Summary

Objectives

Current national estimates of respiratory syncytial virus (RSV)-associated hospital admissions are insufficiently detailed to determine optimal vaccination strategies for RSV. We employ novel methodology to estimate the burden of RSV-associated hospital admissions in infants in England, with detailed stratification by patient and clinical characteristics.

Methods

We used linked, routinely collected laboratory and hospital data to identify laboratory-confirmed RSV-positive and RSV-negative respiratory hospital admissions in infants in England, then generate a predictive logistic regression model for RSV-associated admissions. We applied this model to all respiratory hospital admissions in infants in England, to estimate the national burden of RSV-associated admissions by calendar week, age in weeks and months, clinical risk group and birth month.

Results

We estimated an annual average of 20,359 (95% CI 19,236-22,028) RSV-associated admissions in infants in England from mid-2010 to mid-2012. These admissions accounted for 57,907 (95% CI 55,391-61,637) annual bed days. 55% of RSV-associated bed days and 45% of RSV-associated admissions were in infants <3 months old. RSV-associated admissions peaked in infants aged 6 weeks, and those born September to November.

Conclusions

We employed novel methodology using linked datasets to produce detailed estimates of RSV-associated admissions in infants. Our results provide essential baseline epidemiological data to inform future vaccine policy.

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Key words

Respiratory syncytial virus; RSV; data linkage; respiratory tract infection; bronchiolitis; pneumonia; hospital admissions; infants

Introduction

Respiratory syncytial virus (RSV) is the most important cause of viral lower respiratory tract illness in young children worldwide, and a major cause of hospital admission in UK infants (1–4). The majority of the burden of RSV-associated hospital admissions is accounted for by infants less than six months old, particularly those born around the beginning of the RSV season (4,5). Promising vaccine candidates are now in Phase 2 and 3 clinical trials (6)(7), with several potential future vaccination strategies being considered. These include maternal immunisation to protect neonates, immunisation of very young infants prior to exposure, or a live vaccine targeted to older infants and young children (with the aim of also providing indirect protection to very young infants) (8). However, further information on the burden of RSV-associated admissions according to age and underlying chronic conditions is required to determine the optimal target populations for a potential future vaccine (9).

Currently available methods of estimating the burden of RSV-associated hospital admissions are not sufficiently detailed to determine optimal vaccination strategies for RSV. Only a minority of hospitalised children presenting with acute respiratory infection undergo laboratory testing to identify the causal pathogen (4), so previous studies of the national burden of RSV have either: (a) relied on clinical coding of bronchiolitis in hospital admission databases as a proxy for RSV-associated hospital admissions, or (b) used time-series modelling methods which utilise the seasonality of RSV and other major respiratory viruses to infer the burden of RSV-associated hospital admissions (4,10–12). Neither of these approaches are ideal. Not all bronchiolitis admissions are due to RSV, and while estimates based on time series modelling can be stratified by some key characteristics such as age group and diagnosis (4), they are derived from models based on aggregate data using an ecological study design (inferring causality from the temporal association of the hospital admission and laboratory data). Therefore, outcomes from time series models are limited in the detail they provide, and both approaches are subject to bias.

In this study, we use linked, routinely collected laboratory surveillance and hospital admissions data and employed a novel predictive model to estimate the national burden of RSV-associated hospital admissions in infants in England from mid-2010 to mid-2012. Using

this individual-level data, we estimate both the number and rate of RSV-associated hospital admissions and the number of RSV-associated bed days, with detailed stratification by sex, age in weeks and months, clinical risk group and month of birth for the first time.

Methods

Data sources

Hospital Episode Statistics (HES)

We used the Hospital Episode Statistics (HES) Admitted Patient Care database, held by National Health Service (NHS) Digital. It contains routinely collected data on all admissions to all National Health Service (NHS) hospitals in England (13). Healthcare is free at the point of use in the NHS, and 99% of hospital activity in England takes place in NHS hospitals. Diagnoses are recorded using International Classification of Diseases 10th Revision (ICD- 10) codes, with up to 20 diagnosis codes allowed per HES episode. All admissions in infants <1 year of age (at admission) in England from 01/08/2010 to 31/07/2012 with a respiratory diagnosis (from ICD-10 Chapter X - Diseases of the respiratory system) were included in our extract. The RSV season in England lasts from October to March, with a peak in early December (5). The study period therefore included two RSV seasons.

