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

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

[1]*Farr Institute of Health Informatics Research, London, UK*

[2]*Institute of Child Health, University College London, UK*

[3]*Virus Reference Department, Public Health England, Colindale, London, UK*

[4]*Respiratory Diseases Department, Public Health England, Colindale, London, UK*

[5]*Bristol Public Health Laboratory, Public Health England, Bristol, UK*

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

Running head title: RSV: the importance of birth month

Summary

The epidemiology of laboratory-confirmed 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 less than five years old in England from 2010- 2014. We derived odds ratios with 95% confidence intervals comparing children by birth month, using multivariable logistic regression models adjusted for age, season and sex. 47% of RSV tests (29,851/63,827) and 57% (7,405/13,034) of positive results in children under five years old were in infants younger than six months. Moreover, 38% (4,982/13,034) of positive results were in infants younger than three 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 RSV season to the risk of laboratory confirmed RSV infection. Future control measures should consider protection for these groups.

Introduction

Respiratory syncytial virus (RSV) is a major cause of hospitalisation 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 hospitalisation 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 hospitalisations 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 6-24 months old, although further work is needed to determine the optimal age and target groups for a potential future licensed vaccine (6).

Birth in close proximity to the beginning of RSV season has been shown to be a significant risk factor for RSV-associated hospitalisation 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 less than five years old 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 Public Health England (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. Though 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 six-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: Birmingham, Bristol, Barts and The London, 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 in children less than five years of age. 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 six-week period are assigned a unique identifier to capture a single episode of infection in an individual. We extracted all respiratory samples from LabBase2 from children less than five years of age 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 summarised 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 ≥10%, and the end of RSV season as the last of two consecutive weeks in which the mean percentage of samples 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 and 4 years), sex (male, female and 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 tests and 3,259 RSV positives per year in children less than five years of age 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 week 41 to 43) during the study period and the end of RSV season ranged from January to March (week 4 to week 10). Overall testing peaked during December in each RSV season of the four years studied (Figure 1). The week with the highest proportion of positive RSV laboratory tests in children less than five years of age 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 four 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 (Figure 2). 76% (9,933/13,034) of RSV positive tests in children less than five years of age over the study period were in infants less than one year of age, whereas only 2% (214/13,034) were in in children aged four years. Moreover, 47% of tests (29,851/63,827) and 57% (7,405/13,034) of positives in children less than five years of age over the study period were in infants less than six months of age. The number of RSV positives peaked at age one month (n=2,198). Infants aged 1, 2 and 3 months had the highest rate of RSV positivity: 29% (2,198/7,551) and 29% (1,507/5,194) and 27% (996/3,697) tested positive for RSV, respectively. The highest number of tests was in infants

aged less than one month (n=7,722). Infants less than one year of age 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 less than five years of age over the study period were in infants less than one year of age; only 1% of tests (251/30,669) were in children aged four years**.** The number of RSV positive tests also peaked at age one month (n=5,326). 13% (3,297/25,283) of infants with a positive RSV test in their first year of life recorded in LabBase2 were born in September, 16% (4,088/25,283) were born in October and 15% (3,743/25,283) 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 birth month as well as an age group:birth month interaction term. Infants aged less than one year of age born in September (OR=2.1, 95% 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 (Figure 3). The effect of birth month on odds of a RSV positive test result decreased with increasing age (Figure 4). For example, infants aged four years born in September (OR=0.4, 95% CI 0.3, 0.6) and infants aged four years born in January (OR=0.4, 95% CI 0.3, 0.6) had the same odds of a positive result.

Discussion

This study shows that a significant proportion of laboratory-confirmed RSV infections in England recorded in two laboratory surveillance databases from 2010 -2014 were in infants younger than six months old. In both datasets, there was a peak in RSV positive tests in infants aged one month. RSV circulation was very consistent in timing each year, with a three week range in season onset over the study period. In addition, 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 hospitalised 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, the vast majority of tests in both RDS and LabBase2 were carried out on young children (less than one 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 younger than six months of age and the peak in number and percentage of positive RSV tests in infants aged one month is consistent with existing literature that reports age under six months as a significant risk factor for severe RSV infection (21) and a peak in RSV bronchiolitis at age one 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 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 Organisation (WHO) 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 three 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 generalisability of the RDS results to the long established national surveillance system.

Our finding that birth in months September to 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 RSV season is a risk factor for RSV-associated hospitalisation (7–9,11). Several of these previous studies investigating month of birth as a risk factor for RSV-associated hospitalisation were limited by sample size and all based outside of the UK. The largest study was carried out in the US and suggests children born during December and January had a 2- and 3-fold higher risk, respectively, of RSV-confirmed hospitalisation during infancy than those born in July, though 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 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 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 (less than six months) and birth near the beginning of RSV season in risk of laboratory confirmed RSV infection. Future vaccination programmes and other interventions should ensure protection for these groups is considered.

