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Hospitalizations for respiratory syncytial virus bronchiolitis in preterm infants at <33 weeks gestation without bronchopulmonary dysplasia: the CASTOR study

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SUMMARY

This study was conducted during the 2008–2009 respiratory syncytial virus (RSV) season in France to compare hospitalization rates for bronchiolitis (RSV-confirmed and all types) between very preterm infants (<33 weeks' gestational age, WGA) without bronchopulmonary dysplasia and full-term infants (39–41 WGA) matched for date of birth, gender and birth location, and to evaluate the country-specific risk factors for bronchiolitis hospitalization. Data on hospitalizations were collected both retrospectively and prospectively for 498 matched infants (249 per group) aged <6 months at the beginning of the RSV season. Compared to full-term infants, preterm infants had a fourfold [95% confidence interval (CI) 1·36–11·80] and a sevenfold (95% CI 2·79–17·57) higher risk of being hospitalized for bronchiolitis, RSV-confirmed and all types, respectively. Prematurity was the only factor that significantly increased the risk of being hospitalized for bronchiolitis. The risk of multiple hospitalizations for bronchiolitis in the same infant significantly increased with male gender and the presence of siblings aged ⩾2 years.

Key words: Bronchiolitis, hospitalization, infant, premature, respiratory syncytial virus, risk factors.

INTRODUCTION

Acute bronchiolitis is a common seasonal lower respiratory tract infection (LRTI) and a major cause of respiratory morbidity in the first year of life [1–3]. Respiratory syncytial virus (RSV) is the most prevalent pathogen, responsible for up to 75% of bronchiolitis cases in infants during the epidemic season [1, 4–6]. It usually affects infants aged <2 years, with a peak during the first 3–6 months of life. Hospital admission is required in <2% of cases, with most patients usually being managed in the community [1, 3, 4, 7]. Nevertheless, RSV bronchiolitis is the major cause of hospitalization in infants aged <1 year, with >80% of admissions involving infants aged <6 months [8].

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The majority of children who are hospitalized with RSV-LRTI are otherwise healthy. However, certain groups are at a higher risk of severe disease requiring hospitalization [7, 9]. A large retrospective cohort study of all children aged <3 years hospitalized for RSV infections and enrolled in the Tennessee Medicaid program from July 1989 to June 1993 showed that RSV hospitalizations in the first 6 months of life occurred in 4·4/100 child-years in healthy infants and increased to 8·0–9·4/100 child-years in infants born prematurely; the hospitalization rates were directly correlated with decreasing gestational age, thus indicating that prematurity *per se* was associated with increased severity of RSV infections [10].

The severity of RSV bronchiolitis is likely to be determined by a complex interplay between viral and host factors [3, 11]. Independent clinical risk factors for severe RSV bronchiolitis and hospital admission in paediatric intensive care units (PICUs) comprise: young age at onset of the RSV season [12–14]; lower gestational age, especially birth at <33 weeks' gestational age (WGA) [7, 12–18]; history of neonatal respiratory distress syndrome [16–18]; low birthweight [11, 13]; chronic lung disease [7, 10, 13, 15, 16] and congenital heart disease [7, 14, 17].

Environmental individual risk factors promoting cross-infection – especially crowding due to living with siblings and day-care attendance – have been shown to correlate with a higher risk of severe bronchiolitis [3]. However, the role of such factors is highly dependent on the geographical region as well as on socio-cultural peculiarities, and therefore their evaluation in a given setting is crucial for the accurate identification of specific populations at higher risk of severe disease.

In France there are no prospective epidemiological data on the risk of hospitalization for bronchiolitis (RSV and all types) in very premature infants without bronchopulmonary (BPD), those with BPD being unanimously accepted as being at high risk for severe disease; moreover, the country-specific environmental risk factors for RSV hospitalization in this population have not been previously explored.

In this context, the CASTOR study (Comparison of the rAte of hoSpitalization for RSV bronchioliTis between preterm infants born at 32 weeks' gestational age or less without brOnchopulmonary dysplasia and full-teRm infants) aimed to compare the hospitalization rates for severe RSV bronchiolitis in very preterm infants (<33 WGA) without BPD *vs.* matched full-term infants, all aged <6 months at the beginning of the 2008–2009 RSV season in France, and to evaluate the risk factors for severe disease in this population.

METHODS

A multicentre, ambispective, longitudinal, non-interventional cohort study was conducted in nine French regional perinatal networks.