The Respiratory DataMart System (RDS)

The Respiratory DataMart System (RDS) is a surveillance system established by Public Health England (PHE) in 2010 to collect positive and negative laboratory results for respiratory viruses, including RSV, from 14 laboratories in England (14). We have previously described RSV-positive and RSV-negative records from children in this dataset in detail (5). All RSV test results (positive and negative) in infants <1 year of age from 01/07/2010 to 31/08/2012 from the 13 laboratories in the RDS network with consistent reporting of RSV-positive results to RDS were extracted (5). Note that children testing negative for RSV may have tested positive for another virus.

Data linkage

The patient identifiable information (PII) available in both the RDS and HES extracts for data linkage was: NHS number, date of birth, postcode and sex. While completeness of identifiers was very high in HES (only NHS number having <100% completeness), completeness of identifiers within RDS was much lower (for example, NHS number was only 59% complete and postcode only 77% complete overall, with variation by reporting laboratory – see Supplementary Appendix Table 1.1 and Figure 1.1). Due to this high proportion of missing data on identifying information, we used probabilistic linkage (using all available PII variables) in order to maximise the number of successful links between the datasets. Full details of the linkage methodology used is included in the Supplementary Data section 1. HES hospital admissions beginning within +/-7 days of a linked RDS test were retained (82% of linked admissions). All other linked records where the admission was outside of this time frame of an RDS test were excluded.

To develop the prediction model, we identified hospitals that regularly reported results to RDS laboratories and tested a high percentage of their respiratory admissions (thereby increasing the probability that the paediatric respiratory admissions that were tested for RSV were a representative subsample of all paediatric respiratory admissions). We included only data from NHS hospitals with at least 50 linked RDS records over the study period, and which tested >10% of their total respiratory admissions in infants younger than 1 year of age for RSV across the study period.

Statistical methods

Developing the prediction model to identify hospital admissions as RSV-related

We generated a predictive model for RSV-positivity using a random 2/3 sample of our final linked dataset, and used the remaining 1/3 sample to test the fit of the model.

Multivariable logistic regression models were fitted to identify predictors of RSV-positivity among the RDS tests that had linked to a HES admission in the selected hospitals. The outcome modelled was whether the linked admission was positive for RSV or not (a binary

variable). The independent variables included as potential predictors were: age (continuous variable), sex (binary variable), any diagnosis of bronchiolitis (binary variable, that is a presence of an ICD-10 code for bronchiolitis (J21) in any of the 20 HES diagnosis fields), any diagnosis of unspecified LRTI (indicator variable, ICD-10 J22), any diagnosis of pneumonia (binary variable, J12-J18), any diagnosis of upper respiratory tract infection (URTI) (indicator variable, J00-06), ICD-10 code indicating RSV as cause of disease (indicator variable, B97.4) and clinical high-risk status (binary variable). Patients were classified as being in a clinical high risk group if they had one or more ICD-10 codes in their longitudinal HES record of respiratory admissions within the study period indicating the following conditions: chronic lung disease (including bronchopulmonary dysplasia), congenital heart disease, prematurity, neurological disorders or immunodeficiency. The full list of ICD-10 diagnosis codes used to identify high-risk infants is shown in Supplementary Data Table 2.1. To adjust for the seasonal pattern of RSV transmission, one sine and one cosine function was included in the model, following the methodology of Stolwijk (15) and Edwards (16).

All potential predictors were included in the initial model, and then a backwards stepwise approach was used to remove predictors that did not significantly improve the fit of the logistic regression model (that is, where the likelihood ratio test $p>0.05$). We constructed receiver operator characteristic (ROC) curves by plotting the true-positive rate (sensitivity) against the false-positive rate (1-specificity) (Supplementary Data Figure 3.1).

A cut-off probability threshold of 0.5 was chosen in order to maximise both sensitivity and specificity (Supplementary Data Table 4.1). The model was then validated using the test sample, and the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) calculated to explore predictive accuracy of the model (Supplementary Data Table 5.1).

Estimating the burden of RSV in England

The final logistic regression model to predict whether an admission was RSV-related was applied to the whole HES extract of respiratory admissions in infants <1 year in England (including the children who were included in the model fitting process). All admissions with

a predicted outcome above the probability threshold of 0.5 were classified as RSV-associated admissions. 95% confidence intervals (CIs) for the number of RSV associated admissions were calculated by first generating the CIs for the linear predictors in the logistic regression model and then converting them to probabilities. RSV-associated admissions and the associated number of hospital bed days were described by calendar week, age, birth month, and clinical risk group.

Calendar weeks were defined as blocks of 7 days beginning on 1st January each year, with week 52 allowed more than 7 days. Admissions for <1 day were counted as 0.5 days. Admission rates were calculated using ONS mid-year population estimates for infants <1 year old in England; an average of the ONS mid-year population estimates for 2010 and 2011 were used for the 2010/11 season an average of the ONS mid-year population estimates for 2011 and 2012 were used for the 2011/12 season (17,18). All analysis was carried out in STATA v.13 (19).

