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Epidemiology of laboratory-confirmed respiratory syncytial virus infection in young children in England, 2010–2014: the importance of birth month

R. M. REEVES[1,2,3]*, P. HARDELID[1,2], R. GILBERT[1,2], J. ELLIS[4], H. ZHAO[3], M. DONATI[5] AND R. PEBODY[3]

[1] *Farr Institute of Health Informatics Research, London, UK*
[2] *Institute of Child Health, University College London, UK*
[3] *Respiratory Diseases Department, Public Health England, Colindale, London, UK*
[4] *Virus Reference Department, Public Health England, Colindale, London, UK*
[5] *Bristol Public Health Laboratory, Public Health England, Bristol, UK*

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SUMMARY

The epidemiology of laboratory-confirmed respiratory syncytial virus (RSV) infections in young children has not recently been described in England, and is an essential step in identifying optimal target groups for future licensed RSV vaccines. We used two laboratory surveillance systems to examine the total number and number of positive RSV tests in children aged <5 years in England from 2010 to 2014. We derived odds ratios (ORs) with 95% confidence intervals (CIs) comparing children by birth month, using multivariable logistic regression models adjusted for age, season and sex. Forty-seven percent of RSV tests (29 851/63 827) and 57% (7405/13 034) of positive results in children aged <5 years were in infants aged <6 months. Moreover, 38% (4982/13 034) of positive results were in infants aged <3 months. Infants born in September, October and November had the highest odds of a positive RSV test during their first year of life compared to infants born in January (OR 2·1, 95% CI 1·7–2·7; OR 2·4, 95% CI 2·1–2·8; and OR 2·4, 95% CI 2·1–2·7, respectively). Our results highlight the importance of young age and birth month near the beginning of the RSV season to the risk of laboratory-confirmed RSV infection. Future control measures should consider protection for these groups.

Key words: Children, England, epidemiology, laboratory-confirmed, respiratory syncytial virus.

INTRODUCTION

Respiratory syncytial virus (RSV) is a major cause of hospitalization with lower respiratory tract infections in young children worldwide [1]. RSV infection in early life is associated with development of long-term respiratory morbidity including asthma and recurrent wheezing [1]. In developing countries, RSV is also an important cause of childhood mortality [2]. Risk factors for severe RSV infection resulting in hospitalization have been identified such as prematurity, chronic lung disease and congenital heart disease [3]. However, it has been estimated that four fifths of RSV-associated hospitalizations in infancy occur in previously healthy infants born at term, with young age a significant risk factor for severe RSV infection [4]. Consequently, RSV is a high priority for vaccine development, with several vaccines now in phase two clinical trials [5]. Potential target groups for a future RSV vaccine have been identified, including pregnant women, young infants and children aged 6–24 months, although further work is needed to

* Author for correspondence: Miss R. M. Reeves, Respiratory Diseases Department, Public Health England, 61 Colindale Avenue, London NW9 5EQ, UK.
(Email: Rachel.Reeves@phe.gov.uk)

determine the optimal age and target groups for a potential future licensed vaccine [6].

Birth in close proximity to the beginning of the RSV season has been shown to be a significant risk factor for RSV-associated hospitalization in infancy [7–11]. However, these studies rely solely on clinical diagnoses, are based outside of the UK or are of small study populations [7]. With various causative agents of upper and lower respiratory tract infections and testing only carried out in a minority of cases, relying on clinical diagnoses without laboratory confirmation of RSV may bias any observed associations between patient characteristics and severe RSV infection due to potential low specificity [12–14]. Using laboratory-confirmed RSV infection has the advantage of being highly specific, and is a starting point from which estimates of the burden of RSV in England can be calculated. The epidemiology of laboratory-confirmed RSV infection in infants and young children in England has not recently been described [13–15].

This study uses laboratory surveillance data to examine the relationship between laboratory-confirmed RSV infection and age and birth month in children aged <5 years in England, to contribute to the identification of optimal target groups for any potential future licensed vaccine.