Study design

Participating paediatricians and neonatologists were invited to identify and record in a registry all the preterm infants <33 WGA without BPD born during the 6 months preceding the 2008–2009 RSV season in all the maternity units (public and private) belonging to the nine French regional perinatal networks participating in the study. An equal number of full-term infants (39–41 WGA) were recruited in these maternity units, and matched to preterm infants according to age (±1 month), gender and birth region. To allow strong comparisons on follow-up, participating physicians were invited to include in the registry two full-term infants for each preterm infant.

Because the start date of the 2008–2009 RSV season (i.e. 29 September 2008) was determined during the course of the study, the birth period of the infants was extended from 1 May 2008 to 31 March 2008 in order to align with the inclusion criterion 'chronological age <6 months at the beginning of the RSV season'. The inclusions effectively started on 12 November 2008, and extended up to 31 January 2009 due to certain recruitment difficulties for full-term infants. However, the investigated period was the entire 2008–2009 RSV season (29 September 2008 to 30 April 2009), as the data on bronchiolitis hospitalizations from the beginning of the RSV season to inclusion date were collected retrospectively, and those regarding hospitalizations from inclusion date to the end of the RSV season (30 April 2009) were collected prospectively. The study design is presented in Figure 1.

Selection criteria

Physicians were selected in type 2 (neonatal intermediate care units) or type 3 (neonatal intensive care units) neonatal hospital centres belonging to the nine regional perinatal networks participating the study.

Infants were eligible if their chronological age was <6 months at the beginning of the 2008–2009 RSV season, their parents were able to understand French

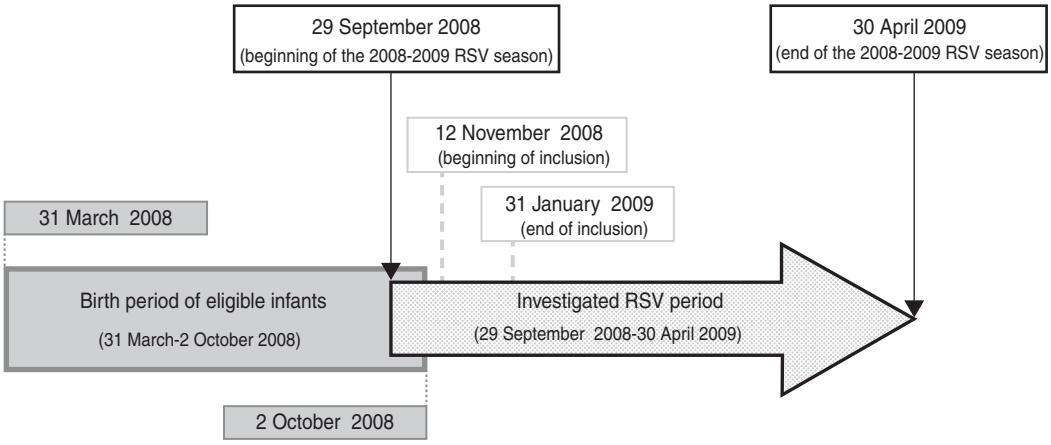

Fig. 1. Study design. RSV, Respiratory syncytial virus.

and agreed to take part in the study and to be contacted by phone. Those born at <33 WGA without BPD (defined according to study protocol as oxygen dependency at 28 days of life) were eligible as preterm infants, and those born between 39 and 41 WGA as full-term infants.

Excluded infants were those receiving or having received specific RSV prophylaxis, and infants whose life expectancy was <6 months, with known immune deficiency or a serious or chronic illness that may have an impact on their health status, including severe congenital heart disease.

The physicians had to match each eligible preterm infant to a full-term infant, according to age (±1 month), gender and geographical location of infant's home or birth in order to ensure comparable sociodemographic characteristics. Infants were included in the study if all inclusion criteria were fulfilled/non-inclusion criteria were not fulfilled, and written participation and phone contact informed consents signed by the parents were received.

Assessments

The participating physicians were free to prescribe, treat and follow-up the included infants according to their usual practice; hospital admission and management for bronchiolitis were based on their medical experience, and their compliance with the corresponding French recommendations [4]. According to the National Agency for Accreditation and Evaluation in Health (ANAES), the term 'bronchiolitis' covers all forms of viral obstructive bronchial disease occurring in epidemics in infants aged 1–24 months, manifesting as dyspnoea with tachypnoea, restricted expiration, chest hyperinflation and respiratory distress potentially interfering with feeding; auscultation is dominated by crepitant or subcrepitant rales, rapidly followed by sibilant rales and wheezing [4]. RSV testing in case of hospitalization for bronchiolitis was not mandatory, but recommended for epidemiological purposes [4].