Ethics

The linkage based on PII was undertaken with permission of section 251, regulation 3, paragraph 1 of the Health Service (Control of Patient Information) Regulations 2002.

Results

Overview of linked dataset

We included data from 24 out of 179 potential NHS trusts contributing data to HES within the study period (with at least 50 linked RDS records over the study period, and which tested >10% of their total respiratory admissions across the study period), representing 80% of the total RDS-HES linked admissions. There were a total of 6,758 linked admissions in infants <1 year old during the study period, with 44% (2,947 admissions) positive for RSV. 49% (1, 445 admissions) of RSV-positive linked admissions were in infants aged <3 months, which was the age group with the highest RSV positivity rate: 53% of linked admissions were RSV-positive in this group of young infants (Table 1). 81% (2,375 admissions) of RSV-positive linked admissions were in infants with a primary diagnosis of bronchiolitis. 85% (2,502 admissions) of RSV-positive linked admissions had no ICD10 code indicating high-risk comorbidity or prematurity recorded.

Table 1. Characteristics of the RSV-positive admissions in the linked dataset used to generate the predictive model.

	Total HES-RDS linked admissions N (%)	RSV-positive N (%)	RSV positivity rate (%)
Total	6,758	2,947	45%
Male	4,011 (59%)	1,672 (57%)	42%
Female	2,747 (41%)	1,275 (43%)	46%
Ratio (M:F)	1.5:1	1.3:1	
Age (months)			
<3	2,744 (41%)	1,445 (49%)	53%
3-5	1,701 (25%)	700 (24%)	41%
6-11	2,313 (34%)	802 (27%)	35%
Risk group			
No risk factor	5,070 (75%)	2,502 (85%)	49%
Risk factor	1,688 (25%)	445 (15%)	26%
Primary diagnosis			
Bronchiolitis	4,047 (60%)	2,375 (81%)	59%
Bronchitis	31 (<1%)	6 (<1%)	19%
Pneumonia	290 (4%)	72 (2%)	25%
URTI	817 (12%)	139 (5%)	17%
Unspecified LRTI	299 (4%)	61 (2%)	20%
Other	1,274 (19%)	24 (10%)	23%

Season			
2010/11	3,221 (48%)	1,380 (47%)	43%
2011/12	3,537 (52%)	1,567 (53%)	44%

There were 3,221 linked admissions in the 2010/11 season and 3,573 in the 2011/12 season (Table 1, Figure 1). In the 2010-11 season, there was a peak in admissions during week 51 (142 admissions) and a peak in positivity-rate during week 50 of 70% (107/158 linked admissions). In the 2011-12 season, there was a peak in admissions during week 50 (178 admissions) and a peak in positivity-rate also during week 50 of 83% (178/215 linked admissions).

