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Respiratory Syncytial Virus Burden in Premature Infants: The Role of Season With and Without RSV Immunoprophylaxis in a Multicenter Study

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ABSTRACT

Objective: To compare the Respiratory Syncytial Virus (RSV) hospitalization burden among 29–34 weeks gestational age (wGA) preterm infants between seasons with and without routine palivizumab prophylaxis, by utilizing the 2021 off-season RSV surge.

Methods: This multi-center retrospective study was conducted in 11 medical centers across Israel. We included infants > 1 year-old, with wGA data, hospitalized with RSV infection from November 2017-August 2021. National palivizumab compliance data were collected separately. We compared two periods: in-season (November−March) with routine palivizumab prophylaxis as the reference, and off-season (April−October) without prophylaxis as the primary risk factor. The primary outcome was the proportion of RSV hospitalizations in 29–34 wGA infants relative to total RSV admissions, calculated separately for each period. Secondary outcomes included clinical severity parameters.

Results: A total of 3296 infants were admitted during the RSV in-season, and 1044 during the off-season. National palivizumab compliance among eligible infants during the in-season study years was 91%−95%. The proportion of 29−34 wGA infants was significantly higher during the off-season compared to the in-season period (7% vs. 2.1%, $p < 0.001$). In a multivariable logistic regression model, the odds of hospitalization for 29–34 wGA preemies were 2.6 times higher during the off-season compared to

Abbreviations: AAP, American Academy of Pediatrics; COVID19, coronavirus 2019 COVID-19; IQR, interquartile range; RSV, respiratory syncytial virus; RSVH, respiratory syncytial virus hospitalization rate; RT-PCR, reverse transcription polymerase chain reaction; SES, socioeconomic; wGA, week of gestational age.

the in-season (95% CI: 1.8–3.9, $p < 0.001$), independent of demographic covariates. Clinical severity was similar between the two periods.

Conclusions: Our results revealed a significantly higher proportion of 29−34 wGA infants hospitalized during seasons without palivizumab prophylaxis compared to seasons with palivizumab prophylaxis. These findings highlight the importance of including 29−34 wGA infants into future RSV immunoprophylaxis recommendations.

1 | Introduction

Respiratory Syncytial Virus (RSV) is the most common cause of acute bronchiolitis and pneumonia in children under 1 year of age and 2−3% of infants < 6 months may require hospitalization. RSV epidemics typically begin in the northern hemisphere between September and December, with most countries experiencing RSV seasons that last around 5−6 months [1–4].

Certain groups, such as premature babies, are at high risk for severe RSV bronchiolitis [1]. Consequently, anti-RSV monoclonal antibodies (palivizumab) have been administered to these high-risk infants during the RSV season. Until recently, there has been an active debate about the importance of providing palivizumab to infants born at 29–34 weeks gestational age (wGA) [5–7]. In 2014, the indications for palivizumab in Israel were expanded to include infants born before 35 wGA [5]. Concomitantly, the American Academy of Pediatrics (AAP) narrowed the indication to infants born before 29 wGA, based on cost-effectiveness analysis considerations and the limited clinical benefits [8–11]. Unlike the AAP, policy-makers in Israel have not implemented a similar restriction. Nirsevimab, a newer monoclonal antibody with extended half-life, has been recently approved by leading regulatory agencies [12, 13]. Nevertheless, its implementation is progressing at a different pace in different countries due to regulation, healthcare priorities, and budgetary constrain [14]. As a result, palivizumab is expected to continue being used in many countries for the upcoming RSV seasons.

During the coronavirus 2019 (COVID-19) pandemic, an exceptionally low incidence of RSV was reported during the winter season (northern hemisphere) [15–18]. In contrast, following the relaxation of COVID-19 measures (April 2021), an out-of-season, delayed surge in RSV infections was observed [19–23]. RSV prophylaxis is administered in Israel only during the months November to March. Thus, the unexpected seasonal shift has left the eligible high-risk infants, including the 29−34 wGA preemies, vulnerable to RSV as compared with the same group that received RSV prophylaxis in-season.

In this study, we aimed to leverage the out-of-season RSV outbreak to evaluate potential differences in RSV hospitalization (RSVH) burden and clinical severity among 29−34 wGA infants hospitalized during seasons with and without routine palivizumab prophylaxis. Our findings provide valuable insights into the justification for RSV immunoprophylaxis in this population and highlight the need for flexibility in its administration during out-of-season surges.

