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Modelling estimates of the burden of respiratory syncytial virus infection in children in the UK

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ABSTRACT

Objective: The burden of respiratory syncytial virus (RSV) illness is not well characterised in primary care. We estimated the burden of disease attributable to RSV in children in the UK between 1995 and 2009.

Design: Time-series regression modelling.

Setting: A multiple linear regression model based on weekly viral surveillance (RSV and influenza, Public Health England), and controlled for non-specific seasonal drivers of disease, estimated the proportion of general practitioner (GP) episodes of care (counted as first visit in a series within 28 days; Clinical Practice Research Datalink, CPRD), hospitalisations (Hospital Episode Statistics, HES) and deaths (Office of National Statistics, ONS) attributable to RSV each season.

Participants: Children 0–17 years registered with a GP in CPRD, or with a respiratory disease outcome in the HES or ONS databases.

Primary outcome measures: RSV-attributable burden of GP episodes, hospitalisations and deaths due to respiratory disease by age. RSV-attributable burden associated with selected antibiotic prescriptions.

Results: RSV-attributable respiratory disease in the UK resulted in an estimated 450 158 GP episodes, 29 160 hospitalisations and 83 deaths per average season in children and adolescents, with the highest proportions in children <6 months of age (14 441/100 000 population, 4184/100 000 and 6/100 000, respectively). In an average season, there were an estimated 125 478 GP episodes for otitis media and 416 133 prescriptions for antibiotics attributable to RSV. More GP episodes, hospitalisations and deaths from respiratory disease were attributable to RSV than to influenza in children under 5 years.

Conclusions: The burden of RSV in children in the UK exceeds that of influenza. RSV in children and adolescents contributes substantially to GP office visits for a diverse range of illnesses, and was associated with an average 416 133 prescribed antibiotic courses per season. Effective antiviral treatments and preventive vaccines are urgently needed for the management of RSV infection in children.

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Strengths and limitations of this study

- We used an indirect statistical modelling strategy to assess the burden of respiratory syncytial virus (RSV). Modelling strategies circumvent some of the limitations of traditional population-based surveillance studies because they do not rely on direct linkage of exposure and outcome data at an individual level, but indirectly assess the effect of pathogens on the rates of health outcomes of interest.
- Using data from large, nationally representative databases over an extended period encompassing 14 seasons, our study provides recent estimates of the RSV-attributable burden of general practitioner episodes, hospitalisations and deaths due to respiratory disease, by age.
- Other strengths include the use of individual patient data for defined outcomes, and a relatively broad definition of respiratory disease to increase sensitivity while maintaining specificity. Furthermore, we report novel data on antibiotic prescribing attributable to RSV.
- The study may be limited by the assumption of a constant seasonal baseline and a sinusoidal pattern of seasonal outcomes. Patients who did not seek care and changes in coding practices or in the quality of diagnoses recorded in the databases over time could not be accounted for in our model. Age groups used for the analysis were not optimal for assessing RSV as they were originally defined for the purpose of assessing the influenza burden. RSV risk stratified by gestational age could not be assessed.
- The inclusion of cyclic terms in the model to account for other winter seasonal pathogens for which weekly incidence data were not available reduced the possibility that the study overestimated the RSV burden.

INTRODUCTION

Respiratory syncytial virus (RSV) is a major cause of acute respiratory disease in young children and is estimated to cause between 50% and 90% of hospitalisations for

bronchiolitis and 5–40% of hospitalised pneumonia in this age group.[1] In temperate climates, RSV epidemics occur almost every winter, affecting a substantial, but unknown percentage of children and adults.[2 3]

Population-based surveillance studies of RSV with laboratory confirmation of infection have nearly all been limited to hospitalised cases and very young infants,[4] with only one such study conducted in the UK to date.[5] The burden of RSV outside the hospitalised setting and among older children is poorly understood due to lack of systematic testing with sensitive assays that are costly and difficult to implement on the large scales required for epidemiological studies. Assessing the total health burden of RSV is crucial to setting appropriate prevention and resource allocation strategies and to make the case for the development of vaccines and therapeutics.

Within the UK, regular surveillance of viral illnesses such as RSV and routine collection of high-quality data on diagnoses leading to general practitioner (GP) visits, hospitalisations and death is conducted. These data stem from different sources and are not all directly linkable at the individual level. Nevertheless, indirect statistical modelling methods may be applied to the data to estimate the RSV-attributable medical burden at the population level. Multiple regression time-series modelling is one such method which has frequently been used for the assessment of an infectious disease burden.[6–8]

We used time-series regression methods to analyse the available data and estimate the RSV-attributable medical burden among children in the UK in terms of GP episodes, hospitalisations and deaths due to respiratory diseases and other outcomes, by age, for the period 1995–2009. Data pertaining to the total population and to adults and the elderly will be published separately.