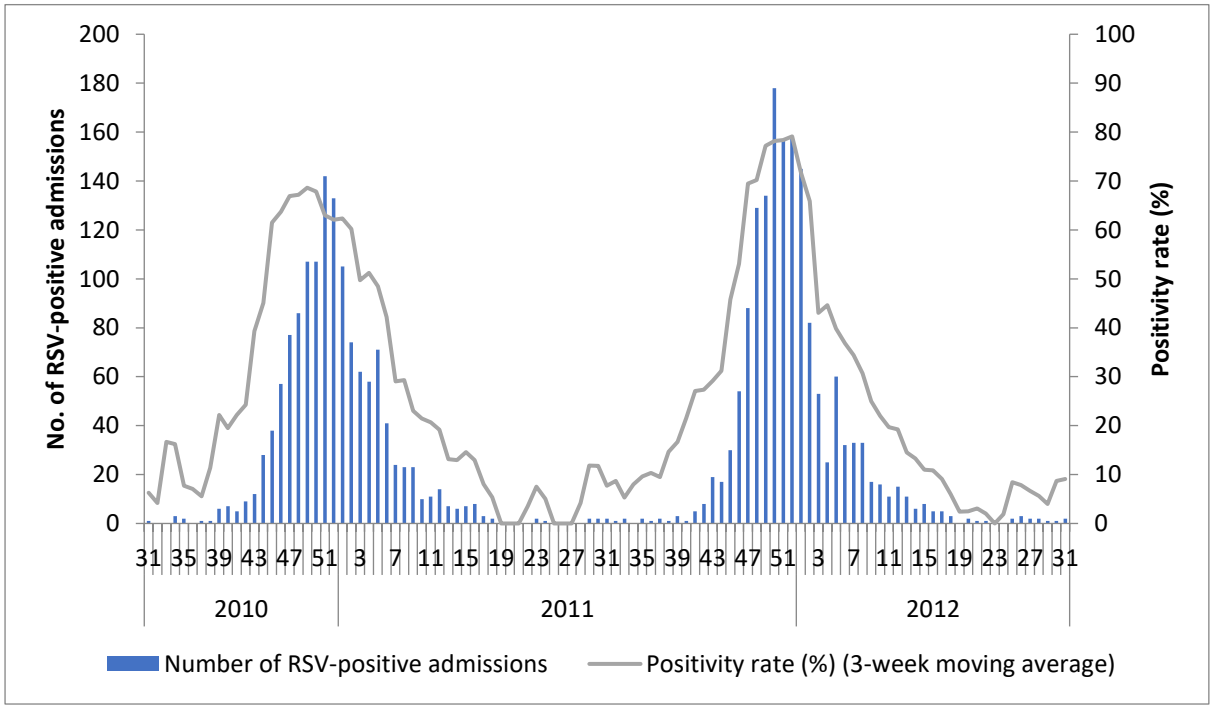

Figure 1. Number of RSV-positive linked admissions and RSV-positivity rate (no. of RSV-positive/total linked, as a 3-week moving average), by calendar week.

Predicting RSV-positivity of linked admissions

The variables included in the final logistic regression prediction model included any diagnosis of bronchiolitis, any diagnosis of unspecified LRTI, RSV-specific diagnosis code, any code indicating high risk status, age, and the cyclical function of calendar week. The equation of the final model was as follows:

$$\log\left[\frac{p}{1-p}\right] = -2.55 + 1.31 * bronchiolitis + 0.54 * unspecifiedLRTI + 2.55 * RSVcode + 0.19 * sex - 1.14 * riskgroup - 0.52 * age - 0.57 * sin(\frac{2\pi t}{52}) + 1.78 * cos(\frac{2\pi t}{52})$$

Infants with a diagnosis of bronchiolitis, unspecified LRTI or with an RSV-specific code had higher odds of RSV-positivity (OR=3.70 (95% CI 3.03-4.51), OR=1.72 (95% CI 1.19-2.50, and OR=12.77 (95% CI 10.06-16.20), respectively). Infants with a known risk factor (i.e. comorbidity or prematurity) had reduced odds of RSV-positivity (OR=0.32, 95% CI 0.26-0.39). RSV-positivity was significantly associated with calendar week and age.

The area under the ROC curve of 0.9 indicated that the final model had good predictive accuracy. The fit of the final model was assessed using the test sample (see Supplementary Data). The PPV of the final model was 79% (95% CI 77-81%) and the NPV 86% (95% CI 84-87%). The sensitivity and specificity of the model were 82% (95% CI 79-84%) and 84% (95% CI 81-86%), respectively.

Estimating the burden of RSV-associated admissions in infants in England

Our predictive model estimated an annual average of 20,359 (95% CI 19,236 - 22,028) RSV-associated admissions, out of a total annual average of 67,854 hospital admissions with any respiratory diagnosis, in infants in England during the study period.. The average annual rate of RSV-associated admissions was 29.63 per 1,000 infants <1 year of age.

The number of estimated RSV-associated admissions by calendar week is shown in Figure 2. During both seasons there was a peak in estimated RSV-associated admissions in week 52

(2010: n=2,281, 95% CI 2,057 – 2,498. 2011: n=2,637, 95% CI 2,348 - 2,848), coinciding with the peak in laboratory reports of RSV-positive respiratory samples from the Public Health England (PHE) national laboratory surveillance system (5). The highest number of RSV-associated admissions as a percentage of all weekly respiratory admissions during the 2010/11 season occurred in week 49 in 2010 (66%, 95% CI 61 – 73%) and during the 2011/12 season occurred in week 52 in 2011 (70%, 95% CI 62 –76%).

