing in response to the initial surge of RSV cases. In addition, the NETVAC project can have partly contributed to the increased detection of RSV cases compared with the pre-pandemic period. The role of each contributing factor is not determinable; however, it should be pointed out that testing practices for RSV in children younger than 2 years hospitalized for ALRI were already widespread before the pandemic. Lastly, as the number of ICU admissions and mechanical ventilation in the 12-month or older age group was small, risk comparisons for these outcomes may be insufficiently powered to detect a statistical difference between the pandemic and pre-pandemic seasons.

The major strength of the study is that the study population effectively represents the entire children population under the age of 2 years in an administrative region covering a large geographical area with approximately 3.7 million residents. Furthermore, it is important to highlight the comprehensive tracking of the hospital care provided to the study population, as there are no other healthcare providers apart from those of the TRPHCS for delivering acute hospital care to children in Tuscany [36,37].

In conclusion, our study showed relevant perturbations of the RSV epidemics over the subsequent two seasons following the easing of pandemic measures. As far as seasonality is concerned, our findings suggest a gradual return to the usual pre-pandemic pattern, although further updated studies are needed to confirm this trend. Findings showed that the RSV epidemic exhibited a persistent increase in disease incidence two seasons after the easing of NPIs, with children of older age groups (12 to 23 months) consistently showing the highest increases. Furthermore, data on disease severity also showed an increased risk of developing severe outcomes limited to older children, particularly in the first season following the easing of pandemic measures. Altogether, these findings do not seem to indicate changes in the severity of the disease itself but rather an increased immunologic vulnerability likely linked to reduced exposure to RSV during the period of strict implementation of containment measures. Our study also suggests that regular exposure to RSV among older children plays a significant role in preserving immunity at a level sufficient to prevent severe outcomes. Overall, our study raises important considerations to be aware of in developing new promising RSV-prevention programs for healthy children—particularly regarding the recommended timing and eligible population—and highlights the need to closely monitor the RSV epidemic in the coming years with an active surveillance project.

Declarations of competing interest

The authors have no competing interests to declare.

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Ethical approval

The study was approved by the Ethics Committee of the Tuscany Region (no. 183-2020). The informed consent was not required as the study was based on administrative routinely collected anonymous data.

Author contributions

VL designed the study, interpreted the data analysis, wrote the first draft of the manuscript, and revised the manuscript; GA, MDR, MP, MP, RG analyzed data, and participated in data interpretation; The remaining authors critically reviewed the manuscript. All authors reviewed the final manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2024.107231.

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