METHODS

Data sources

The Respiratory DataMart System (RDS) is a surveillance system established by Public Health England (PHE) during the 2009 influenza A(H1N1) pandemic to collect both positive and negative laboratory results for major respiratory viruses [16]. RSV test results through this system are available from 2010 onwards. Fourteen PHE and National Health Service (NHS) laboratories in England currently submit data to the RDS through automatic electronic outputs. The majority of tested samples have been collected from hospitals [16]. Respiratory samples are tested for a range of respiratory viral pathogens including RSV, influenza A and B, parainfluenza, rhinovirus and human metapneumovirus (hMPV) using real-time reverse transcription–polymerase chain reaction (rRT–PCR), and adenovirus using real-time PCR. Although not all participating laboratories test for all viruses, all test for RSV. In RDS, de-duplication is carried out during the data importation process; samples taken from the same individual within a 6-week period are grouped as one record to capture a single episode of infection in an individual [16]. We included data from 13 of the 14 laboratories with consistent reporting of RSV results during the study period: Barts and The London, Birmingham, Bristol, Cambridge, Leeds, Leicester, Manchester, Newcastle, Nottingham, Royal Free Hospital, Southampton, Truro and the Reference Laboratory at PHE Colindale. Weekly data was extracted from calendar week 27 in 2010 to week 26 in 2014 for children aged <5 years. The extracted data include information on patient's date of birth, sex, date of sample, and whether the RSV laboratory test was positive for RSV, negative for RSV but positive for another respiratory virus, or negative for all viruses including RSV.

We compared the RDS study population to the national laboratory surveillance system, LabBase2, also held by PHE. LabBase2 is a long established laboratory surveillance system that covers England, Wales and Northern Ireland, but only includes records of positive RSV tests. Positive RSV test data from laboratories submitting to the RDS are also submitted to the national LabBase2 database. Several different types of laboratory tests are used for diagnosis of RSV infection by laboratories contributing to LabBase2, with the majority using genome or antigen detection methods. Similarly to the RDS, de-duplication is carried out during the data importation process; samples taken from the same individual within a 6-week period are assigned a unique identifier to capture a single episode of infection in an individual. We extracted data on all RSV-positive respiratory samples from LabBase2 from children aged <5 years tested in all laboratories in England from week 27 in 2010 to week 26 in 2014, and only included the first sample of each episode of infection in this analysis.

Statistical analysis

The total number of RSV tests (positive and negative) in the RDS extract, the number of positive RSV tests in the RDS extract and the number of positive episodes in the LabBase2 extract were summarized by age, month of birth, year [between week 27 (2010) and week 26 (2014)] and sex. We calculated the RSV positivity rate as the number of RSV-positive tests divided by the total number of RSV tests in the RDS extract by age, month of birth, sex and year. We defined RSV season onset as the first of two consecutive weeks in which the mean percentage of samples testing positive for RSV in the RDS was $\geqslant 10\%$, and the end of RSV season as the last of two consecutive weeks in which the mean percentage of samples

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Table 1. *Total number of tests (Respiratory DataMart System; RDS), number of respiratory syncytial virus (RSV)-positive tests (RDS), RSV positivity rate (RDS) and number of RSV-positive tests (LabBase2) in children aged <5 years from week 27 (2010) to week 26 (2014) by sex, age, birth month if tested for RSV in the first year of life, and year (week 27 to week 26)*