The primary endpoint was to compare hospitalization rates for RSV-confirmed bronchiolitis between the group of preterm infants <33 WGA without BPD and the group of matched full-term infants followed-up during the 2008–2009 RSV season in France.

Secondary endpoints included the comparison of hospitalization rates for all types of bronchiolitis (RSV confirmed or not) between the two groups, description of the sociodemographic and medical characteristics of hospitalized infants, description of the therapeutic care of infants hospitalized for RSV-confirmed bronchiolitis in both groups of infants, and evaluation of the risk factors for bronchiolitis hospitalization in the French setting.

Data collection

Data on bronchiolitis hospitalizations from the beginning of the investigated RSV season (i.e. 29 September 2008) to inclusion (i.e. 12 November 2008) were collected retrospectively; those regarding the hospitalizations from inclusion to the end of the study (i.e. 30 April 2009) were collected prospectively. The data were collected from the medical files of eligible infants, and during the follow-up period until the end of the RSV season (30 April 2009) via information recorded by the investigators and parents.

Physicians had to complete for each included infant, at inclusion and at end of study, a case report

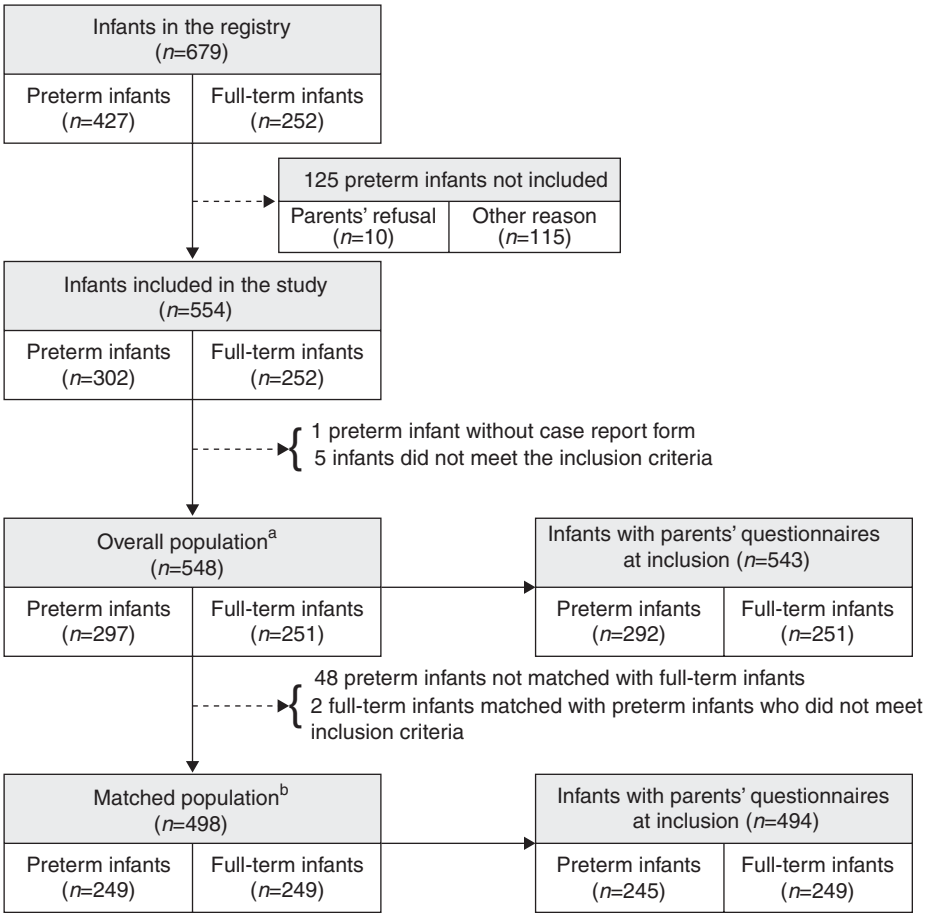

Fig. 2. Disposition of infants. [a] All infants who met inclusion and non-exclusion criteria. [b] All infants who met inclusion and non-exclusion criteria and who were matched.

form with all the medical data regarding the admissions for bronchiolitis during the follow-up period.