2 | Methods

2.1 | Study Design and Population

A multi-center observational retrospective study was conducted in 11 medical centers located at the central, south, and north of Israel. These centers collectively represent about 50% of annual births and admissions in the country.

We included Israeli resident infants with available wGA data who were hospitalized with laboratory-confirmed RSV illness at <1 year old between November 1, 2017, and August 31, 2021. Infants lacking gestational age data were excluded. We collected data until August 2021, as palivizumab was introduced earlier than expected in September 2021 due to the RSV summer surge. RSV confirmation was based on reverse transcription polymerase chain reaction (RT-PCR). Among all participating medical centers, there is a consistent practice of testing for RSV every infant presenting with clinical symptoms of bronchiolitis.

We categorized the study period into two distinct periods: in-season (November through March), when palivizumab prophylaxis is routinely administered, serving as the reference period; and off-season (April through October), when prophylaxis is not typically given, representing the primary risk period. We presented the results for the whole cohort and specifically for $29-34^{+6}$ wGA.

Palivizumab compliance: To evaluate palivizumab compliance among eligible infants during the study period, we obtained the aggregated palivizumab compliance data from the four national health maintenance organizations (HMOs) who provide universal healthcare to all Israeli residents.

2.2 | Data

We retrieved demographic and clinical data of all eligible children from the electronic medical records in each participating medical center. Perinatal data included date of birth, birth weight, wGA, comorbidity (congenital heart disease, bronchopulmonary dysplasia [BPD], and trisomy 21). Demographic characteristics included sex, population group and socioeconomic status (SES).

Home addresses were used to assign each patient to a specific geographic area. SES was defined according to the Central Bureau of Statistics of the Ministry of Health, based on geographic area. Each geographic area was categorized into one of 10 SES ranks, with 1 being the lowest and 10 the highest [24]. These SES ranks were further grouped into SES clusters: low SES was defined as clusters 1−5, and high SES as clusters 6−10.

2.3 | Demographic Characteristics

Age, sex and SES cluster were assessed for the entire study population and for 29−34 wGA for each period (in-season vs. off-season) for comparison.

2.4 | Clinical Outcomes

Primary outcome: The proportion of 29−34 wGA admissions among the total number of RSV infection admissions in infants under 1 year old during the in-season and off-season study periods.

Secondary outcomes: Clinical severity parameters for 29−34 wGA infants in each period (in-season vs. off-season). These parameters included length of stay (LOS), pediatric intensive care unit (PICU) admissions, lowest oxygen saturation, use of mechanical ventilation and mortality.

Considering that RSV immunoprophylaxis is administered to $33-34^{+6}$ wGA infants up to 6 months of age, as compared to infants born at $\leq 32^{+6}$ wGA, who receive it until the age of 1 year, we conducted separate subgroup analyses for $29-32^{+6}$ wGA and $33-34^{+6}$ wGA infants.

Complementary Data: We collected data on birth rates and prematurity trends to address potential bias from birth rate fluctuations during the study period. This analysis included birth registry data from participating medical centers, focusing on the rate of 29−34 wGA infants among total births. Detailed findings from this analysis are presented in the Supporting Information Material (Table S1).

2.5 | Statistical Analysis

Statistical analysis was performed using IBM SPSS statistics for windows, version 28, (IBM Corporation, Armonk, NY, USA). We compared the demographic and clinical characteristics of hospitalized patients between the in-season period (when palivizumab prophylaxis is routinely administered) and the off-season period (when palivizumab prophylaxis is not routinely administered) using a Student *t*-test or non-parametric test for continuous variables and Chi-square or Fisher's exact test for categorical variables. We performed these analyses for the entire cohort and for the 29−34 wGA infants separately. To study the effect of seasonality, which serves as a proxy for palivizumab prophylaxis, on the likelihood of RSV admissions in the 29−34 wGA infants, we conducted a multivariable logistic regression analysis adjusting for sex, population group, SES cluster and age at admission. Odds ratio and corresponding 95% confidence interval were calculated. We further explored our data using a linear regression model that included gestational age as an independent continuous variable and seasonality groups as an independent variable, while adjusting for demographic covariates. For the comparison of the clinical severity parameters, we further analyzed our data in subgroups of infants aged 0−3 months, 3−6 months, and 6−12 months.