	Respiratory DataMart System			LabBase2
	Total tests *N* (%)	RSV positive *N* (%)	RSV positivity rate	RSV positive *N* (%)
Total	63 827	13 034	20%	30 669
Sex				
Male	31 278 (49%)	6165 (47%)	20%	17 050 (56%)
Female	23 577 (37%)	4848 (37%)	21%	13 332 (43%)
Unknown	8970 (14%)	2021 (16%)	23%	287 (1%)
Sex ratio (M:F)	1·3:1	1·3:1		1·3:1
Age				
<3 months	20 467 (32%)	4982 (38%)	24%	12 641 (41%)
3–5 months	9384 (15%)	2423 (19%)	26%	6526 (21%)
6–11 months	11 712 (18%)	2528 (19%)	22%	6116 (20%)
1 year	10 439 (16%)	1815 (14%)	17%	3703 (12%)
2 years	4905 (8%)	670 (5%)	14%	922 (3%)
3 years	3929 (6%)	402 (3%)	10%	510 (2%)
4 years	2991 (5%)	214 (2%)	7%	251 (1%)
Birth month (if <1 year old)*				
January	3271 (8%)	586 (6%)	18%	1384 (5%)
February	2774 (7%)	404 (4%)	15%	994 (4%)
March	2970 (7%)	436 (4%)	15%	1066 (4%)
April	2818 (7%)	448 (5%)	16%	1132 (4%)
May	3038 (7%)	525 (5%)	17%	1344 (5%)
June	3056 (7%)	646 (7%)	21%	1519 (6%)
July	3173 (8%)	700 (7%)	22%	1906 (8%)
August	3484 (8%)	906 (9%)	26%	2484 (10%)
September	3833 (9%)	1210 (12%)	32%	3297 (13%)
October	4626 (11%)	1593 (16%)	34%	4088 (16%)
November	4575 (11%)	1565 (16%)	34%	3743 (15%)
December	3945 (9%)	914 (9%)	23%	2326 (9%)
Year				
2010–2011	19 751 (31%)	4103 (31%)	21%	8327 (27%)
2011–2012	14 804 (23%)	2919 (22%)	20%	7228 (24%)
2012–2013	15 021 (24%)	3013 (23%)	20%	7495 (24%)
2013–2014	14 251 (22%)	2999 (23%)	21%	7619 (25%)

* Percentage denominator is the total number in infants aged <1 year [i.e. total tests (RDS) = 41 563, RSV positive (RDS) = 9933 and RSV positive (LabBase2) = 25 283].

testing positive for RSV was ⩾10%, a method which has been used in previous studies [17, 18].

We used multivariable logistic regression models to estimate the odds of a positive result (if tested for RSV) by birth month, using the RDS extract. Age group (0, 1, 2, 3, 4 years), sex (male, female, unknown) and year (2010–2011, 2011–2012, 2012–2013, 2013–2014) were investigated as potential confounders and were added to the model in a forward stepwise manner. We also included an interaction term between age group and birth month. We used likelihood ratio tests to determine whether the inclusion of a variable significantly improved the fit of the model; a likelihood ratio test P value of <0·05 was considered significant. Robust standard errors were used to allow for clustering by laboratory. Infants born in January were used as the baseline group.

RESULTS

Characteristics of the study population are shown in Table 1. In the RDS there was an average of 15 986

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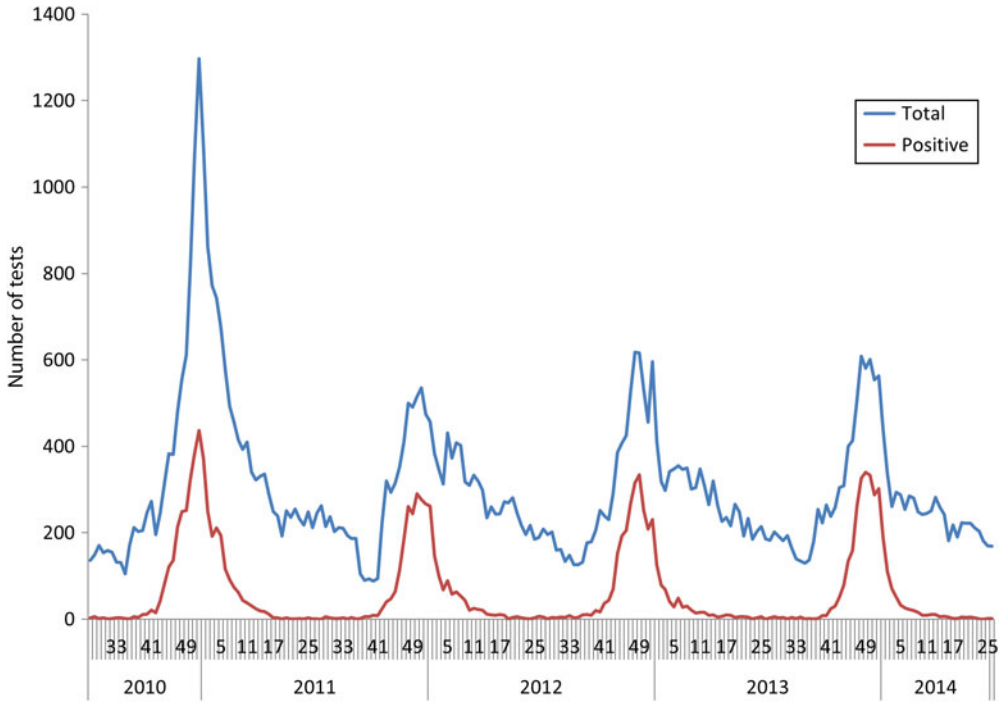