The parents were contacted at inclusion – to collect sociodemographic data – and then monthly during the follow-up period to collect data regarding hospitalizations for bronchiolitis. A hospitalization diary helped parents to remember hospitalization episodes, and to identify the managing practitioners in order to obtain further information if necessary. Between two phone contacts, parents were able to report any hospital admission for bronchiolitis through a freephone number.

Statistical analysis

Statistical analyses were performed using SAS software, version 9.2 (SAS Institute, USA).

For comparison of hospitalization rates between preterm and full-term infants, χ^2 or Fisher's exact tests were used. A level of significance of 5% was set.

Zero-inflated Poisson (ZIP) models were used to further explore the risk of hospitalization for bronchiolitis [19]. This model was retained in order to take into account the high estimated proportion of non-events, and applied to evaluate the risk of hospitalization for bronchiolitis in the overall study population. The following covariates were first included in a univariate ZIP model: chronological age at the beginning of the RSV season (<60, 60–89, 90–119, 120–149, $\geqslant 150$ days), gestational age, gender, breastfeeding, geographical location, environmental risk factors, multiple pregnancy, and intrauterine growth restriction (defined as birthweight below the 10th percentile of the corresponding standard) [20]; all the covariates that were significant at the threshold of 25% were then entered in a ZIP multivariate model. The least significant covariate in a model was dropped from the model and the process continued until all remaining covariates were significant at 5%.

Table 1. *Sociodemographic characteristics at inclusion* (*matched population*)

Variables*	Preterm infants ($n=249$)	Full-term infants ($n=249$)	P value
Demographic characteristics			
Age at beginning of 2008–2009 RSV season, months	2·8 ± 1·6	2·9 ± 1·6	0·7633
Age at inclusion, months	5·9 ± 1·8	6·0 ± 1·8	0·7251
Gender			
Boys	128 (51·4)	127 (51·0)	0·9286
Girls	121 (48·6)	122 (49·0)	
Multiple pregnancy	95 (38·2)	1 (0·4)	<0·0001
Birth weight, g	1588 ± 305	3399 ± 428	<0·0001
Birth height, cm	40·5 ± 2·7	50·1 ± 1·7	<0·0001
At least one sibling	161 (64·7)	144 (57·8)	0·0804
Hospital stay at birth			
Type of birth centre			
Type 3	201 (80·7)	165 (66·3)	0·0006
Type 2	40 (16·1)	76 (30·5)	
Length of stay, days	39·6 ± 11·6	4·9 ± 6·1	<0·0001
Hospitalization in neonatology services†	249 (100)	8 (3·2)	<0·0001

* Results are presented as mean ± S.D. or *n* (%) when appropriate.
† Distinct hospital units dedicated to the post-natal management of preterm infants and/or newborns with an altered health status.

RESULTS

Of the 679 infants (427 preterm infants <33 WG and 252 full-term infants) entered in the initial study registry, 548 infants (297 preterm, 251 full-term) were included in the overall study population, and 498 infants (249 infants in each group) in the matched study population as shown in Figure 2.

Similar characteristics at inclusion were found in the matched and the overall study population (data not shown).

Study population

Characteristics of the matched population at inclusion are summarized in Table 1. The mean age at birth for preterm infants was 31·4 ± 0·9 WGA; 94% were born at 30–32 WGA, and none was born at <28 WGA. At their first bronchiolitis hospitalization, preterm infants were slightly younger (5·8 ± 2·0 months) than full-term infants (6·0 ± 1·6 months).

Regarding birth hospitalization, all preterm infants compared to only 3·2% of full-term infants were hospitalized in Neonatology services (Table 1), and significantly more preterm infants required ventilatory support compared to full-term infants (69·8% *vs.* 0·4%, $P<0·0001$) as shown in Table 2.

Preterm infants were significantly more exposed than full-term infants to antenatal smoking, and received significantly less breastfeeding; conversely, they had a lower attendance at day-care centres (Table 3).

Hospitalizations for bronchiolitis

During the 2008–2009 RSV season, 35 preterm and five full-term infants were admitted for bronchiolitis irrespective of the aetiology, accounting for 41 and nine hospitalizations, respectively, as shown in Table 4.