METHODS

This study (NCT01706302) was an extension of a previous study conducted to evaluate the burden of influenza disease in the UK (NCT01520935), controlling for RSV incidence. The study protocol was approved by the Independent Scientific Advisory Committee from the Clinical Practice Research Datalink (CPRD). All data were anonymised and informed consent was not required.

Data sources
General practitioner data
The CPRD is a primary care database drawn from the computer systems used by GPs to maintain the clinical and prescribing records within their practices, and contains all records primary care deemed relevant to patient care. The CPRD is the largest anonymised primary care database in the UK.[9] At the midpoint of the study (January 2001), the monitored population was around 3.7 million. Patients included in the study were registered at ~500 distinct practices. All diagnoses and patient interventions are summarised and stored as READ codes. The READ system generally maps onto

International Classification of Diseases (ICD) codes, with one or more READ codes per ICD code and additional non-ICD diagnostic codes for presenting symptoms which are widely used in primary care to describe minor illness. Under the guidance of two experts, we defined sets of READ codes corresponding to ICD codes of interest (ICD codes summarised in table 1; READ equivalents available on request). In addition, preliminary searches of the CPRD dictionary were made to assess the frequency of symptom and other diagnostic codes used during three influenza peak periods, and the frequency in periods in which influenza did not circulate. This procedure revealed codes used by GPs to code patients who present with symptoms of acute respiratory infection during periods of influenza (and by extension RSV) activity.

A GP episode was counted as the first in a series of consultations for a particular diagnosis/diagnostic group which took place after a minimum of 28 days following any previous consultation for that same diagnosis/diagnostic group. Antibiotic prescription data (broad spectrum penicillins, macrolides, tetracyclines) were identified from prescriptions generated within the GP recording systems. Outcomes of interest were extracted from 1995 to 2009.

Hospitalisation data
The Hospital Episode Statistics (HES) database captures discharge data from all patients admitted to National Health Service non-psychiatric hospitals in England and Wales. We used ICD-10 codes corresponding to the outcomes of interest and listed as the primary diagnosis to extract records for each emergency admission from 1997 until 2009 (table 1).

Mortality data
The Office of National Statistics (ONS) records all deaths in the UK using ICD classification of cause (ICD-9 prior to 2001 and ICD-10 thereafter). As recommended by ONS,[10] for respiratory outcomes that departed from trend estimates between 2000 and 2001 ('all respiratory diagnoses', 'pneumonia and influenza' and 'bronchitis and bronchiolitis'), the average baseline incidence was adjusted by multiplying the 1996–2000 outcome counts by a constant (1.22 for 'all respiratory diagnoses', 1.69 for 'pneumonia and influenza' and 2.09 for 'bronchitis and bronchiolitis') to produce time series that were not substantially different from 2000 to 2001 (transition period from ICD-9 to ICD-10). Outcomes of interest were extracted from 1996 to 2009.

Virology data
Weekly influenza and RSV counts were obtained from the UK national surveillance system at Public Health England (PHE). Reports of RSV come primarily from laboratory-confirmed infections in young children admitted to hospital with respiratory disease, whereas

Table 1 Outcomes: GP episodes (CPRD), hospitalisations (HES) and deaths (ONS)

Outcome	ICD-10 codes	GP (CPRD)*	Hospitalisation (HES)†	Deaths (ONS)
Respiratory outcomes				
Respiratory disease	J00-99	X‡	X	X
Cardiorespiratory disease	I00-99, J00-99		X	X
Acute upper respiratory disease	J00, J02-06	X		
Pneumonia and influenza	J09-18	X	X	X
Bronchitis/bronchiolitis	J20-22, J40	X	X	X
Chronic respiratory disease	J41-47	X	X	X
Drug prescriptions				
Antibiotics (broad-spectrum penicillins, macrolides, tetracyclines)§		X	–	–
Non-respiratory control outcomes				
Otitis media	H65-66, H70	X	X	–
Accidents	V00-99, X00-99, Y00-99		X	
Urinary tract infection	N39	X	X	X