Fig. 1. Total number (blue) and number of positive (red) respiratory syncytial virus tests in children aged <5 years recorded in the Respiratory DataMart System from week 27 (2010) to week 26 (2014), over time.

tests and 3259 RSV positives per year in children aged <5 years during the study period. Laboratory-confirmed RSV positivity showed a clear and consistent seasonal pattern; RSV season onset was in October each year (ranging from calendar weeks 41–43) during the study period and the end of RSV season ranged from January to March (weeks 4–10). Overall testing peaked during December in each RSV season of the 4 years studied (Fig. 1). The week with the highest proportion of positive RSV laboratory tests in children aged <5 years each season was week 48 in 2010–2011 (42% positive), week 1 in 2011–2012 (55% positive), and week 49 in 2012–2013 and 2013–2014 (52% and 55% positive, respectively). Of the 4 years included in the study, the highest number of RSV laboratory tests was carried out during the 2010–2011 RSV season. Of the RSV-positive tests in the RDS during the study period ($n = 13\,034$), 16% were also positive for at least one other respiratory virus. Of the RSV-negative tests in the RDS during the study period ($n = 50\,793$), 41% were positive for at least one other respiratory virus.

The results by age, birth month and sex were very similar in the RDS and LabBase2 extracts (Table 1). The RDS results demonstrated that both the total number of tests and the number of positive tests decreased with increasing age (Fig. 2). Seventy-six per cent (9933/13 034) of RSV-positive tests in children aged <5 years over the study period were in infants aged <1 year, whereas only 2% (214/13 034) were in in children aged 4 years. Moreover, 47% (29 851/63 827) of tests and 57% (7405/13 034) of positives in children aged <5 years over the study period were in infants aged <6 months. The number of RSV positives peaked at age 1 month ($n = 2198$). Infants aged 1, 2 and 3 months had the highest rate of RSV positivity: 29% (2198/7551), 29% (1507/5194) and 27% (996/3697) tested positive for RSV, respectively. The highest number of tests was in infants aged <1 month ($n = 7722$). Infants aged <1 year who were born in September, October and November had the highest number and proportion of positive test results (Table 1). In LabBase2, 82% (25 283/30 669) of positive results in children aged <5 years over the study period were in infants aged <1 year; only 1% of tests (251/30 669) were in children aged 4 years. The number of RSV-positive tests also peaked at age 1 month ($n = 5326$). Thirteen per cent (3297/25 283) of infants with a positive RSV test in their first year of life recorded in LabBase2 were born in September, 16% (4088/25 283) were born in October and 15% (3743/25 283) were born in November. In both datasets the sex ratio (M:F) was 1·3:1.