The hospitalization rate was significantly higher in the preterm than in the full-term group (14·1% *vs.* 2·0%, $P<0·0001$); preterm infants had a sevenfold increased risk of hospitalization for all types of bronchiolitis compared to matched full-term group [95% confidence interval (CI) 2·79–17·57].

There was no difference in hospitalization rates for all types bronchiolitis between preterm infants requiring ventilatory support during birth hospitalization compared to their non-ventilated counterparts (14·9% *vs.* 11·9%, $P=0·5821$).

Table 2. *Types of ventilation required during birth hospitalization* (*matched population*)

Type of ventilation*	Preterm infants ($n=249$)	Full-term infants ($n=249$)	P value
MV only	14 (5·6)	0 (0)	<0·0001
NIV ventilation only	91 (36·5)	1 (0·4)	
MV and/or NIV	69 (27·7)	0 (0·0)	
None	67 (26·9)	232 (93·2)	

MV, Mechanical ventilation; NIV, non-invasive ventilation.
Results are presented as *n* (%).
* Missing data included in calculation of percentages, but excluded in the statistical testing.

Table 3. *Environmental risk factors for bronchiolitis at inclusion* (*matched population*)

Environmental risk factors*	Preterm infants ($n=245$)	Full-term infants ($n=249$)	P value
Smoking status of the mother during pregnancy – yes	66 (26·9)	45 (18·1)	0·0178
Smoking status of the family since birth – yes	23 (9·4)	30 (12·0)	0·3841
Number of siblings	1·1 ± 1·1	0·9 ± 0·9	0·0147
Breastfeeding – yes	125 (51·0)	165 (66·3)	0·0006
Type of child care			
Day-care centre	3 (1·2)	23 (9·2)	<0·0001
Child minder	47 (19·2)	69 (27·7)	
Family	193 (78·8)	138 (55·4)	
Other	0 (0·0)	19 (7·6)	

Results are presented as mean ± S.D. or *n* (%) when appropriate.
* Missing data included in calculation of percentages, but excluded in the statistical testing.

The majority of infants (90·2% of preterm, 88·9% of full-term) required non-medicinal care – perfusion or parenteral nutrition (35·0%), enteral nutrition with stomach tube (26·0%), oxygen therapy (44·0%), mechanical ventilation (5·0%), non-invasive ventilation (12·5%) and respiratory physiotherapy (54·0%) – and all recovered.

Hospitalizations for RSV-confirmed bronchiolitis

The majority of hospitalizations for bronchiolitis were RSV-tested (nasopharyngeal aspirate and viral immunofluorescence) as shown in Table 4. Seven infants (five preterm, two full-term) were hospitalized more than once for bronchiolitis (RSV-positive/RSV-negative/not tested) during the studied season.

Hospitalization rates for RSV bronchiolitis were significantly higher in the preterm group than in the full-term group as presented in Figure 3; preterm infants had a fourfold increased risk of hospitalization for RSV bronchiolitis compared to the matched full-term group (95% CI 1·36–11·80).

These results were further confirmed with sensitivity analyses to handle missing RSV tests using a high hypothesis, i.e. imputing missing RSV tests as positive tests, as well as a crossed hypothesis, i.e. by adding to each study group a number of RSV hospitalizations obtained by adjusting the number of missing RSV tests in the group to the percentage of RSV-positive tests in the other group (Fig. 3).

Similar results were found in the overall study population, with a hospitalization rate for RSV-confirmed bronchiolitis significantly higher in preterm

Table 4. *Bronchiolitis hospitalizations and respiratory syncytial virus (RSV) testing (matched population)*

	Preterm infants ($n=249$)	Full-term infants ($n=249$)
Hospitalized infants, *n*	35	5
Total number of RSV tests, *n* (%)	27 (77·1)	4 (80)
RSV-positive tests, *n*	16	4
RSV-negative tests, *n*	11	0
Missing RSV tests, *n*	8	1
Hospitalizations for bronchiolitis, *n*	41	9
Total number of RSV tests, *n* (%)	33 (80·5)	7 (77·8)
RSV-positive tests, *n*	17	4
RSV-negative tests, *n*	16	3
Missing RSV tests, *n*	8	2