CPRD does not provide any ranking of diagnostic codes. HES database outcomes listed as the primary discharge diagnosis were studied. ONS database outcomes listed as any mention of the outcome as the cause of death were studied.
*Any CPRD GP episode, including office visits, home visits, telephone consults and other types, for participants with participants registered with research quality data in CPRD. CPRD diagnostic data are coded using READ codes. CPRD diagnostic and antibiotic codes are available on request.
†Only unscheduled, 'emergency' hospitalisations were included.
‡Respiratory disease was broadly defined to consider CPRD READ codes corresponding to all ICD-listed codes related to respiratory disease as well as READ codes corresponding to selected symptoms and diagnoses in the CPRD (see description of selection procedure in Methods): these included cough, breathing abnormalities, viral infections, sepsis and septicaemia.
§Antibiotics relevant to respiratory disease.
CPRD, clinical practice research datalink; GP, general practice; HES, hospital episode statistics; ICD10, international classification of diseases V.10; ONS, office of national statistics.

reports of influenza are community-derived from individuals with influenza-like illness.

Study inclusion criteria

The inclusion criterion was registration during the study period within a GP meeting the 'research standard' checks of data quality and consistency in the CPRD, or registration with a respiratory disease outcome in either the HES with an admission date between 1997 and 2009, or the ONS mortality database between 1996 and 2009 (table 1).

Definitions of study outcomes and strata

The main study outcomes were GP episodes, hospitalisations and deaths due to respiratory disease. Respiratory disease was broadly defined to consider all ICD-listed codes (or corresponding CPRD READ codes) related to respiratory disease as well as READ codes corresponding to selected symptoms and diagnoses in the CPRD (see previously described selection procedure): these included cough, breathing abnormalities, viral infections, sepsis and septicaemia. In addition to cardiorespiratory disease (all ICD respiratory disease codes+cardiovascular codes) and other subcategories of respiratory disease, we examined the RSV-attributable burden associated with the selected antibiotic prescriptions (GP episodes only). Accidents and urinary tract infections, which have no seasonal pattern and no association to RSV or influenza, were used as negative control outcomes to assess the

possibility of bias in model attribution over the entire study period. Outcomes related to GP episodes were defined according to any mention of a diagnostic READ code of interest. For hospitalisations (HES database), outcomes listed as the primary discharge diagnosis were studied. For deaths (ONS database) we studied any mention of the outcome as the cause of death.

Estimates were stratified by age. Data are presented in this manuscript for the following age groups: <6 months, 6–23 months, 2–4 years and 5–17 years. Adult-specific data will be presented in a separate publication.

Statistical methods

Statistical analyses were performed using SAS V.9.2. We used data restricted to the subset of patients that were covered by each source (ie, those residing in England which comprises 80% of the UK population). UK population by age (2001 data: ONS)[11] were used to weigh the CPRD population to reflect the UK profile and the results were extrapolated to the entire UK population.

Weekly time series for influenza and RSV were calculated using PHE surveillance data. The number of the week was calculated as ISO 8601 V-weeks, which begin with '1' near the beginning of the calendar year. Owing to a change from using viral culture to PCR methods at PHE during the seasons studied, pathogen data were split into pre-July and post-July 2001 season periods. Weekly time series for each health outcome were generated and stratified by age. The same multiple linear

regression model was applied to each age stratum and outcome of interest (GP, hospitalisations and deaths). The model attributes outcomes to RSV based on the association between temporal variations in outcome frequency and RSV circulation, while controlling for pre-existing temporal trends in the outcome, seasonal variations potentially triggered by other pathogens and disease drivers, and for influenza circulation, as follows:

$$
\begin{aligned}
Y = {} & \beta_0 + \beta_{s1}t + \beta_{s2}t^2 + \beta_{s3}t^3 + \beta_{s4}\sin(2\pi t/52) \\
& + \beta_{s5}\cos(2\pi t/52) + \beta_{p1a}\,\text{influenza A}\,(\text{pre} - \text{July 2001}) \\
& + \beta_{p1b}\,\text{influenza A}\,(\text{post} - \text{July 2001}) \\
& + \beta_{p2a}\,\text{influenza B}\,(\text{pre} - \text{July 2001}) \\
& + \beta_{p2b}\,\text{influenza B}\,(\text{post} - \text{July 2001}) \\
& + \beta_{p3a}(\text{RSV})\,(\text{pre} - \text{July 2001}) \\
& + \beta_{p3b}(\text{RSV})\,(\text{post} - \text{July 2001})
\end{aligned}
$$