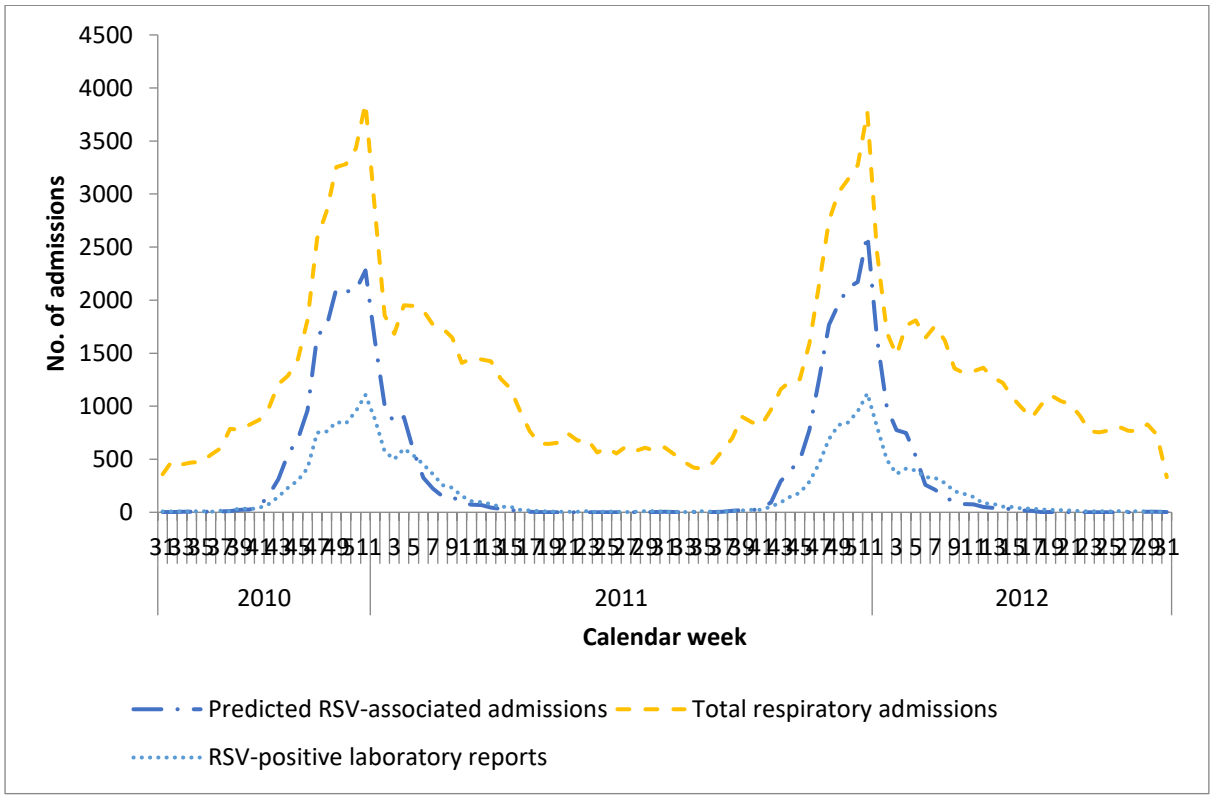

Figure 2. Estimated RSV-associated hospital admissions in infants <1 year old in England, by calendar week. RSV-positive laboratory reports from Public Health England (PHE) national surveillance system in children <5 years shown to illustrate timing of RSV circulation (previously reported (4)).

We estimate an average annual of 57,907 (95% CI 55,391-61,637) bed days due to RSV-associated admissions in infants <1 year of age each year in England (Table 2). 31% (6,368/20,359) of RSV-associated admissions were for <1 day, accounting for 5% (6,368/57,199) of RSV-associated bed days.

A total of 74% (15,126/20,359) of our estimated RSV-associated admissions were in infants younger than 6 months, accounting for 80% (46,124/57,907) of the annual bed days due to

RSV (Table 2). 55% (31,987/57,907) of bed days and 45% (9,130/20,359) of RSV-associated admissions were in infants younger than 3 months. The annual number of RSV-associated admissions peaked at age 6 weeks (n=1,019, 95% CI 974-1,052), then declined with increasing age (Figure 3). RSV-associated admissions also peaked in infants born in September (n=2,730, 95% CI 2,612-2,861), October (n=3,252, 95% CI 3,148-3,384) and November (n=2,716, 95% CI 2,624-2,944) (Figure 4).

Only 5% (944/20,359) of the RSV-associated admissions were in infants with an ICD-10 code indicating high-risk status, but these accounted for 21% (12,160/57,907) of bed days.

Table 2. Average estimated annual number of hospital admissions and bed days due to RSV in infants <1 year old in England - stratified by age, risk group, birth month and primary diagnosis.