2.6 | Ethical Considerations

The study was approved by the Institutional Review Board (IRB) at each participating institution. The approval number for the leading hospital was 0152-21.

This study was exempted from informed consent requirements by the IRBs of the participating centers, as it involved analysis of existing medical records without additional patient interventions, and all data were de-identified to ensure patient privacy.

3 | Results

3.1 | Study Participants

A total of 4939 children < 1 year of age were admitted to 11 medical centers due to respiratory symptoms with laboratory-confirmed RSV infection during the study period. After excluding 599 patients (12.1%) due to missing gestational age data, our cohort included 4340 children. The median age at admission was 2.9 months (IQR 1.4−6.4), 57% were males and 64% belonged to the Jewish population group. A total of 3296 infants were admitted during the RSV in-season and 1044 infants were admitted during the off-season (855 off-season of 2021, 189-off-season of 2018−2020). Figure 1 presents the distribution of hospitalized infants during the study period.

Palivizumab Compliance: The overall compliance reported by the four national HMOs ranged from 91% to 95% of eligible infants during the study years. Thus, we considered the in-season period as a season with RSV prophylaxis.

Demographic and clinical characteristics of all participants and the subgroup of 29−34 wGA infants, categorized by seasonality, are presented in Table 1. We found significantly higher proportions of Jewish population group ($p < 0.001$) and higher SES ($p < 0.001$) in children admitted off-season compared to in-season.

3.2 | Clinical Outcomes

The proportion of 29-34 wGA out of total admissions: 162 children were born at 29−34 wGA, with 88 categorized as seasonal RSV and 76 as off-season. The proportion of 29−34 wGA infants was significantly higher off-season compared to in-season, 7% versus 2.1%, $p < 0.001$. Table 2 presents the proportion of each wGA group out of total admissions categorized by seasonality group-period and a subgroup analysis for 29−32 wGA and 33−34 wGA at 0−6 months and 6−12 months, respectively.

A logistic regression analysis with seasonality group-period (off season vs in-season) as the dependent variable and 29−34 wGA as the independent variable with population group, SES, age, and sex as covariates, revealed 2.6-fold higher relative-odds for 29−34 wGA infants to be hospitalized off-season than in-season. This result was independent when adjusted for population group, SES, sex, and age (Table 3). Indeed, the results of a

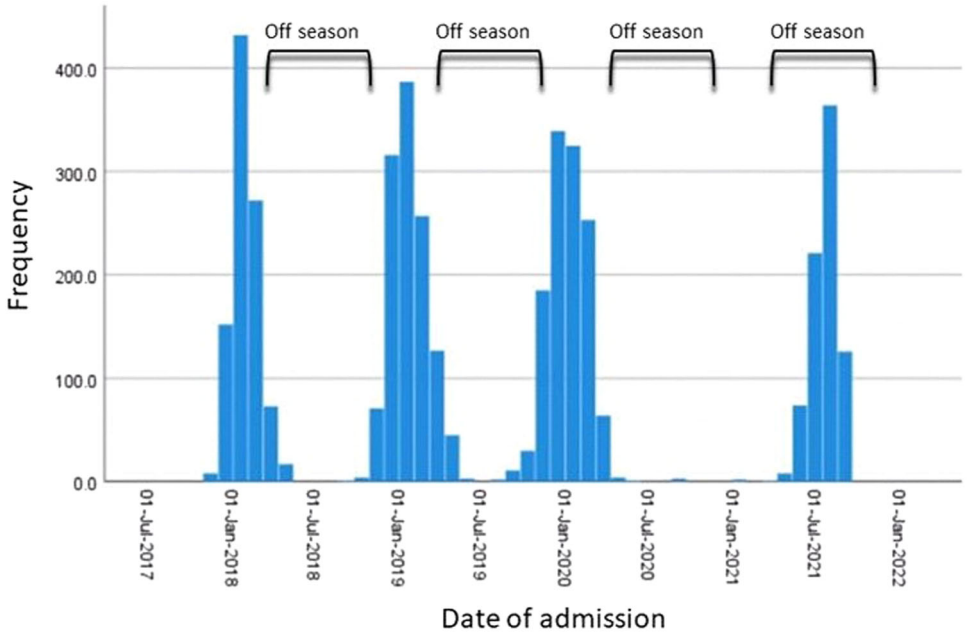

FIGURE 1 | Distribution of Hospitalized RSV Patients < 1 year of age. Bars represent the monthly number of hospitalized patients. [Color figure can be viewed at wileyonlinelibrary.com]

further regression model that included gestational age, as an independent continuous variable, indicated that off-season admissions are associated with significant decreases in wGA (OR 0.92, 95% CI 0.88−0.95, $p < 0.001$). This model showed similar levels of significance for SES, population group, age, and gender as observed in the previous model.