where, Y=weekly rates of outcomes; t=time since 1 July 1995, in weeks; β_0=intercept; $\beta_{s1}t + \beta_{s2}t^2 + \beta_{s3}t^3$=secular polynomial; $\beta_{s4}\sin(2\pi t/52) + \beta_{s5}\cos(2\pi t/52)$=secular cyclical terms included to account for other seasonal events, including epidemics of other winter-seasonal pathogens; β_{p1a} influenza A(pre-July 2001)+β_{p1b} influenza A(post-July 2001)=pathogen influenza A; β_{p2a} influenza B (pre-July 2001)+β_{p2b} influenza B(post-July 2001)=pathogen influenza B; β_{p3a}(RSV)(pre-July 2001)+β_{p3b}(RSV) (post-July 2001)=pathogen RSV; influenza A, influenza B and RSV are observed counts of positive tests from the PHE data set.

The attribution to each virus for each week was computed as the product of the model parameter and corresponding explanatory variable, and the weekly estimates were summed over each season to provide seasonal estimates. Thus, the RSV burden was derived from parameters β_{p3a} and β_{p3b} in the equation above. The CIs were based on the SE of the pathogen parameter estimate. Specifically, we first multiplied each weekly point estimate by the regression coefficient, then aggregated the weekly estimates over the entire season. We then repeated the procedure using the lower and upper 95% estimates for the regression parameter to obtain the seasonal upper and lower CIs. Results for influenza-attributable respiratory outcomes derived from the model were used to calculate the ratio of RSV-attributable outcomes as a proportion of all disease attributable to either influenza or RSV. The time series of antibiotic prescriptions was modelled in the same way as the time series for health outcomes to estimate antibiotic prescribing attributable to RSV.

RESULTS
Model fit
RSV infection in the UK is largely confined to the winter months. We therefore restricted our study to the period between September and mid-May. The outcome and pathogen time series were smoothed using a moving average of order 3 (ie, the smoothed value of X at week t is $(X_t{-}1{+}X_t{+}X_t{+}1)/3$) in order to adjust for irregular utilisation of health services over the critical Christmas and New Year holiday periods. The model did not attribute any positive RSV burden to control outcomes.

In the 2003/2004 season, unlike all other seasons during the study period, RSV circulation peaked later than influenza, thus providing an opportunity to observe the effects of RSV without confounding by influenza. During the 2003/2004 season RSV circulation and hospitalisation peaked simultaneously in children younger than 5 years of age, confirming the expectation that this is an RSV-related outcome and that RSV-positive samples come predominantly from hospitalised children.

GP episodes
In the seasons studied, we estimate that RSV infection resulted in 450 158 children and adolescents (all persons <18 years of age) consulting a GP for an episode of respiratory disease per season (table 2). In each season studied, GP episodes for RSV-attributable respiratory disease were highest in children <6 months of age (figure 1A). RSV was attributed to between 10.8% and 14.2% of all GP episodes for respiratory disease among children <5 years of age. More children (<5 years) consulted a GP for RSV-attributable respiratory disease than for influenza-attributable respiratory disease (ratio of RSV to influenza (A+B) between 2.4 and 8.4 to 1), acute respiratory tract infection (RTI; ratios between 1.9 and 7.2 to 1), and bronchitis/bronchiolitis (ratios between 7.4 and 18.1 to 1).

RSV was estimated to cause 125 478 cases of otitis media, with the most number of cases among children between 6 months and 4 years of age. There were 416 133 prescriptions for antibiotics written for RSV-associated respiratory disease per season. Around 8.3% of children <6 months of age and 11.9% aged 6–23 months received antibiotics for an RSV-attributed infection in an average season.

The model did not attribute any positive RSV burden to the control outcomes (urinary tract infection and accidents).

Hospitalisations
In an average season, there were 29 160 hospitalisations for RSV-attributable respiratory disease among children and adolescents, most of which (92%, 26 724/29 160) were in children <2 years of age (table 3).