The best fitting multivariable logistic regression model included sex, calendar year, age group and

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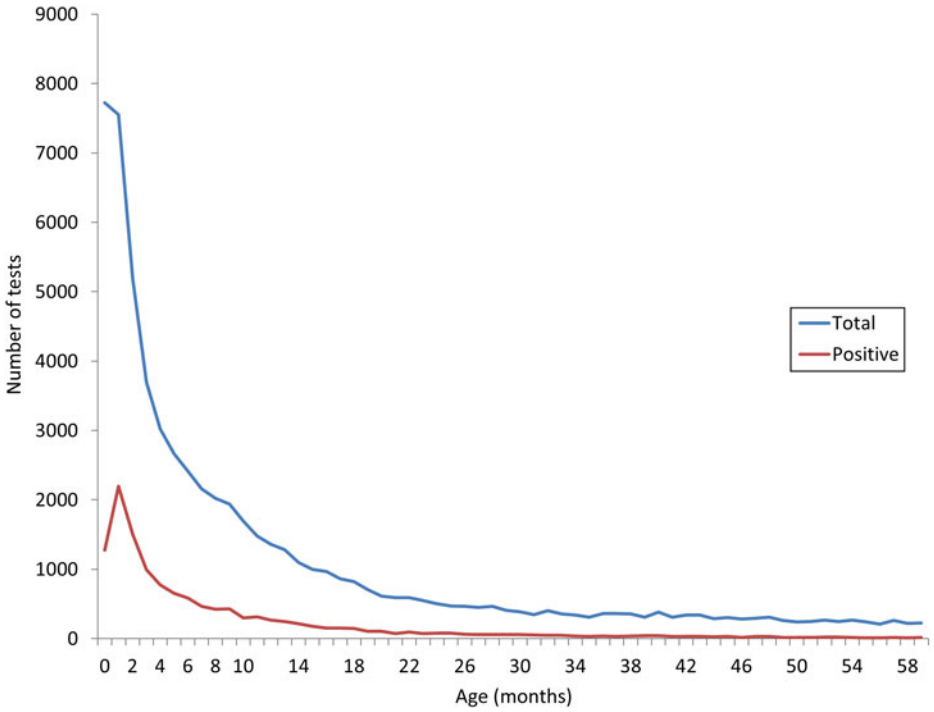

Fig. 2. Total number (red) and number of positive (green) respiratory syncytial virus tests in children aged <5 years recorded in the Respiratory DataMart System from week 27 (2010) to week 26 (2014), by age in months.

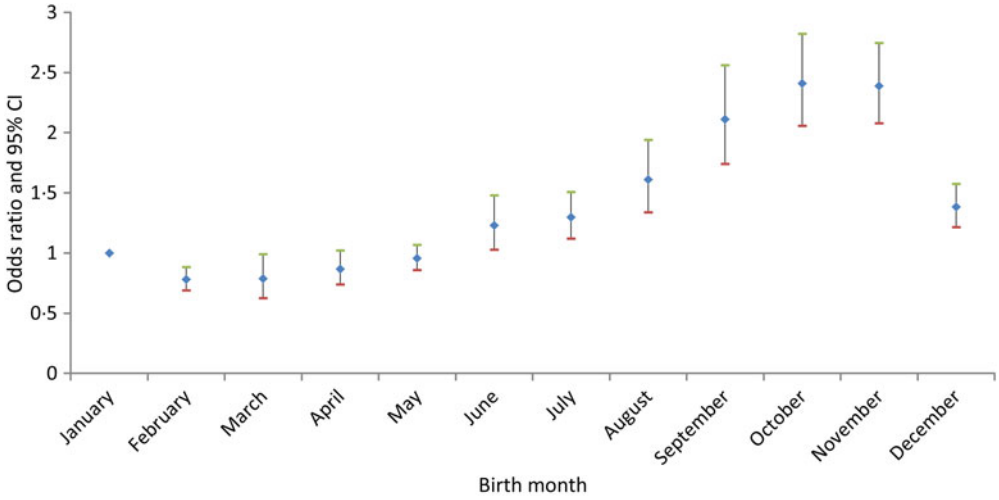

Fig. 3. Odds ratios and 95% confidence intervals (CI) from final multiple logistic regression model using Respiratory DataMart System data to compare odds of a positive result if tested for respiratory syncytial virus by birth month, showing results for infants aged <1 year only. Infants born in January are the baseline group.