Clinical severity parameters for the whole cohort were similar in the off-season and in-season periods. There were no differences in LOS ($p = 0.64$), or minimal oxygen saturation ($p = 0.67$) between off-season and in-season periods. There were also similar rates of PICU admissions (in-season group-7.2% vs. off-season group 7.3%, $p = 0.95$), rate of mechanical ventilation (in-season group-2.5%, off-season group 1.6%, $p = 0.099$), and mortality rate ($p = 0.43$). Clinical severity parameters in the 29−34 wGA preterm subpopulation are presented in Table 4. None of these parameters were found significant between the 2 periods. Likewise, in the subgroup analysis of infants aged 0−3 months, 3−6 months, and 6−12 months, no statistically significant differences were observed for both the entire cohort and for the 29−34 wGA infants.

4 | Discussion

In this multi-center study, we exploited the unprecedented off-season RSV resurgence during the summer of 2021, to assess the association between the complete lack of RSV immunoprophylaxis and the relative burden of RSVH among 29−34 wGA infants.

Our results indicated a significant increase in the proportion of RSVH among 29−34 wGA infants aged < 12 months during the "off-season" RSV periods compared with the on-season RSV periods. Overall, our results showed significant increase in the proportion of hospitalizations of 29−32 wGA infants and 33−34 wGA infants < 12 and <6 months of age, respectively. Furthermore, these findings were independent of age, sex, population group or SES, thereby demonstrating the significant impact of the lack of RSV immunoprophylaxis. As we observed no increase, and even a decrease, in births at 29−34 weeks' gestational age during the COVID-19 pandemic study period, our results are unlikely to be biased by potential off-season increases in preterm births.

Published recommendations from various national guidelines on the use of palivizumab prophylaxis differ considerably, specifically in 29−34 wGA preterm infants. For instance, the AAP [8] and the Canadian Pediatric Society [25, 26] only advocate RSV prophylaxis for infants < 29 wGA, while other societies, such as those from Spain [26], Italy [27], and Israel [5] have more liberal criteria that include 29−34 wGA infants. The evidence for the AAP recommendations, which were reaffirmed in 2019, was based on the observation that RSVH rates for infants born ≥ 29 wGA were closer to those ≥ 35 wGA. A cost–benefit analysis provided further support for these recommendations. However, published studies do not provide a clear threshold of wGA for which palivizumab is beneficial [28–30]. This controversy highlights the importance of understanding the impact of withholding prophylaxis from 29 to 34 wGA preterm infants.

Several real-world studies, employing different methodologies, have generated conflicting results concerning the impact of the changes in the 2014 AAP RSV immunoprophylaxis guidance on the burden of RSVH among preterm infants. A retrospective US study reported no difference in RSVH rates following the introduction of the restrictive AAP 2014 policy (pre: 5.37/1000 vs. post: 5.78/1000; $p = 0.622$) [30]. In Italy, a similar restrictive policy was implemented in 2016, resulting in a decrease in the rate of RSVH from 6.3/1000 to 5.5/1000 [31]. However, in these studies, the adoption of the restricted guidelines was reported to

TABLE 1 | Characteristics of study participants.