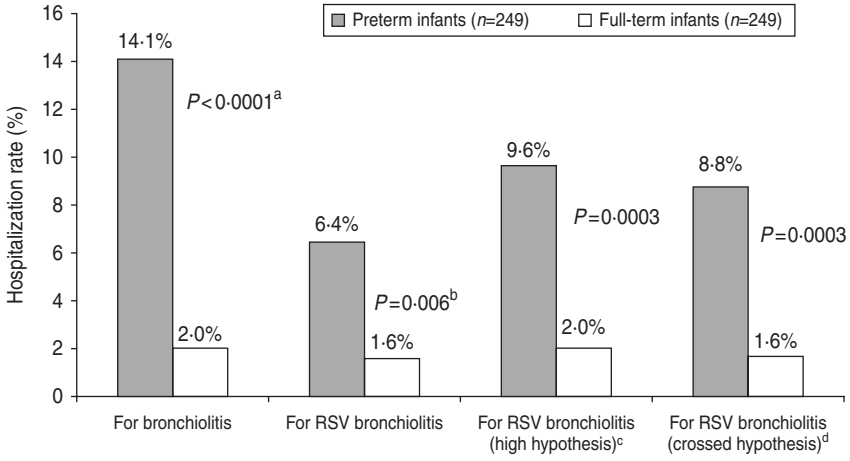

Fig. 3. Hospitalizations for bronchiolitis [respiratory syncytial virus (RSV) and in general] during the 2008–2009 RSV season (matched population). [a] Relative risk 7·00 (95% CI 2·79–17·57); [b] relative risk 4·00 (95% CI 1·36–11·80). Two approaches were considered in the sensitivity analysis to handle missing RSV tests: [c] High hypothesis imputed missing RSV tests as positive tests. [d] Crossed hypothesis added a number of adjusted RSV hospitalizations to each study group.

compared to full-term infants (5·7% *vs.* 1·6%, $P=0·012$), corresponding to a relative risk for RSV bronchiolitis hospitalization of 3·59 (95% CI 1·22–10·54) for preterm compared to full-term infants.

Preterm infants with RSV-confirmed bronchiolitis were mainly hospitalized in general paediatric (88·2%) or in neonatology (11·8%) units; only a few (5·9%) preterm infants were admitted to PICUs. Preterm infants hospitalized with RSV-confirmed bronchiolitis had longer episodes and longer hospital stays compared to those hospitalized with RSV-negative bronchiolitis; the mean duration of episodes was $9·5\pm3·4$ days for RSV-positive *vs.* $6·8\pm2·6$ days for RSV-negative ($P=0·0183$) bronchiolitis, and the mean length of hospital stay was $7·2\pm3·3$ days for RSV-confirmed cases *vs.* $5·5\pm2·7$ days for RSV-negative cases ($P=0·1901$). The same trend was observed in the full-term group, without any significant differences between RSV-positive and RSV-negative cases (data not shown).

In the preterm group, bronchiolitis hospitalizations that were tested for RSV appeared to be more severe compared to the non-tested cases as the preterm infants in the tested group had longer hospital stays and needed more non-medicinal care than the non-tested group (Table 5).

Predictive factors of the risk of hospitalization and the number of hospitalizations for bronchiolitis

The multivariate ZIP model applied to explore the risk of hospitalization for bronchiolitis demonstrated

Table 5. *Characteristics of respiratory syncytial virus (RSV)-tested and non RSV-tested bronchiolitis hospitalizations (matched very preterm group)*

Characteristics of bronchiolitis hospitalizations	Tested for RSV ($n=33$)	Not tested for RSV ($n=8$)
Length of hospital stay (days)		
Mean (S.D.)	6·4 (3·1)	2·4 (1·6)
Median	5·0	2·0
Min–Max	2·0–13·0	0·0–5·0
Non-medicinal therapeutic care (*n*, %)		
Yes	31 (93·9)	6 (75·0)
No	2 (6·1)	2 (25·0)
Type of care* (*n*, %)		
Perfusion or parenteral nutrition	11 (33·3)	—
Enteral nutrition with stomach tube	10 (30·3)	3 (37·5)
Oxygen therapy	18 (54·5)	1 (12·5)
Assisted breathing	1 (3·0)	—
Non-invasive ventilation	5 (15·2)	—
Respiratory physiotherapy	19 (57·6)	3 (37·5)

* For each hospitalization, several types of care could have been required.