birth month as well as an age group × birth month interaction term. Infants aged <1 year born in September [odds ratio (OR) 2·1, 95% confidence interval (CI) 1·7–2·7], October (OR 2·4, 95% CI 2·1–2·8) or November (OR 2·4, 95% CI 2·1–2·7) had the highest odds of a positive result if tested for RSV in the first year of life compared to infants born in January (Fig. 3). The effect of birth month on odds of a RSV positive test result decreased with increasing age (Fig. 4). For example, infants aged 4 years born in September (OR 0·4, 95% CI 0·3–0·6) and infants aged 4 years born in January (OR 0·4, 95% CI 0·3–0·6) had the same odds of a positive result.

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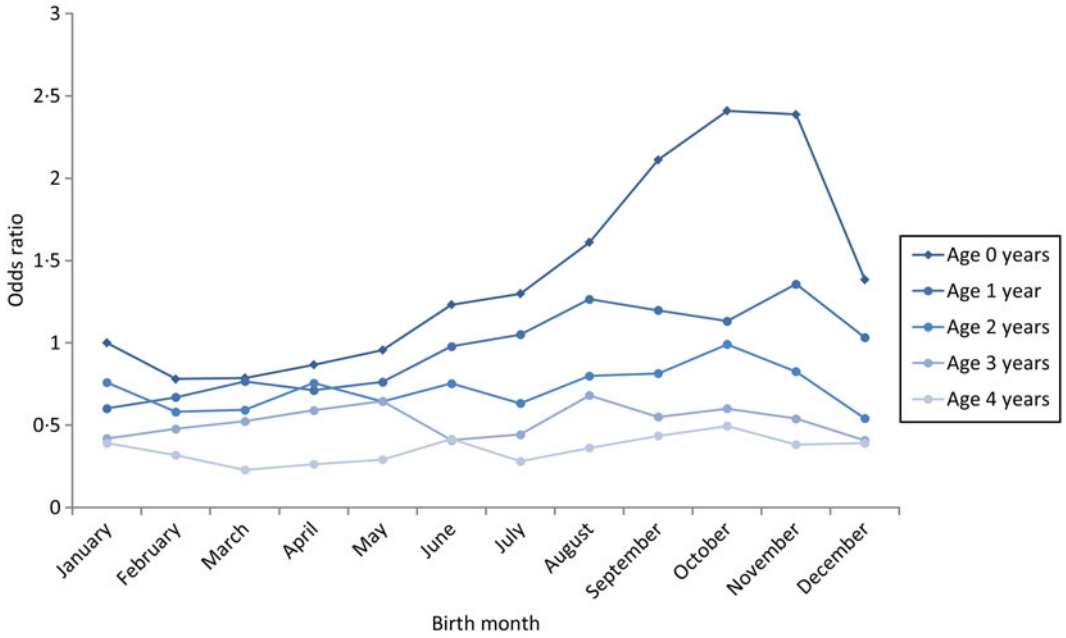

Fig. 4. Odds ratios from final multiple logistic regression model using Respiratory DataMart System data to compare odds of a positive result if tested for respiratory syncytial virus by birth month, stratified by age in years. Infants born in January are the baseline group.

DISCUSSION

This study shows that a significant proportion of laboratory-confirmed RSV infections in England recorded in two laboratory surveillance databases from 2010 to 2014 were in infants aged <6 months. In both datasets, there was a peak in RSV-positive tests in infants aged 1 month. RSV circulation was very consistent in timing each year, with a 3-week range in season onset over the study period. Moreover, infants born near the beginning of an RSV season had significantly increased odds of a positive result if tested for RSV during the first year of life.

