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ORIGINAL ARTICLE

Birth characteristics as predictors of respiratory syncytial virus hospitalisation in newborns to optimise immunisation schedule

Emanuele Amodio | Vincenzo Pisciotta | Dario Genovese | Giuseppe Vella | Maria Gabriella Verso | Mario Giuffrè | Francesco Vitale

Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties "G. D'Alessandro", University of Palermo, Palermo, Italy

Correspondence
Dario Genovese, Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties "G. D'Alessandro" – University of Palermo, Palermo, Italy.
Email: dario.genovese@unipa.it

Abstract

Aim: To examine birth characteristics that influence infant respiratory syncytial virus (RSV) hospitalisation risk in order to identify risk factors for severe RSV infections.

Methods: Retrospective cohort study of 460 771 Sicilian children under 6 months old from January 2007 to December 2017. Hospital discharge records were consulted to identify cases and hospitalisations with International Classification of Diseases, Ninth Revision, Clinical Modification codes 466.11 (RSV bronchiolitis), 480.1 (RSV pneumonia) and 079.6 (RSV). RSV hospitalisation risk was estimated using adjusted odds ratios (aOR) and 95% confidence intervals (95% CI).

Results: Overall, 2420 (5.25 per 1000 infants) RSV-related hospitalisations were identified during the study, with girls accounting for 52.8%. RSV hospitalisation risk increased for full-term, transferred, extreme immature, and preterm neonates with serious issues (aOR 3.25, 95% CI 2.90–3.64; aOR 1.86, 95% CI 1.47–2.32; aOR 1.54, 95% CI 1.11–2.07; and aOR 1.48, 95% CI 1.14–1.90). Compared to children born in June, the risk of RSV hospitalisation was significantly higher in children born in January (aOR 28.09, 95% CI 17.68–48.24) and December (aOR 27.36, 95% CI 17.21–46.99).

Conclusion: This study identified birth month and diagnosis-related groups as key predictors of RSV hospitalisations. This could help manage monoclonal antibody appropriateness criteria.

KEYWORDS
birth month, diagnosis-related group, hospitalisation, respiratory syncytial virus, risk factors

1 | INTRODUCTION

The human respiratory syncytial virus (RSV) is a common seasonal virus, with human circulation. It is a single-stranded ribonucleic acid (RNA) negative-sense pneumovirus of the *paramyxoviridae* family with three membrane proteins: small hydrophobic protein, attachment glycoprotein and fusion glycoprotein.[1]

Respiratory syncytial virus is one of the most common viral pathogens causing respiratory tract infections in infants, the elderly, and immunocompromised individuals, causing a major disease burden globally each year.[2]

More than 60% of all children are infected with RSV within 1 year of birth, and nearly all children are infected with RSV at least once within 2 years of birth.[3] The severity of the disease in children

Abbreviations: 95% CI, 95% confidence interval; aOR, adjusted odds ratio; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; RSV, respiratory syncytial virus.

is significantly dependent on the age of first infection, with preterm birth and infants <6 months being associated with severe disease.[4–6] A number of known risk factors, including congenital heart disease, chronic lung disease, neuromuscular impairment and immunodeficiency, have been proven to play a major contribution in the severity of RSV infection.[4,5,7] In addition, RSV infections are associated with an increased risk of allergic asthma that can last until early adulthood.[8]

Virus transmission in Italy generally occurs from October or November to March or April, with a peak incidence in January and February and an epidemic curve that overlaps with the influenza virus.[3,9] The COVID-19 pandemic caused an almost complete absence of RSV circulation in 2020–2021. In contrast, RSV transmission in 2021–2022 was anomalous in both chronological and quantitative terms, peaking several weeks earlier and more intensely than in previous years.[10–12] This phenomenon has also been reported in a number of Italian regions, where it has been partially attributed to a primary RSV infection among the young population.[13,14]