Table 6. *Results of the final Zero-inflated Poisson (ZIP) model in the overall population ($n=548$): parameter estimates of both logistic model and Poisson model component of the ZIP model*

Parameter		Estimate	95% CI	*P* value
Logistic model component				
Intercept		−0·06	−1·21 to 1·10	0·9253
Preterm/full-term infants (ref. = preterm)	Full-term	2·59	1·37 to 3·80	<0·0001
Poisson model component				
Intercept		−0·42	−1·05 to 0·22	0·2018
Gender (ref. = male)	Female	−1·23	−1·93 to −0·52	0·0006
One or more siblings aged ⩾2 years (ref. = yes)	No	−0·67	−1·27 to −0·07	0·0291

CI, Confidence interval.

a good fit to the data, and in particular did not show any overdispersion. The only explanatory variable kept in the logistic model component of the ZIP model was gestational age, with a positive parameter estimate (parameter estimate 2·59), indicating that full-term infants had a greater chance of not being hospitalized for bronchiolitis than preterm infants <33 WGA. The Poisson model component of the ZIP model, which reflects the risk of multiple hospitalizations, included gender of infant and having one or more siblings aged ⩾2 years: the parameter estimates for both female infants and infants without siblings aged ⩾2 years was lower than 0 indicating a lower risk of multiple hospitalizations for bronchiolitis in these infants (Table 6).

DISCUSSION

The French CASTOR study showed that very preterm infants (<33 WGA) without BPD had a fourfold increased risk of hospitalization for RSV-confirmed bronchiolitis compared to matched full-term infants, all aged <6 months at the beginning of the 2008–2009 RSV season, and confirmed these data in the overall study population.

RSV testing using nasal swabs, recommended but not mandatory, was performed in nearly 80% of hospitalizations. RSV-positive bronchiolitis was found in one out of every two RSV-tested cases, and estimated in up to 72·5% of hospitalized bronchiolitis cases when considering a high hypothesis to count missing

tests as RSV-positive. The decision to perform a RSV test on admission for bronchiolitis seemed most probably related to the severity of disease as tested cases had longer hospital stays and required more non-medicinal therapeutic care compared to non-tested cases. These results are consistent with the Spanish data issued from a study conducted by the IRIS study group, where RSV testing was performed in 75% of admissions in preterm infants (<33 WGA), with 66% of cases being RSV-positive [15].

A recent literature review of the diagnosis and testing in bronchiolitis concluded that RSV testing, although commonly used to document the cause of bronchiolitis, rarely changes the clinical management or the outcomes of hospitalized infants [21]. In their review on bronchiolitis, Smyth & Openshaw stated that there is no good evidence on the effectiveness of this approach, despite of the fact that many hospitals require routine RSV testing to allow infected infants to be cohorted together in order to reduce the risk of cross-infection [22]. In this context of heterogeneous RSV detection practices, it appears important to evaluate the hospitalization rates for all types of bronchiolitis, RSV confirmed or not.

All preterm infants included in the CASTOR study were hospitalized in neonatology units after birth compared to only 3% of matched full-term infants; moreover, the duration of birth hospitalization was nine times longer in the preterm group, reflecting an increased need for postnatal care.

It should be noted that the recruitment of full-term infants was performed in type 3 centres, therefore favouring the inclusion of possibly more fragile infants, which could have diminished the observed differences in the risk of hospitalization for bronchiolitis between the very preterm group compared to the full-term group.

The comparison of the environmental risk factors for bronchiolitis between preterm *vs.* full-term infants hospitalized for bronchiolitis in our study showed a higher prevalence of multiple pregnancies and antenatal smoking exposure in the preterm group; this finding is consistent with previous international reports [7, 14, 23, 24]. However, the relatively small number of infants hospitalized for bronchiolitis in both groups could explain the lack of significant correlation with the risk of being hospitalized and/or of having multiple hospitalizations observed via the multivariate ZIP model in the present study.

Regarding child care, the protective attitude of French parents towards their preterm infants could have limited the bronchiolitis hospitalization rates in the preterm group of the present study, as these infants were mostly kept within the family, and therefore less exposed to viral cross-contamination.

Nevertheless, very preterm infants without BPD included in the CASTOR study were four times more at risk of being hospitalized for RSV-confirmed bronchiolitis compared to their full-term counterparts. This finding is in line with data from the retrospective analysis by Boyce *et al.*, which found a 3·3-fold increased risk of hospitalization for RSV bronchiolitis (95% CI 2·3–4·7) in preterm infants (29 to <33 WGA) aged 6–12 months compared to full-term infants [10]. Comparable RSV hospitalization rates have been reported by Stevens *et al.* [25] based on the analysis of a large US retrospective cohort of 1029 very preterm infants (⩽32 WGA), of which 4·4% of those born at 30–32 WGA were hospitalized for RSV-associated illness until 1 year of corrected age.