	Average RSV annual admissions (95% CI)		Average annual bed days (95% CI)	
	***N* (95% CI)**	**%**	***N* (95% CI)**	**%**
Total	20,359 (19,236 - 22,028)	-	57,907 (55,391-61,637)	-
Sex				
Male	11,725 (11,022-12,630)	58%	32,177 (30,816-34,119)	56%
Female	8,632 (8,213-9,395)	42%	25,727 (24,573-27,515)	44%
Ratio (M:F)	1.3:1	-	1.3:1	-
Age (months)				
<1	1,772 (1,712-1,913)	9%	10,529 (10,088-11,483)	18%
1	4,174 (3,995-4,312)	21%	12,729 (12,297-13,112)	22%
2	3,184 (3,073-3,371)	16%	8,729 (8,510-9,118)	15%
3	2,323 (2,201-2,451)	11%	5,745 (5,539-5,979)	10%
4	2,013 (1,895-2,174)	10%	4,809 (4,481-5,052)	8%
5	1,661 (1,563-1,791)	8%	3,584 (3,412-3,851)	6%
6	1,359 (1,269-1,502	7%	2,819 (2,647-3,069)	5%
7	1,121 (1,051-1,274)	6%	2,601 (2,484-2,827)	4%
8	911 (836-1,051)	4%	2,053 (1,948-2,286)	4%
9	771 (698-897)	4%	1,759 (1,636-1,971)	3%
10	580 (528-693)	3%	1,508 (1,425-1,679)	2%
11	493 (419-603)	2%	1,045 (924-1,211)	2%
Clinical risk group				
No	19,415 (18,318-20,961)	95%	45,747 (43,819-48,456)	79%
Yes	944 (919-1,0671)	5%	12,160 (11,572-13,181)	21%
Birth month				
January	896 (790-1,042)	4%	3,018 (2,842-3,348)	5%
February	694 (634-805)	3%	1,985 (1,772-2,241)	3%
March	831 (770-986)	4%	2,123 (1,980-2,414)	4%
April	996 (912-1,147)	5%	2,237 (2,080-2,507)	4%
May	1,270 (1,192-1,406)	6%	2,937 (2,668-3,176)	5%
June	1,434 (1,353-1,546)	7%	3,001 (2,867-3,164)	5%
July	1,764 (1,695-1,913)	9%	4,288 (4,171-4,668)	7%
August	2,134 (2,009-2,225)	10%	5,357 (5,114-5,682)	9%
September	2,730 (2,612-2,861)	13%	7,198 (6,974-7,436)	12%
October	3,252 (3,148-3,384)	16%	10,060 (9,701-10,351)	17%
November	2,716 (2,624-2,944)	13%	9,609 (9,430-10,194)	17%
December	1,643 (1,501-1,771)	8%	6,095 (5,792-6,455)	12%

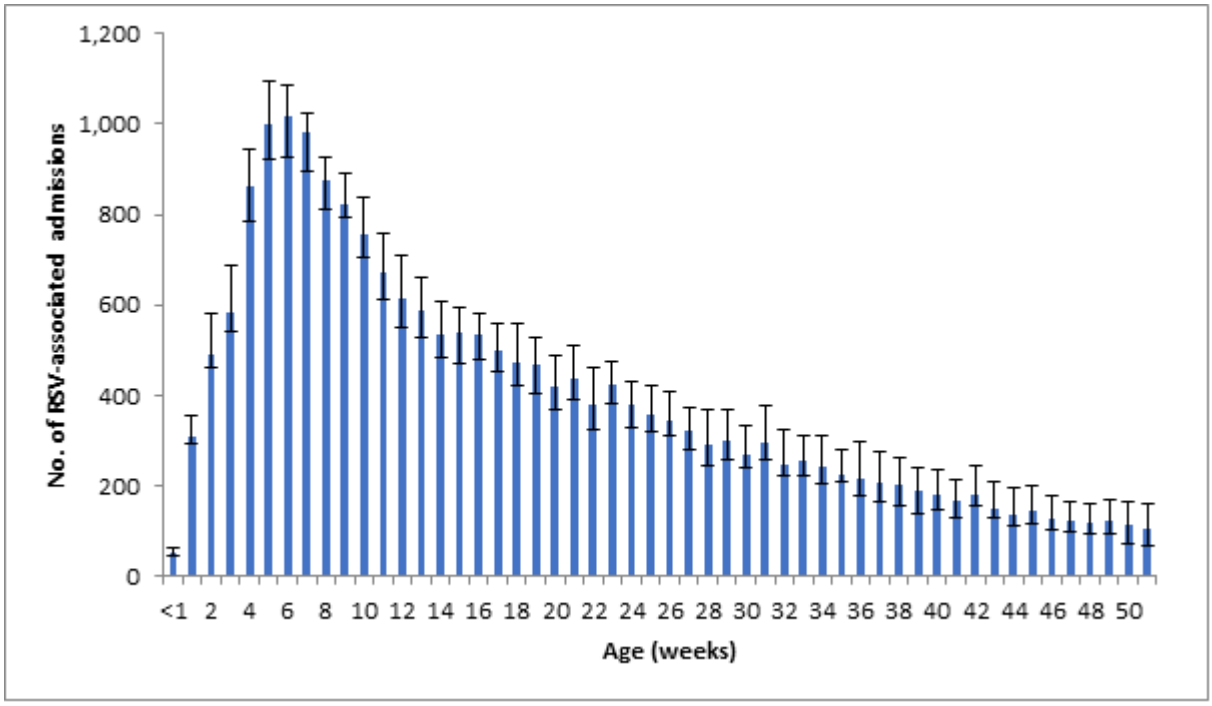

Figure 3. Annual estimated number of RSV-associated admissions, by age in weeks.