To lessen the impact of RSV infection, in 1998 the US Food and Drug Administration (FDA) licensed for administration palivizumab, a humanised monoclonal antibody that neutralises the fusion glycoprotein via binding.[15,16] Several studies have shown that palivizumab, when administered monthly during the RSV season, reduces the risk of hospitalisation due to severe RSV infection.[15,16] Because of the high costs and the need for monthly administration due to the drug's short half-life, the drug is only reimbursed in Italy for preterm infants born ≤35 weeks and who are less than 6 months old at the onset of the seasonal RSV epidemic (November), and for children less than 2 years old who have significant risk factors.[3] Recently, the European Medicines Agency (EMA) approved nirsevimab, a novel monoclonal long-acting antibody binding to the prefusion conformation of the fusion glycoprotein, which will be available soon for RSV prevention in European newborn children.[17]

However, one of the major issues linked with administering nirsevimab to a larger target group could be the high costs, as well as the necessity to develop criteria for appropriate applications in infants.

In light of the substantial associated costs with novel therapeutic strategies, there is a growing need for understanding about the risk factors for RSV severe infections and hospitalisations in order to ensure appropriate care and immunoprophylaxis administration.[18] In accordance with these scientific goals, the aim of this study is to evaluate whether there are any characteristics existing at birth that can raise the risk of RSV hospitalisation in children and, as a result, to recommend a more appropriate and targeted use of monoclonal antibodies. Therefore, this study aimed to examine the association between birth characteristics and RSV hospitalisations in the first 6 months of life.

Key Notes

- Determining whether birth-related factors can increase the risk of hospitalisation for respiratory syncytial virus (RSV) in children can potentially guide more targeted monoclonal antibody usage.
- Prior research on birth-related RSV risk factors resulted in few data pertinent to clinical practice.
- The identification of birth month and diagnosis-related group as significant predictors of RSV hospitalisations suggests potential contributions to the development of more appropriate criteria for monoclonal antibody administration.

2 | METHODS

This was an observational retrospective cohort study that followed up on all children under the age of 6 months who resided in Sicily between 1 January 2007 and 31 December 2017, to assess the risk of RSV hospitalisation.

Sicily is an Italian region with approximately 5 million inhabitants and an average newborn cohort of approximately 42 000 infants per year for the whole study period.

Hospital discharge records (HDR) were received from the Health Regional Office of Sicily, which gathers these data on a regular basis from all regional public and private hospitals. Each HDR contains demographic information, such as birthplace, residence, gender and date of birth. Moreover, it contains admission and discharge dates, discharge status categorised as "discharged/transferred" or "dead", up to six discharge diagnoses (one principal and five secondary diagnoses), and one diagnosis related group (DRG) code. Each discharge diagnosis was coded in accordance with the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).

The HDRs of all Sicilian children born between 1 January 2007 and 31 December 2017 were examined to ascertain the presence of risk factors at birth.

To obtain data concerning the at-birth condition of each recruited subject, the following information was gathered by searching the DRG codes: 386 (neonate, extreme immaturity); 387 (prematurity with major problems); 388 (prematurity without major problems); 389 (full-term neonate with major problems); 390 (neonates with other significant problems); 391 (normal newborn). Furthermore, to gain a more comprehensive understanding of the health conditions recognised among RSV-positive infants, an assessment was conducted on the ICD-9-CM codes referring to their childbirth.

Second, occurrences of RSV hospitalisation were acquired throughout a 6-month (180-day) follow-up period from birth by using the ICD-9-CM diagnosis codes 466.11 (RSV bronchiolitis), 480.1 (RSV pneumonia) and 079.6 (RSV).

Because of the retrospective nature of the study, no formal consent from the patients or Ethics Committee approval were required, according to the Italian law. The research was performed in accordance with the Helsinki Declaration.

2.1 | Statistical analyses

Categorical data was summarised as absolute and relative (expressed as percentages) frequencies. RSV hospitalisation rates were calculated as cases per 1000 at risk subjects per year.

The univariate analysis was carried out by the Chi-squared test. A multivariable logistic regression analysis using a backward stepwise approach was used to assess the contribution of each risk factor to RSV hospitalisation, considering sex, year of birth, month of birth and DRG at birth. Adjusted for the year of study, regression coefficients were used to model the percentage reduction in hospitalisation rates per percentage unit increase in vaccination coverage.