Conversely, much higher hospitalization rates for respiratory disease have been reported by Cunningham *et al.* in a cohort including 133 infants born at <33 WGA that were discharged from the NICU department of a tertiary-care facility serving an 18-county region in central New York State. In this cohort, preterm infants aged <33 WGA without BPD had a hospitalization rate of 25% *vs.* 14·1% hospitalization for all types of bronchiolitis in the CASTOR preterm group, while similar hospitalization rates were reported in full-term subgroups from both studies (2·5% and 2%, respectively) [16]; this difference could be due to the different evaluation end-points, i.e. hospitalization for respiratory disease in the US cohort compared to hospitalization for bronchiolitis only in the present study.

Recent data from a Swiss prospective cohort of 462 children aged <3 years hospitalized in intermediate or intensive care units for a RSV-related illness showed that only 2% of the very preterm infants (<33 WGA) without BPD were admitted to these services compared to 6·4% hospitalized for RSV-confirmed bronchiolitis in our study [26]; the same trend was observed in the full-term groups, with 0·1% hospitalization rate in the Swiss cohort *vs.* 1·6% in the French CASTOR study. These differences are possibly due to country-dependent medical practices and hospitalization guidelines. In spite of these specificities, the median length of admission for RSV-confirmed bronchiolitis in the preterm group of our study (5 days, range 2–13 days) is comparable, for

example, to the median length of stay for RSV-bronchiolitis (7 days, range 5–9 days) reported by Carbonell-Estrany *et al*. [15] in Spanish very preterm infants hospitalized for RSV infections.

In the CASTOR study, prematurity of <33 WGA increased the risk of being hospitalized for severe bronchiolitis, whether RSV-confirmed or all aetiologies, but had no significant impact on the number of hospitalizations. Several factors, including pulmonary and immune system immaturity, are likely to predispose preterm infants to severe LRTI [7, 9, 27]. It has been suggested that healthy infants born prematurely have smaller sized airways relative to their lung volume and therefore persistent lower pulmonary function compared to infants born at term [28–30]; furthermore, RSV infection in premature infants was associated with abnormal lung function at follow-up [22, 27].

The CASTOR study also showed that, in the French setting, male gender and the presence of siblings aged $\geqslant 2$ years are independent risk factors for multiple bronchiolitis hospitalizations [12, 15].

Our study has several limitations. As RSV testing was not mandatory, hospitalization rates for RSV bronchiolitis could have been underestimated in both groups of infants. Furthermore, we can not exclude that certain preterm infants were not included because of the presence of associated environmental risk factors generating the physician's decision to administer specific RSV prophylaxis to prevent severe RSV infections [31]. Moreover, the high proportion (67%) of full-term infants recruited in type 3 centres might have determined an inclusion bias by favouring the inclusion of more fragile full-term infants, thus leading to a potential overestimation of the bronchiolitis hospitalization rate in this group. All these limitations would probably diminish the observed differences in the hospitalization rates for bronchiolitis, RSV-confirmed and all types, between very preterm infants without BPD and their full-term counterparts; in spite of this, our study revealed important differences between the cases and the controls.

CONCLUSION

The CASTOR study highlighted that, in the French setting, very preterm infants (<33 WGA) without BPD are at significantly increased risk of hospitalization for severe bronchiolitis, RSV-confirmed and all aetiologies compared to matched full-term infants. The preterm group was also prone to more severe disease, as suggested by longer hospital stays and the requirement of more therapeutic care compared to the full-term group.

Moreover, we showed that in France, prematurity <33 WGA was the only factor that significantly increased the risk of being hospitalized for bronchiolitis, and that the risk of multiple hospitalizations for bronchiolitis in the same infant significantly increased with male gender and the presence of siblings aged $\geqslant 2$ years.

As RSV bronchiolitis is an important healthcare issue, leading to significant morbidity in preterm infants with or without associated BPD, larger prospective studies are clearly needed to further explore the specific risk factors and outcomes in this high-risk population. This approach could improve the identification of those infants most likely to develop severe disease, and contribute to the improvement of their healthcare in the future.

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DECLARATION OF INTEREST

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