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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 <5 years of age 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 - 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%)	6,165 (47%)	20%	17,050 (56%)
Female	23,577 (37%)	4,848 (37%)	21%	13,332 (43%)
Unknown	8,970 (14%)	2,021 (16%)	23%	287 (1%)
Sex ratio (M:F)	1.3:1	1.3:1		1.3:1
Age				
<3 months	20,467 (32%)	4,982 (38%)	24%	12,641 (41%)
3-5 months	9,384 (15%)	2,423 (19%)	26%	6,526 (21%)
6-11 months	11,712 (18%)	2,528 (19%)	22%	6,116 (20%)
1 year	10,439 (16%)	1,815 (14%)	17%	3,703 (12%)
2 years	4,905 (8%)	670 (5%)	14%	922 (3%)
3 years	3,929 (6%)	402 (3%)	10%	510 (2%)
4 years	2,991 (5%)	214 (2%)	7%	251 (1%)
Birth month (if <1 year old)[1]				
January	3,271 (8%)	586 (6%)	18%	1,384 (5%)
February	2,774 (7%)	404 (4%)	15%	994 (4%)
March	2,970 (7%)	436 (4%)	15%	1,066 (4%)
April	2,818 (7%)	448 (5%)	16%	1,132 (4%)
May	3,038 (7%)	525 (5%)	17%	1,344 (5%)
June	3,056 (7%)	646 (7%)	21%	1,519 (6%)
July	3,173 (8%)	700 (7%)	22%	1,906 (8%)
August	3,484 (8%)	906 (9%)	26%	2,484 (10%)
September	3,833 (9%)	1,210 (12%)	32%	3,297 (13%)
October	4,626 (11%)	1,593 (16%)	34%	4,088 (16%)
November	4,575 (11%)	1,565 (16%)	34%	3,743 (15%)
December	3,945 (9%)	914 (9%)	23%	2,326 (9%)

Year				
2010-2011	19,751 (31%)	4,103 (31%)	21%	8,327 (27%)
2011-2012	14,804 (23%)	2,919 (22%)	20%	7,228 (24%)
2012-2013	15,021 (24%)	3,013 (23%)	20%	7,495 (24%)
2013-2014	14,251 (22%	2,999 (23%)	21%	7,619 (25%)

[1] Percentage denominator is the total number in infants <1 year old [i.e. Total tests (RDS) = 41,563, RSV positive (RDS) = 9,933 and RSV positive (LabBase2) = 25,283]