The risk matrix with hospitalisation risk, measured as RSV hospitalisations per 1000, was built by applying the resulting model coefficients to calculate predicted values from the logistic equation: $P = 1/[1 + \ln(-x\beta)]$, where ln was the natural logarithm. A p-value <0.05 was considered as statistically significant.

Analyses and figures were performed using R Software analysis version 4.2.2, (R Foundation for Statistical Computing, Vienna, Austria).[19]

3 | RESULTS

As shown in Table 1, 460 771 (52.8% of which girls) children were followed up on over the course of the 11-year study period. Overall, 2420 infants (5.25 per 1000) tested positive for RSV, with boys having a slightly higher hospitalisation rate than girls (5.4 vs. 5.1 per 1000 neonates; $p = 0.0068$). In comparison to the cohort of non-RSV hospitalised children, the proportion of RSV infected infants with a longer hospital stay at birth was statistically significantly higher (10.3 cases per 1000 among those with 7 days or more; $p < 0.001$).

Respiratory syncytial virus infection rates were higher in neonates with complex DRG at birth, especially full-term with severe issues (DRG 389, 14.7 cases per 1000 births; $p < 0.001$), accounting for 370 cases over the study period. However, most RSV hospitalisations were among newborns who had no concerns at birth (overall 1666 cases accounting for 4.5 per 1000 newborns).

The supplementary file contains a comprehensive summary of the diagnoses that were given during the childbirth hospital admissions. As can be observed in Table S1, the most frequent diagnoses pertained to the issues "certain conditions originating in the perinatal period" (591 newborn infants out of 2420 RSV-positive subjects), "congenital anomalies" (103 infants), and "diseases of the respiratory system" (97 newborn infants). Interestingly, with respect to "certain conditions originating in the perinatal period," numerous diagnoses pertain to "other respiratory conditions of foetus and newborn" (184 subjects) and "disorders relating to short gestation and low birthweight" (169 infants). Furthermore, it is remarkable that just 93 of 2420 individuals were diagnosed at the time of their birth with "acute bronchiolitis due to respiratory syncytial virus (RSV)" (code 466.11). A summary of the entire contents of this report can be found in Table S1.

TABLE 1 Main characteristics of the cohort observed from 2007 to 2017 and RSV positive cases.

	Observed children *N* (%)	RSV positive children *N* (cases/1000)	*p*-value
Total	460 771 (100%)	2420 (5.25)	
Sex			
Male	235 092 (51%)	1279 (5.4)	0.0068
Female	225 679 (49%)	1141 (5.1)	
Length of stay (at birth), in days			
0–3	326 568 (70.9%)	1629 (4.9)	<0.001
4–6	100 991 (21.9%)	448 (4.4)	
7 or more	33 212 (7.2%)	343 (10.3)	
DRG			
391 – Normal newborn	371 348 (80.6%)	1666 (4.5)	<0.001
390 – Neonates with other significant problems	27 640 (6%)	137 (4.9)	
389 – Full-term neonate with major problems	25 091 (5.4%)	370 (14.7)	
388 – Prematurity without major problems	11 953 (2.6%)	67 (5.6)	
387 – Prematurity with major problems	9373 (2%)	62 (6.6)	
386 – Neonate, extreme immaturity	6058 (1.3%)	41 (6.8)	
385 – Transferred neonate	9308 (2%)	77 (8.3)	

Figure 1A shows that the incidence of RSV hospitalisation was higher between November and February, with a peak between December and January reaching a hospitalisation rate of 11.6 cases per 1000, and a decreased incidence rate throughout the summer (about 0.5 cases per 1000 between July and August). Furthermore, children born from November to February of each year appeared to