A strength of our study is the use of laboratory-confirmed RSV infection rather than clinically diagnosed RSV. Using clinical diagnoses of RSV infection may include misclassification of diagnoses when laboratory tests were not carried out, as specific respiratory viral aetiologies cannot be differentiated clinically [19, 20]. The use of clinical diagnoses alone may therefore lead to bias in associations between patient characteristics and RSV infection. However, a limitation of our study is that no clinical information on the individuals tested was available in either dataset. The majority of RSV records in the RDS and LabBase2 are from hospitalized patients [16], and it is likely that only severe or complex cases requiring hospital admission will require laboratory confirmation of RSV infection as it would usually be unnecessary to investigate mild infection for the presence of RSV. However, without clinical information it is not possible to confirm whether or not this assumption is correct. In addition, most tests in both RDS and LabBase2 were carried out on young children (<1 year). It is therefore possible that differences in testing according to age means that RSV is less likely to be picked up in older children. Linkage between administrative hospital data and laboratory data would allow analysis of the potential association between clinical presentation, patient characteristics, the probability of being tested, and RSV positivity.

The considerable number of tests and RSV-positive results in infants aged <6 months and the peak in number and percentage of positive RSV tests in infants aged 1 month is consistent with existing literature that reports age <6 months as a significant risk factor for severe RSV infection [21] and a peak in RSV bronchiolitis at age 1 month [12, 22]. Young infants have been a high priority for vaccination due to the serious complications and subsequent morbidity that can occur following RSV infection in early life [6]. However, young infants are at risk of enhanced disease following vaccination as demonstrated during testing of the first candidate vaccine, formalin-inactivated RSV, in the 1960s [6]. The immaturity of the immune

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system and significant heterogeneity in the presence of maternal antibodies also present major challenges to vaccine development for this target group [23]. Nonetheless, a World Health Organization consultation in early 2015 on the development of RSV vaccines suggests it is likely that an RSV vaccine will be available commercially within 5–10 years [24], as major advances in the understanding of the biology of RSV and innovations in immunogen design have resulted in a number of promising potential vaccine candidates in clinical trials [25]. Our results highlight the importance of developing optimal strategies to prevent disease in young infants with these potential future vaccines.

Our analysis found RSV circulation to be highly consistent in timing each year, with only a 3-week range in season onset over the study period. The large peak in infants being tested for RSV during 2010–2011 can be attributed to the intense influenza season during this first post-pandemic winter period, as the RDS holds records of the results of samples tested simultaneously for multiple respiratory viruses including influenza and RSV [16, 26]. The large number of tests performed outside of the RSV season can also be attributed to testing for a range of respiratory viruses. The consistency between results from the RDS and LabBase2 suggest generalizability of the RDS results to the long established national surveillance system.

Our finding that birth in months September–December was associated with increased odds of a positive result if tested for RSV in the first year of life in England supports the results of previous studies that show birth around the beginning of the RSV season is a risk factor for RSV-associated hospitalization [7–9, 11]. Several of these previous studies investigating month of birth as a risk factor for RSV-associated hospitalization were limited by sample size and all based outside of the UK. The largest study was carried out in the United States and suggests children born during December and January had a two- and threefold higher risk, respectively, of RSV-confirmed hospitalization during infancy than those born in July, although these cases were identified by International Classification of Diseases (Ninth Revision) codes only [7]. The increased risk of severe RSV infection in infants born close to the beginning of the RSV season is likely due to these infants having a longer exposure to RSV at a young age in combination with lower levels of maternal antibodies during the beginning of the RSV season and immaturity of the lungs [21]. The exact birth months with the highest risk of severe RSV infection in infancy varies between countries due to differences in the timing of RSV season, which highlights the importance of country-specific epidemiology studies including birth month as a potential risk factor when analysing severe RSV infection.

This study highlights the importance of young age (<6 months) and birth near the beginning of the RSV season in risk of laboratory-confirmed RSV infection. Future vaccination programmes and other interventions should ensure protection for these groups is considered.

DECLARATION OF INTEREST

None.

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