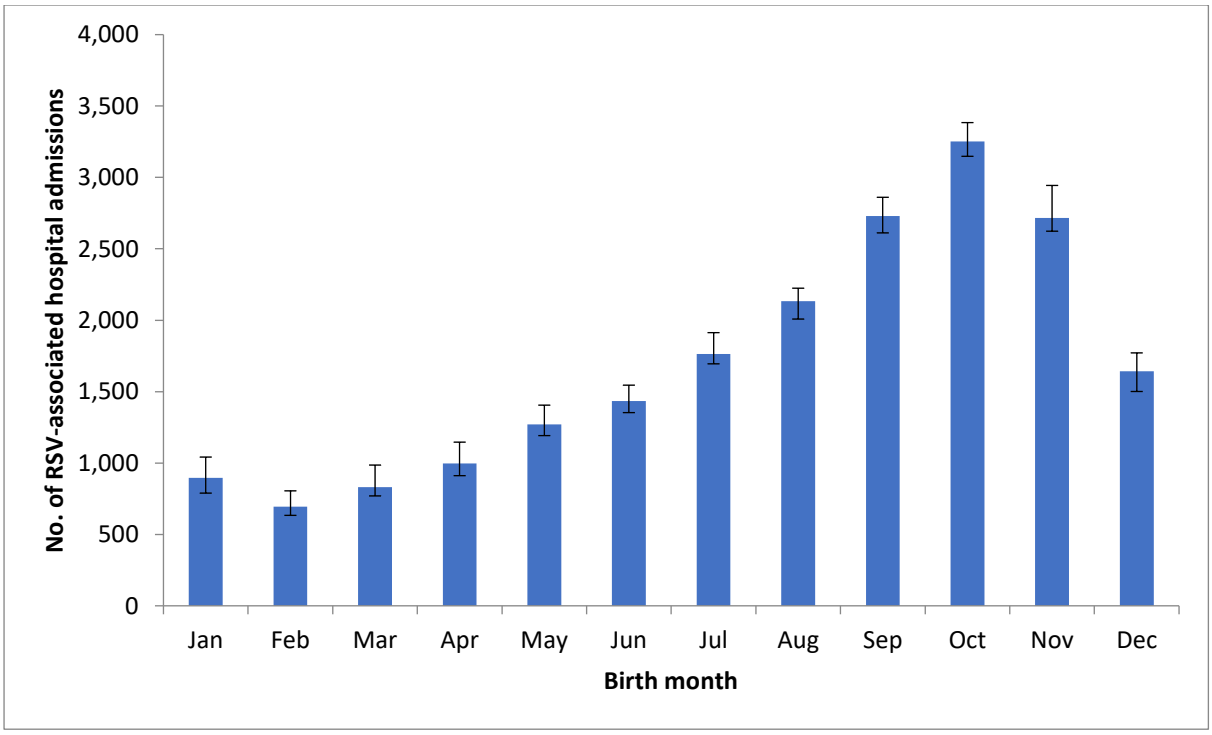

Figure 4. Annual estimated number of RSV-associated admissions, by birth month.

Discussion

Our study is the first to use linked routinely collected laboratory and hospital records to estimate the national secondary care burden of RSV in infants. Using our linked dataset which included both RSV-positive and RSV-negative admissions, we estimate a total annual average of 20,359 (95% CI 19,236-22,028) RSV-associated admissions in infants younger than 1 year of age in England during the two-year period from mid-2010 to mid-2012. These admissions accounted for approximately 57,907 (95% CI 55,391-61,637) annual hospital bed days. Approximately 55% of RSV-associated bed days and 45% of RSV-associated admissions were in infants younger than 3 months. There was a peak in RSV-associated admissions in infants aged 6 weeks, as well as in infants born in September, October and November. Only 5% of RSV-associated admissions were in high-risk infants, but these infants accounted for 21% of the estimated bed days.