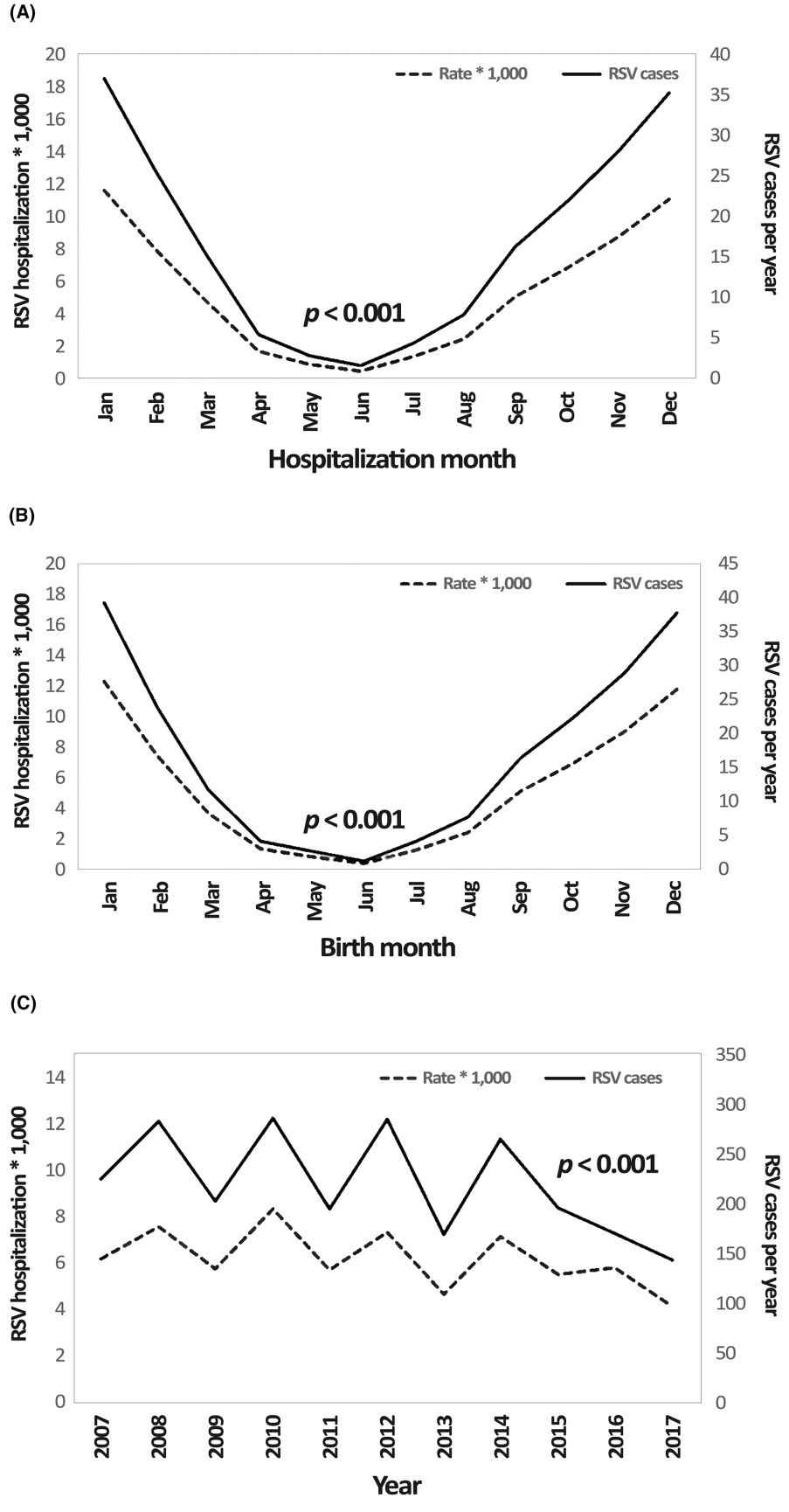

FIGURE 1 RSV hospitalisations in the first 6 months of life by month of hospitalisation (A), birth month (B) and hospitalisation year (C).

be the most likely to be hospitalised for RSV infection, with hospitalisation rates of around 10 cases per 1000 compared to around 0.7 cases per 1000 in children born in May or June (Figure 1B). Finally, a 2-year recurrence of epidemics was observed, with higher hospitalisation rates (Figure 1C).