Characteristics of the entire cohort (*N* = 4340)	**In -season admissions (*N* = 3296)**	**Off season admissions (*N* = 1044)**	***p* value**
Age (months), median [IQR]	2.9 [2–4]	3.18 [2–4]	0.72
Male, *N* (%)	1893 (57.4)	584 (55.9)	0.41
Gestational age (week), median [IQR]	39 [38–40]	39 [37.4–40]	**< 0.05**
Birth weight, mean (SD), gr	3147 (548)	3104 (649)	**< 0.001**
SES cluster[a]			
High, *N* (%)	1486 (45.1%)	575 (55.1%)	**<0.001**
Low[a], *N* (%)	1810 (54.9%)	469 (44.9%)	
Population group[a], *N* (%)			
Jewish	1812 (59.2%)	775 (80.1%)	**<0.001**
Arab	1170 (38.2%)	171 (17.7%)	
Other	77 (2.5%)	21 (2.2%)	
Comorbidities			
BPD, *N* (%)	25 (0.8%)	13 (1.2%)	0.18
CHD, *N* (%)	63 (1.9%)	28 (2.7%)	0.13
Trisomy 21, *N* (%)	19 (0.6%)	5 (0.5%)	0.81
Characteristics of the 29–34 wGA preterm born infants	**In season admissions (*N* = 88)**	**Off season admissions (*N* = 74)**	***p* value**
Age (months), median [IQR]	3.68 [1.99–7.29]	3.42 [2.32–5.07]	0.34
Male, *N* (%)	53 (60%)	44 (59%)	1
Gestational age (week), median [IQR]	33.45 [32–34]	33 [31–34]	**< 0.01**
Birth weight, mean (SD), gr	1938 ± 413	1892 ± 465	0.52
SES cluster[b]			
High, *N* (%)	38 (36%)	47 (57%)	**< 0.05**
Low[a], *N* (%)	50 (64%)	27 (43%)	
Population group[b], *N* (%)			
Jewish	43 (53.1%)	55 (85.9%)	**< 0.001**
Arab	34 (42%)	8(12.5%)	
Other	4 (4.9%)	1 (1.65%)	
Comorbidities			
BPD	2 (2.3%)	7 (9.5%)	0.08
CHD	2 (2.3%)	2 (2.7%)	1
Trisomy 21	0 (1.4%)	0(0%)	0.45

Note: A student *t*-test or non-parametric test was used for continuous variables and Chi-square or Fisher's exact test for categorical variables. *p* value for the comparison between the in-season group (when RSV prophylaxis is routinely administered) versus the off-season group (when RSV prophylaxis is not routinely administered).
Abbreviations: BPD, bronchopulmonary dysplasia, CHD, congenital heart disease; IQR, interquartile range; RSV, respiratory syncytial virus; SD, standard deviation; SES, socioeconomic status.
[a]Calculated using available data (population group-10.5% missing data, SES-13.5% missing data).
[b]Calculated using available data (population group-7.2% missing data, SES-11.7% missing data).

be partial, with limited reduction in Palivizumab utilization [31, 32]. Additionally, some of these studies lacked laboratory confirmation of RSV, while others lacked the power to detect differences among preterm subgroups [31, 33]. Albeit, the design of our study, and the high level of compliance with palivizumab recommendations in Israel allowed a clear distinction between "in-season' RSV periods, with high level of compliance to palivizumab use, and 'off-season RSV periods'" in which palivizumab was not used.

Indeed, in accordance with our findings, other studies reported an at least twofold increase in RSVH rates following implementation of a more restrictive policy [34–38]. Rajah et al. found a significant increase in the proportion of RSVH among 29–34 wGA infants aged < 6 months in 2014–2015 (7.1%) compared to 2013–2014 (3.5%; $p = 0.01$) [34]. Similarly, Kong et al.'s retrospective analysis showed that a significant 45%–95% decrease in palivizumab administration to 29–34 wGA infants in the 2014–2015 seasons compared to 2013–2014 was

TABLE 2 | Proportion of wGA groups out of total admissions categorized into in-season and off-season RSV admissions.

Age range (months)	Gestational age group (week)	In-season RSV admissions (% out of total) $N = 3296$	Off season RSV admissions (% out of total) $N = 1044$	p value
0–12	29–34	88 (2.7%)	74 (7.1%)	<0.001
Subgroup analysis of 29–34 wGA infants by age range[a]				
0–6	29–32	21 (0.9%)	28 (3.7%)	<0.001
	33–34	38 (1.6%)	32 (4.2%)	<0.001
6–12	29–32	8 (0.9%)	7 (2.5%)	0.065
	33–34	21 (2.4%)	7 (2.5%)	1
0–12	29–32	29 (0.9%)	35 (3.4%)	<0.001
	33–34	IR	IR	NA

Note: A Chi-square test or Fisher's exact test was used to compare the in-season group (when RSV prophylaxis is routinely administered) and the off-season group (when RSV prophylaxis is not routinely administered).
Abbreviations: IR, irrelevant; RSV, respiratory syncytial virus; wGA, week of gestational age.
[a]Based on specific palivizumab indications (RSV prophylaxis is administered to $33–34^{+6}$ wGA infants up to 6 months of age, as compared with infants born until wGA 32^{+6}, who receive it until the age of 1 year).