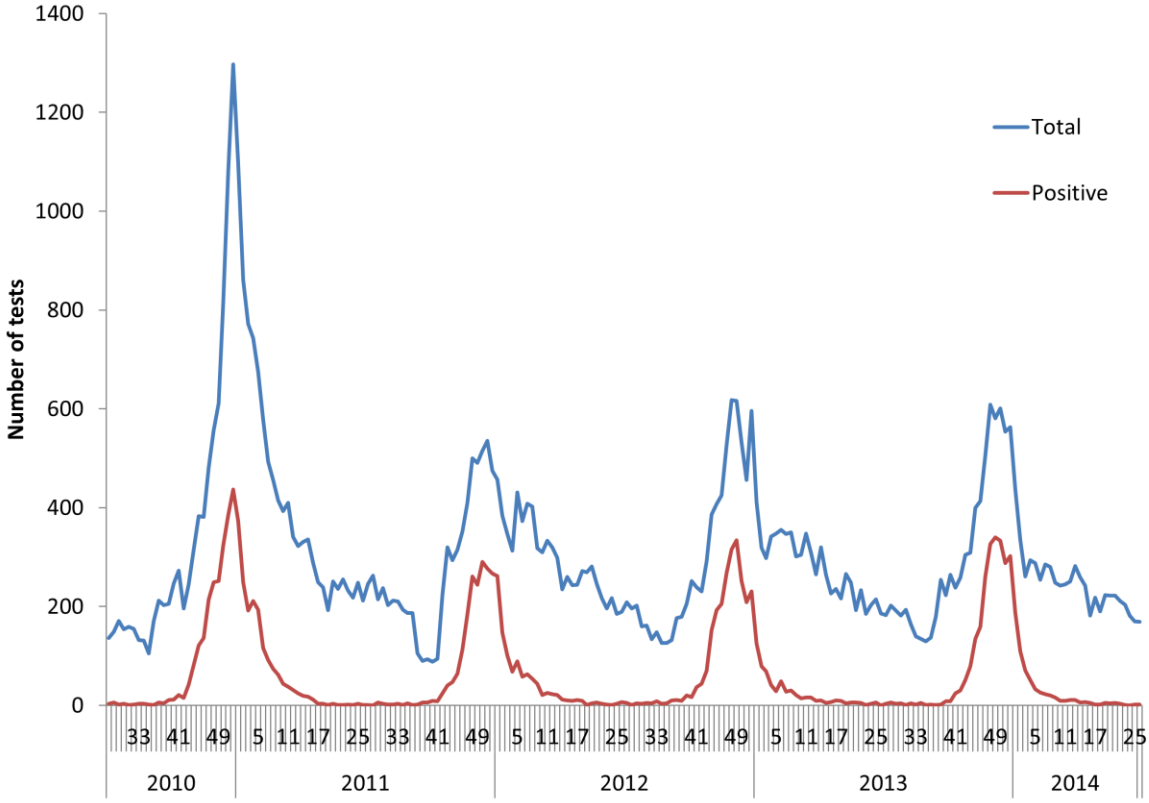

Figure 1. Total number (blue) and number of positive (red) respiratory syncytial virus tests in children aged <5 year recorded in the Respiratory DataMart System from week 27 (2010) to week 26 (2014), over time.

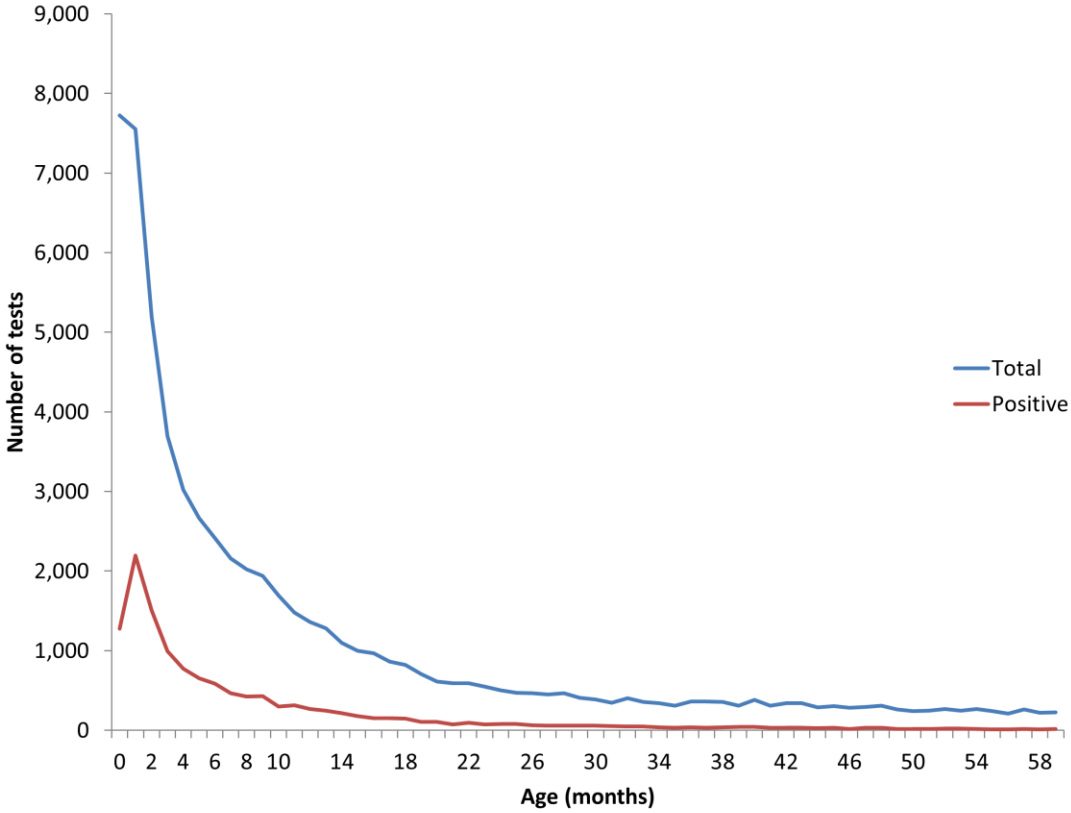

Figure 2. Total number (red) and number of positive (green) respiratory syncytial virus tests in children aged <5 years recorded in the Respiratory DataMart System from week 27 (2010) to week 26 (2014), by age in months.