Figure 2 depicts the forest plot of the multivariable analysis on factors involved in hospitalisation risk. Full term neonates with major problems (aOR 3.25, 95% CI 2.90–3.64; $p < 0.001$), transferred neonates (aOR 1.86, 95% CI 1.47–2.32, $p < 0.001$), neonates with extreme immaturity (aOR 1.54, 95% CI 1.11–2.07; $p = 0.007$), and premature neonates with major problems (aOR 1.48, 95% CI 1.14–1.90; $p = 0.002$) had a higher risk of RSV hospitalisation. When we focused on birth months, we observed a statistically significant increase in the risk of RSV hospitalisation in January (aOR 28.09, 95% CI 17.68–48.24; $p < 0.001$) and December (aOR 27.36, 95% CI 17.21–46.99; $p < 0.001$) compared to June.

Finally, Figure 3 depicts a risk matrix of RSV hospitalisation based on multivariable analysis fitting, comprising statistically significant variables and their regression coefficients. In the months of December and January, there was an exceptionally high risk for full-term neonates with major problems (DRG 389; 3.23% and 3.31%, respectively).

4 | DISCUSSION

In recent years, the global burden of RSV has continued to rise, particularly among newborns and children in their first year of life. Therefore, this study was designed primarily to identify epidemiological criteria helping clinicians identify risk variables for RSV hospitalisation and, thus, emphasise the need for prophylactic administration at birth. Our findings indicate that the birth month and the birth DRG are key factors in determining the risk of RSV hospitalisation in infants over their first 6 months of life. In contrast, the lack of statistical significance prevented us from determining if sex may play a role.

Respiratory syncytial virus is one of the leading causes of LRTI in children, with considerable rates of morbidity and mortality,[20] especially in newborns who are not adequately protected by maternal immunoglobulins.[21] Maternal antibodies can reach the foetus through the placenta, but they can only protect infants for the first months of life, so protection is usually relatively limited.[22]

As previously stated, palivizumab was licensed in several countries, including Italy, in 1998, and was restricted to premature infants, excluding others from the benefits.[23] More recently, nirsevimab approved for commercialisation and use, which requires a single administration and helps prevent RSV for at least 5 months, may provide new opportunities.[22] Both monoclonal antibody therapies have relatively high costs and restrictive administration criteria, so it is critical to develop strategies for their proper use and distribution.

To this purpose, we investigated risk variables that may increase the risk of RSV hospitalisation, finding that the birth month and birth DRG are key factors in infants' first 6 months of life.

Intriguingly, we observed a potential higher risk among boys, which corresponds to some studies indicating that boys are more

Variable		N	Odds ratio	p
Hospitalization Year	2007	42295	Reference	
	2008	44117	1.20 (1.01, 1.44)	0.039
	2009	42678	0.90 (0.74, 1.08)	0.260
	2010	41484	1.28 (1.07, 1.53)	0.006
	2011	41107	0.88 (0.73, 1.07)	0.196
	2012	46256	1.17 (0.98, 1.39)	0.088
	2013	44077	0.71 (0.58, 0.87)	<0.001
	2014	44815	1.12 (0.94, 1.34)	0.211
	2015	41000	0.90 (0.74, 1.09)	0.264
	2016	38093	0.82 (0.67, 1.00)	0.054
	2017	34849	0.77 (0.62, 0.95)	0.014
Sex	Female	225679	Reference	
	Male	235092	1.05 (0.97, 1.14)	0.238
DRG	Normal newborn	371348	Reference	
	Full-term neonate with major problems	25091	3.25 (2.90, 3.64)	<0.001
	Neonate, extreme immaturity	6058	1.54 (1.11, 2.07)	0.007
	Neonates with other significant problems	27640	1.08 (0.91, 1.29)	0.365
	Prematurity with major problems	9373	1.48 (1.14, 1.90)	0.002
	Prematurity without major problems	11953	1.25 (0.97, 1.58)	0.078
	Transferred neonate	9308	1.86 (1.47, 2.32)	<0.001
Birth Month	June	36452	Reference	
	January	38402	28.09 (17.68, 48.24)	<0.001
	February	33972	19.39 (12.13, 33.44)	<0.001
	March	36470	8.76 (5.39, 15.28)	<0.001
	April	34254	3.46 (2.02, 6.25)	<0.001
	May	36973	2.04 (1.14, 3.80)	0.020
	July	40788	2.86 (1.67, 5.17)	<0.001
	August	41475	5.25 (3.18, 9.26)	<0.001
	September	43498	10.41 (6.46, 18.04)	<0.001
	October	41902	14.75 (9.21, 25.45)	<0.001
	November	38165	20.94 (13.13, 36.04)	<0.001
	December	38420	27.36 (17.21, 46.99)	<0.001