TABLE 3 | Multivariable logistic regression analysis of odds ratios for off-season versus in-season RSV admissions in infants born at 29–34 wGA.

	Odds ratio	95% CI	Adjusted p value
Gestational age 29–34 wGA (Off-season vs. in-season)[a]	2.6	1.8–3.75	<0.001
Population group (Jewish vs. Arabs)	3.2	2.55–4.01	<0.001
SES cluster (high vs. low)	1.1	0.93–1.3	0.277
Sex	1.026	0.867–1.215	0.76
Age	0.99	0.97–1.02	0.72

Note: A linear regression model was used, including gestational age as a continuous independent variable and seasonality groups as an independent categorical variable, while adjusting for demographic covariates.
Abbreviations: RSV, respiratory syncytial virus; SES, socioeconomic status; wGA, week of gestational age.
[a]The in-season group serves as the reference group and the off-season group as the risk factor.

TABLE 4 | Clinical severity in the subgroup of 29–34 wGA preterm infants.

	In-season group $N = 88$	Off-season group $N = 72$	p value
LOS, days, median (IQR)	3 (3–7)	4 (3–7.2)	0.96
PICU yes/no, *N* (%)	15 (17%)	10 (13.5%)	0.663
Mechanical ventilation, *N* (%)	5 (5.7%)	4 (5.4%)	1
Mortality, *N* (%)	3 (0.1%)	2 (0.1%)	0.426
Oxygen nadir (%)	87.2 ± 6.9	87.2 ± 6	0.99

Note: A student *t*-test or non-parametric test was used for continuous variables and Chi-square or Fisher's exact test for categorical variables.
Abbreviations: LOS, length of stay; PICU, pediatric intensive care unit; RSV, respiratory syncytial virus; wGA, week of gestational age.

associated with a 2.65-fold increase in RSVH rates among 29–34 wGA infants aged < 3 months in 2014–2015 [35]. Goldstein et al. demonstrated a significantly higher risk of RSVH for 29–34 wGA preterm infants compared with term infants after the 2014 guidance change by AAP [37]. The latter findings were supported by studies by Greenberg et al, Blake et al. and Capizzi et al. [36, 38, 39].

For infants born at 29–32 wGA, aged 6–12 months, we observed the same overall 2.67-fold higher proportion of admissions during the off-season RSV period compared to the in-season RSV period. Although the observed difference only exhibited a borderline statistical significance ($p = 0.064$), it is plausible that a larger cohort would have detected a significant difference.

Despite the higher likelihood of hospitalization for unvaccinated 29–34 wGA preterm infants during the "off-season" period, our data demonstrate comparable clinical severity of RSVH as measured by LOS, minimal oxygen saturation, PICU admissions, mechanical ventilation and mortality between the two periods. Our findings contradict Rajah et al results, which indicated increased morbidity in the youngest chronological age group (<3 months of age) in these group of preterm infants following the implementation of the 2014 AAP revision [34]. In our study, we employed a different approach

than other studies by studying hospitalizations during different calendar weeks with different seasonality. Hence, there is a possibility that the disease severity might differ between seasons, due to weather differences, potential co-infection with other circulating pathogens or variations in the infecting RSV subtype and genotype. However, several studies reported that the same prevalent RSV genotypes remained dominant both before and during the resurgence of RSV infections after the relaxation of COVID-19 mitigation measures [40–43].

Notably, our results regarding the rates of mechanical ventilation and mortality, which are considered the two most reliable markers of illness severity, align with those reported in other studies, particularly following the implementation of the 2014 AAP guidance revision [44, 45]. This similarity in clinical severity of RSVH observed in our study may also be attributed to the significant pre-hospitalization effect of palivizumab on the RSV infection severity.