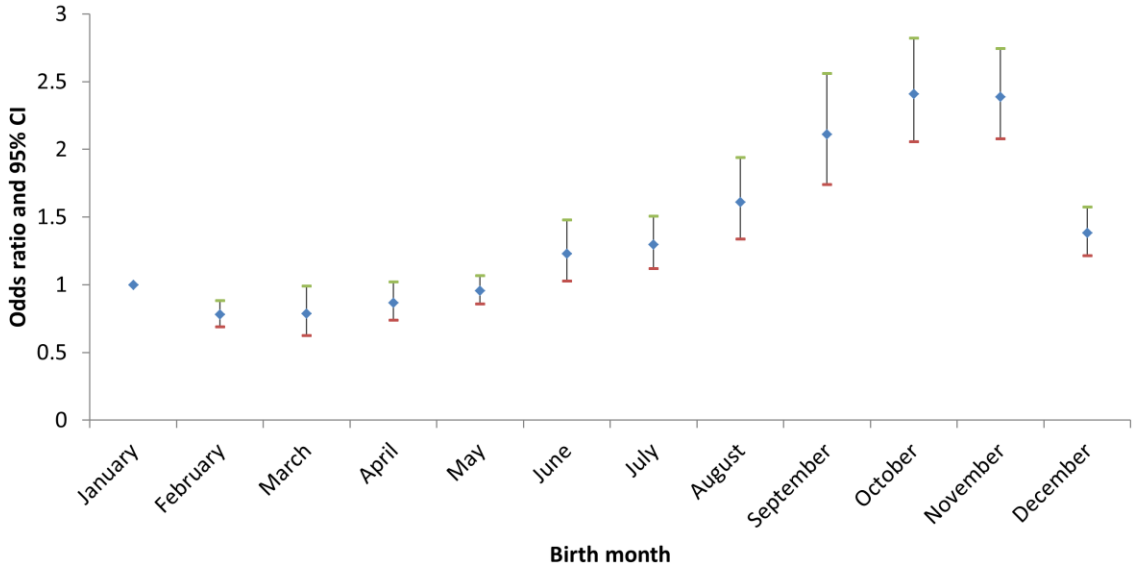

Figure 3. Odds ratios and 95% confidence intervals (CI) from final multiple logistic regression model using Respiratory DataMart System data to compare odds of a positive result if tested for respiratory syncytial virus by birth month, showing results for infants aged <1 year only. Infants born in January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

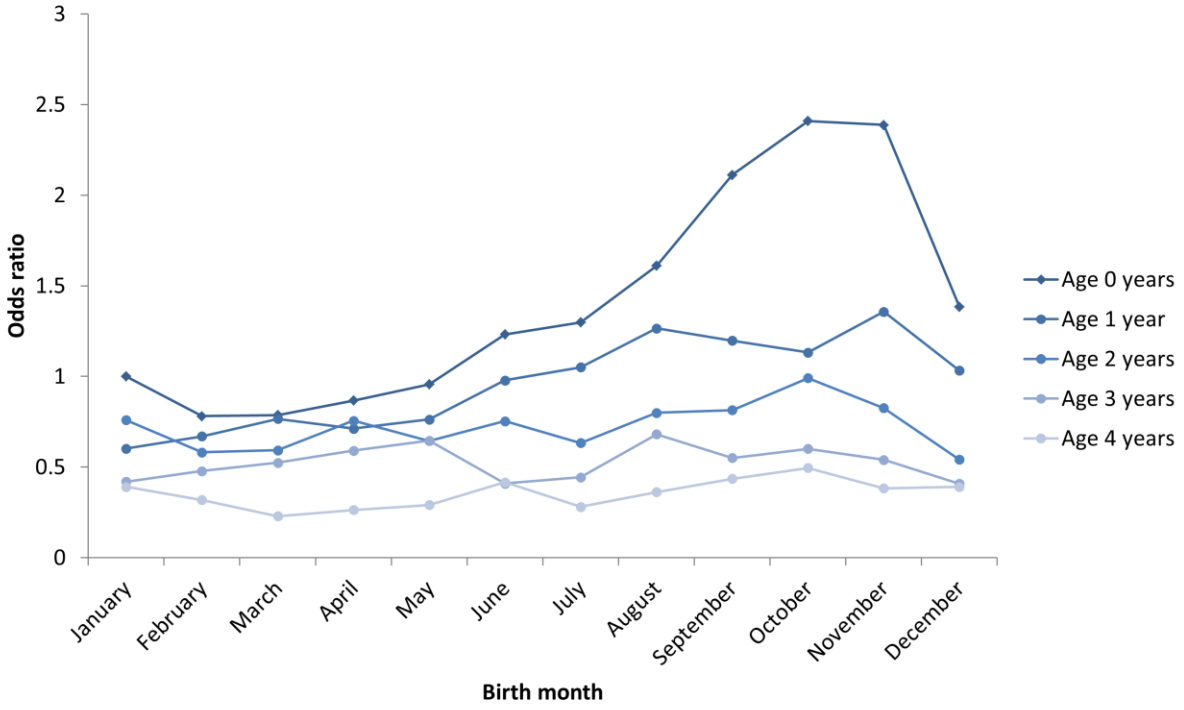

Figure 4. Odds ratios from final multiple logistic regression model using Respiratory DataMart System data to compare odds of a positive result if tested for respiratory syncytial virus by birth month, stratified by age in years. Infants born in January are the baseline group.