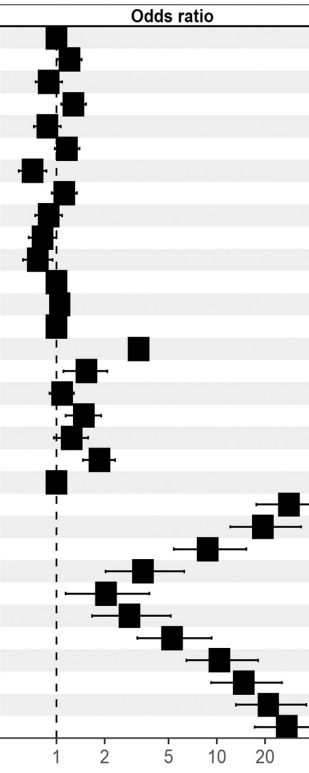

FIGURE 2 Multivariable analysis on factors involved in the risk of RSV hospitalisation (Sicily, 2007–2017) adjusted for hospitalisation year, sex, DRG, birth month and hospital length of stay.

	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
385 - Transferred neonates	1.92%	1.33%	0.61%	0.24%	0.14%	0.07%	0.20%	0.36%	0.72%	1.02%	1.44%	1.87%
386 - Neonate, extreme immaturity	1.59%	1.11%	0.50%	0.20%	0.12%	0.06%	0.16%	0.30%	0.60%	0.84%	1.19%	1.55%
387 - Prematurity with major problems	1.54%	1.07%	0.48%	0.19%	0.11%	0.06%	0.16%	0.29%	0.58%	0.81%	1.15%	1.50%
388 - Prematurity without major problems	1.29%	0.90%	0.41%	0.16%	0.10%	0.05%	0.13%	0.24%	0.48%	0.68%	0.97%	1.26%
389 - Full-term neonate with major problems	3.31%	2.31%	1.06%	0.42%	0.25%	0.12%	0.35%	0.64%	1.25%	1.76%	2.49%	3.23%
390 - Neonates with other significant problems	1.13%	0.78%	0.35%	0.14%	0.08%	0.04%	0.12%	0.21%	0.42%	0.60%	0.84%	1.10%
391 - Normal newborn	1.04%	0.72%	0.33%	0.13%	0.08%	0.04%	0.11%	0.20%	0.39%	0.55%	0.78%	1.01%

FIGURE 3 Fitted risk of RSV hospitalisation (as percentage risk) according to the multivariable model adjusted for sex, hospitalisation year and hospital length of stay.

vulnerable to severe outcomes from respiratory viral infections.[24] However, the precise relevance of sex remains debatable, and in our study, this factor loses statistical significance in the multivariable analysis.

Contrary to sex, DRGs and month of birth in our results absolutely determine significant differences in RSV hospitalisation risk. Notably, full-term neonates with major problems are nearly three times more likely to be hospitalised than full-term and healthy newborns. Similarly, transferred newborns appear to have a doubled risk of being hospitalised due to RSV, and premature neonates with or without major problems are around 50% more likely to be hospitalised due to RSV. Unfortunately, no other research has investigated DRG at birth as a risk predictor of future RSV hospitalisation; therefore, no comparison with other experiences is possible.

However, the relatively low risk observed for premature newborns in comparison to those who were full term with major problems should be considered. This study cannot determine the reasons for such a difference, but we may hypothesise that palivizumab could have been used to treat a large number of preterm newborns, considerably lowering the likelihood of future RSV hospitalisations.[23] On the contrary, during the study period, full-term infants with major problems were not a target category for monoclonal antibody prophylaxis, which could explain their extremely high risk of subsequent RSV hospitalisation. As a result, the risk data shown in the risk axis may be biased for preterm infants and should be interpreted with caution.