Our study revealed unexpected findings regarding SES and population group distribution of patients in relation to seasonal hospitalizations. During "off-season" periods, we observed a higher proportion of patients from the Jewish population group and patients from higher SES cluster, while "in-season" RSVH showed a higher proportion of patients from the Arab population group. These disparities were observed among both term and 29−34 wGA preterm infants. Possible explanations include reduced RSV exposure among higher-SES mothers during the COVID-19 pandemic, leading to diminished RSV immunity in their infants [46]. Additionally, decreased compliance with prescribed palivizumab among low-SES patients could contribute to these disparities. These findings, though indirect, highlight the potential importance of ensuring equitable access to RSV preventive interventions, such as palivizumab or newer options like nirsevimab, across socioeconomic groups. Barriers to accessing these protective measures, whether due to insurance coverage, healthcare utilization, or other social determinants of health, may exacerbate the burden of RSV disease among high-risk infants from lower SES backgrounds [46, 47].

A major strength of our study is the use of comprehensive data from a large cohort of infants across multiple medical centers, and the ability to rely on birth registries and reliable palivizumab utilization data. Another strength of our study is the laboratory-confirmation of RSV. In contrast, some studies used RSV-codes to identify RSVH, which are known to underestimate the true rate of RSVH [47].

Importantly, our results should be read in the context of the new era of novel RSV immunoprophylaxis and vaccines, including nirsevimab and the active bivalent RSV prefusion F protein-based (RSVpreF) vaccine for pregnant women [12, 13, 48]. Given the anticipated delay in the widespread implementation of nirsevimab, palivizumab will likely to remain in use for at least the next several seasons in many countries, thus maintaining the applicability of our results. Defining which high-risk groups may benefit from RSV immunoprophylaxis remains important for targeted protection and optimal resource allocation. This relevance may extend to nirsevimab as well. Regarding a maternal vaccine, premature babies may not benefit significantly, as they might miss out on a substantial portion of the passively transferred RSV antibodies. Consequently, our findings highlight the importance of including 29−34 wGA prematurity in the indications for RSV vaccination, while raising the question of whether one dose of nirsevimab could provide long term protection in the event of another out-of-season RSV outbreak in the future. These results emphasize the need for responsive and flexible RSV immunoprophylaxis policies that leverage real-time surveillance data to protect high-risk children, especially during potential future off-season outbreaks.

Our study has several limitations. The retrospective design carries a potential for ascertainment bias and we appreciate that the rate of RSV infection may have been underestimated. However, it is reasonable to conclude that institutional RSV testing strategies remain constant between RSV seasons, and it is therefore likely that high-risk patients such as preterm infants are tested. Another limitation is that the lack of widespread RSV typing and molecular analysis which precludes the comparison of the off-season outbreak to previous seasonal waves of disease. However, as was previously demonstrated, a temporal variation of RSV epidemics is not necessarily affected by a dominant subtype [41–43]. Additionally, confounding factors, including multi-viral co-infections, weather differences and nursery attendance could impact the RSVH comparisons between different seasons. Notably, these possible confounding factors are similar for all wGA age groups in the same season. Furthermore, the generalizability of our findings should be interpreted within the unique context of the COVID-19 pandemic. We also appreciate that our study includes data from 11 different medical centers and therefore variability across sites regarding admission thresholds could have influenced our results. Lastly, we were unable to collect data on individual palivizumab administration status during the study period. Instead, we relied on the overall palivizumab compliance data as reported by all national healthcare providers, which reflect a very high compliance rate during seasons with routine RSV prophylaxis.

In conclusion, our study compared the relative burden and clinical severity of RSVH among 29–34 wGA preterm infants between seasons with and without routine palivizumab prophylaxis. We demonstrated a significantly higher proportion of hospitalized 29−34 wGA infants aged < 1 year during the "off-season" periods, compared with the in-season periods, when palivizumab was routinely administered.

These findings support the beneficial effect of RSV immunoprophylaxis in 29−34 wGA preterm infants, emphasizing the necessity of incorporating this cohort into forthcoming recommendations for novel RSV vaccines. Moreover, our study underscores the importance of flexibility in responding to unpredictable off-season RSV surges.

Author Contributions

Keren Armoni Domany: conceptualization, investigation, writing – original draft, methodology, validation, writing – review and editing, formal analysis, data curation, visualization. **Avigdor Mandelberg:** methodology, formal analysis, data curation. **Nitzan Burrack:**

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The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.