This point estimate of annual RSV-associated admissions is similar to our previous estimate of 23,310 (95% CI 21,816-25,738) RSV-associated admissions in infants younger than 1 year in England, with overlap of the 95% CIs. The previous estimate was derived using time-series modelling, and is the only other published estimate in England covering the same time period (4). The novel methodology that we have developed in this study allows the examination of RSV burden in more detail (by age and other risk factors) than is possible using time-series modelling. That the point estimate from the current study is 13% lower than the time-series modelling estimate could be due to our model in the current study under-predicting admissions with a diagnosis of unspecified LRTI, pneumonia or URTI as being related to RSV (since there were less linked RSV-positive admissions with these diagnoses). Alternatively, it could be due this being a more accurate prediction. Both analyses only include respiratory admissions and do not capture admissions with non-respiratory ICD-10 codes which may also be due to RSV (e.g. R06.2 - Wheezing). The results of this study are therefore likely a minimum estimate of the true burden of RSV-associated admissions in infants in England.

We demonstrated a large burden of RSV-associated admissions in infants younger than 3 months of age, which is consistent with previous studies in Western countries (21).

Protecting this group therefore has the potential to significantly reduce the secondary care burden of RSV. A recent study in England suggests that a seasonal vaccination strategy, targeting young infants born around the beginning of RSV season, may provide the most direct benefits of vaccination (22). While these infants may be targeted via maternal immunisation, vaccine coverage in pregnant women in England is low, ranging from 45% for influenza to 60% for pertussis (23). Alternatively, very young infants could be targeted via a monoclonal antibody with higher potency and extended half-life compared to Palivizumab (Synagis®, MedImmune) (24).

In our study, infants with known clinical risk factors for severe RSV-associated illness (prematurity, CHD, CLD, immunodeficiency, neurological disorder) accounted for one-fifth of bed days but only 5% of admissions. However, we relied on coding for these conditions within the longitudinal record of respiratory admissions in our extract and therefore likely underestimated the number of children with these high-risk comorbidities. In addition, we were unable to capture additional risk factors such as low birth weight. Nonetheless, our results highlight the increased severity of RSV-associated illness in these infants with known clinical risk factors. Evaluations of potential vaccine impact should take into consideration the number of hospital bed days potentially prevented by a future vaccination programme, not just the number of preventable hospital admissions, to account for the increased severity of disease in these infants with known clinical risk factors.

Our study is the first to estimate hospital admissions caused by RSV – and their associated bed days – on a national level using population-based linkage of laboratory surveillance and hospital admissions data. A previous study in Ontario explored the diagnostic accuracy of RSV-specific ICD10 codes within routinely collected data, and our predictive model has higher sensitivity and specificity compared to that model which used ICD10 codes alone . That our estimates are similar to previous studies using statistical modelling techniques offers validation of our methodology. Our methodology offers the opportunity to examine the national secondary care burden of RSV in more detail than has previously been achieved, with stratification by key patient and clinical characteristics. However, there are several limitations to our study. Firstly, it is not possible for us to fully ascertain the accuracy of our linkage methodology as we cannot disentangle missed links due to missing

patient identifiable information from missing links due to the laboratory test being carried out in primary care (RDS records laboratory tests from primary and secondary care, but lacks complete information on which setting the sample was from). Secondly, our HES dataset only included patients admitted to hospital with an ICD-10 code belonging to Chapter X: Diseases of the Respiratory System. Therefore, patients with non-respiratory codes (such as wheeze symptoms) are not included and our analysis should be considered an underestimate of the true secondary care burden of RSV. Thirdly, we only included two years of data, and more recent trends in admissions will not be reflected in our results. Fourthly, we had no information on coinfections and assumed that an RSV-positive laboratory result during a respiratory hospital admission was indicative of RSV being the cause of that admission. In addition, our laboratory surveillance data only covered a subset of laboratories in England. Although we limited the population used for predictive modelling to only trusts that tested >10% of their respiratory admissions, we cannot be sure of the representativeness of this population. Finally, there is a lack of data on important risk factors like gestational age, presence of older siblings etc. It is possible to develop birth cohorts within routinely collected datasets which would capture some of these additional risk factors (20), however birth record data was not available to do so for this study.

We have demonstrated that population-based linkage of laboratory surveillance and hospital admissions data for RSV facilitates the estimation of the total national secondary care burden of RSV in more detail than has previously been achieved using time series modelling approaches. Our methodology has the potential to be utilised in other countries and for other pathogens, particularly in similar instances where only a minority of cases undergo laboratory testing to identify the causal pathogen. The detailed baseline epidemiological data that we have produced can be used in vaccine modelling and economic evaluation studies to determine optimal target populations for a potential future vaccine programme.

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