Finally, the month of birth, which has been demonstrated to have a major influence on a possible RSV infection, should be thoroughly discussed. This characteristic may also be strategic for managing monoclonal antibody immunisation. Our findings show that infants born from November to February had a 20-fold to 27-fold higher risk of hospitalisation than those born in June or May. Children born in March, September and October have a slightly better situation, but they are still at high risk, with a more than doubled risk of RSV hospitalisation. The relevance of birth date has already been investigated in other studies, which confirm our results with similar risks.[25,26] As previously stated, the COVID-19 pandemic resulted in a fairly close absence of transmission of other respiratory viruses, especially RSV, throughout the world, including Italy, until the 2021–2022 season, when there was an atypical resurgence in both magnitude and timing.[10–14] However, this peak may be the result of an immunity gap induced by reduced RSV exposure during the pandemic as a result of preventive measures such as social distancing, mask use, and hand hygiene.[27] When this phase concludes and the immunity gap is bridged, we do not foresee anything different from what we have observed in our analyses. The European Respiratory Virus Surveillance Summary (ERVISS) epidemic curves for the 2022–2023 season match those of the epidemic seasons preceding the COVID-19 outbreak, supporting this thesis.[28]

Interestingly, by fitting a multivariable analysis, all previously discussed variables were included in a matrix risk that could be beneficial in the future for addressing and regulating criteria administration of monoclonal antibody immunisation. Several researchers have attempted to contribute to important tasks for improving the appropriateness of care in recent years.[29]

Lastly, although less significant in comparison to the other factors, we noticed an unexpected fluctuation in the incidence of hospitalisation from 1 year to the next, as previously reported elsewhere.[30] We believe that this is another important factor that requires further confirmation.

4.1 | Limitations

This study had some major limitations. First, RSV hospitalisation may underestimate the true disease burden since some children may not undergo sensitive laboratory tests, leading to misclassification bias (possible false-negative patients). Furthermore, other factors that could contribute to the risk of RSV hospitalisation such as monoclonal antibody prophylaxis, the presence of specific comorbidities, and exposure to lifestyle risk factors such as passive smoking, were not accounted for in the present study. Finally, DRG codes are non-specific with respect to some comorbidities whereas socioeconomic deprivation factors, namely maternal education, lower levels of income, and housing quality, that could have a major role in RSV infection were not analysed.

Despite these significant potential limitations, this study has the merit of including a large cohort of about half a million infants over

an 11-year period and investigating birth characteristics that could predict the RSV hospitalisation risk.

5 | CONCLUSION

This study identified some predictors (birth month, DRG and year of birth) that appear to play a major role in forecasting future RSV hospitalisations in the first 6 months of life.

It is imperative to develop strategies to prevent RSV infection in order to rescue children from severe illness and hospitalisation/death, as well as to promote the proper use of health and economic resources. This study focused on predictive factors that, if present at birth, could raise the risk of RSV hospitalisation, with the goal of preventing infection.

As a result, the risk data shown in the risk ax may be biased for preterm infants and should be interpreted with caution. More data confirmations and studies on the correlation between identified factors and severe outcomes/hospitalisation are needed, but our findings represent a good starting point for developing scores that could be used to identify patients at high risk of hospitalisation and, as a result, appropriately administer monoclonal antibodies to prevent infection.

AUTHOR CONTRIBUTIONS

Dario Genovese: Writing – original draft; visualization; formal analysis; data curation. **Emanuele Amodio:** Conceptualization; writing – original draft; methodology; formal analysis; supervision; software. **Vincenzo Pisciotta:** Writing – original draft; data curation; project administration; formal analysis. **Giuseppe Vella:** Writing – review and editing; data curation; visualization. **Maria Gabriella Verso:** Writing – review and editing; supervision. **Mario Giuffrè:** Writing – review and editing; supervision. **Francesco Vitale:** Writing – review and editing; conceptualization; supervision; resources; methodology.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

ETHICS STATEMENT

The Hospital Discharge Records (HDRs) were gathered from the official databases of the Health Regional Office of Sicily in compliance with current Italian legislation. Research performed under the Italian Legislative Decree 101/2018 on the protection of personal data, does not require Ethical Committee approval or formal patient consent.

ORCID

Dario Genovese https://orcid.org/0000-0001-6977-9268

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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