In each season studied, hospitalisations for RSV-attributable respiratory disease were highest in children <6 months of age, and were at least threefold higher than in children aged 6–23 months (figure 1B). Around 3.8% of all children <6 months of age were estimated to be hospitalised for RSV-attributed acute bronchitis/bronchiolitis, representing 79.3% of all hospitalisations

Table 2 Average seasonal RSV-attributable burden of general practice episodes (CPRD) with any mention* of a respiratory disease diagnosis in the UK (1995–2009) by outcome and age

Respiratory outcome	Age	N	Episodes/100 000 population (range)	Per cent of all events attributable to RSV†	RSV: influenza ratio‡
Respiratory disease	<6 months	47 844	14 441 (10 537–17 088)	14.2	8.4:1
	6–23 months	130 758	12 936 (9209–14 934)	10.8	4.4:1
	2–4 years	161 540	7549 (4865–9636)	10.2	2.4:1
	5–17 years	110 016	1114 (632–1596)	3.5	0.5:1
Acute upper respiratory disease	<6 months	28 441	8585 (6420–10 411)	12.9	7.2:1
	6–23 months	74 377	7358 (5485–8895)	10.4	3.7:1
	2–4 years	78 931	3689 (2521–4417)	9.4	1.9:1
	5–17 years	48 437	491 (277–705)	3.0	0.4:1
Bronchitis/ bronchiolitis	<6 months	24 853	7502 (5094–9049)	41.5	18.1:1
	6–23 months	57 096	5649 (3942–6598)	29.7	16.1:1
	2–4 years	43 685	2042 (1398–2440)	24.6	7.4:1
	5–17 years	23 939	242 (162–298)	8.9	0.9:1
Pneumonia and influenza	<6 months	458	138 (71–214)	25.9	1.3:1
	6–23 months	1680	166 (109–208)	19.6	0.6:1
	2–4 years	2233	104 (63–141)	15.4	0.3:1
	5–17 years	2375	24 (7–49)	4.6	0.1:1
Otitis media	<6 months	1533	463 (203–783)	9.1	2.5:1
	6–23 months	23 426	2318 (1295–3359)	8.9	3.0:1
	2–4 years	56 201	2626 (1437–3870)	13.0	3.4:1
	5–17 years	44 318	449 (226–702)	6.3	1.3:1
Antibiotic prescription	<6 months	27 592	8328 (5547–10 265)	19.7	9.8:1
	6–23 months	120 447	11 916 (8432–13 684)	14.6	6.9:1
	2–4 years	160 368	7495 (5084–9051)	13.6	3.8:1
	5–17 years	107 726	1091 (686–1427)	4.2	0.8

*For CPRD data, there is no ordered listing or ranking of diagnostic codes. N=average seasonal number of specified RSV-attributable events for each outcome.
†Per cent of RSV-attributable events among all events due to outcome.
‡Ratio of proportions/100 000 RSV/(influenza A+B).
Range=range of estimates per season.
CPRD, clinical practice research datalink; RSV, respiratory syncytial virus.

for bronchitis/bronchiolitis in this age group in an average season. In children <5 years of age, there were more hospitalisations for RSV-attributable disease than for influenza-attributable disease for all of the outcomes studied (ratio of RSV to influenza (A+B) between 1.9 and 70.2 to 1).

Deaths

There were few deaths in children that were attributable to RSV in each of the seasons studied (figure 1C). In an average season, RSV was estimated to cause 83 deaths in children and adolescents (table 4). In children <5 years of age, there were more deaths due to any of the reported outcomes that were attributable to RSV than to influenza (ratio of RSV to influenza (A+B) between 1.6 and 12.4 to 1, table 4).

DISCUSSION

In children aged 4 years and younger, the burden of GP office visits, hospitalisations and deaths attributed to RSV in our study was much larger than the burden attributed to influenza, across all respiratory diagnoses.

Influenza vaccine coverage in the UK during the study was 15% as measured in CPRD across all ages, but was lower in younger age groups. While the highest incidences of RSV-attributable GP episodes, hospitalisations and deaths were in infants <6 months of age, the burden of GP episodes remained high until 4 years of age. Indeed, around 36% of GP episodes for RSV-attributable respiratory disease occurred in children 2–4 years of age. As well as acute bronchitis and bronchiolitis, which are well-recognised clinical syndromes associated with RSV infection in children, between 6.3% (5–17 years old) and 13.0% (2–4 years old) of otitis media was also attributed to RSV in our study. This is consistent with studies that assessed viral pathogens in middle ear fluid, which have frequently identified RSV as the infectious agent in children with otitis media.[12–14] Our study points to a large burden in terms of GP episodes for RSV-associated otitis media in children of all ages, particularly in children aged <5 years. Moreover, RSV infection was associated with substantial antibiotic use in the community; there were an average 416 000 prescribed antibiotic courses per season. These results indicate that RSV infection in children constitutes a major health and economic
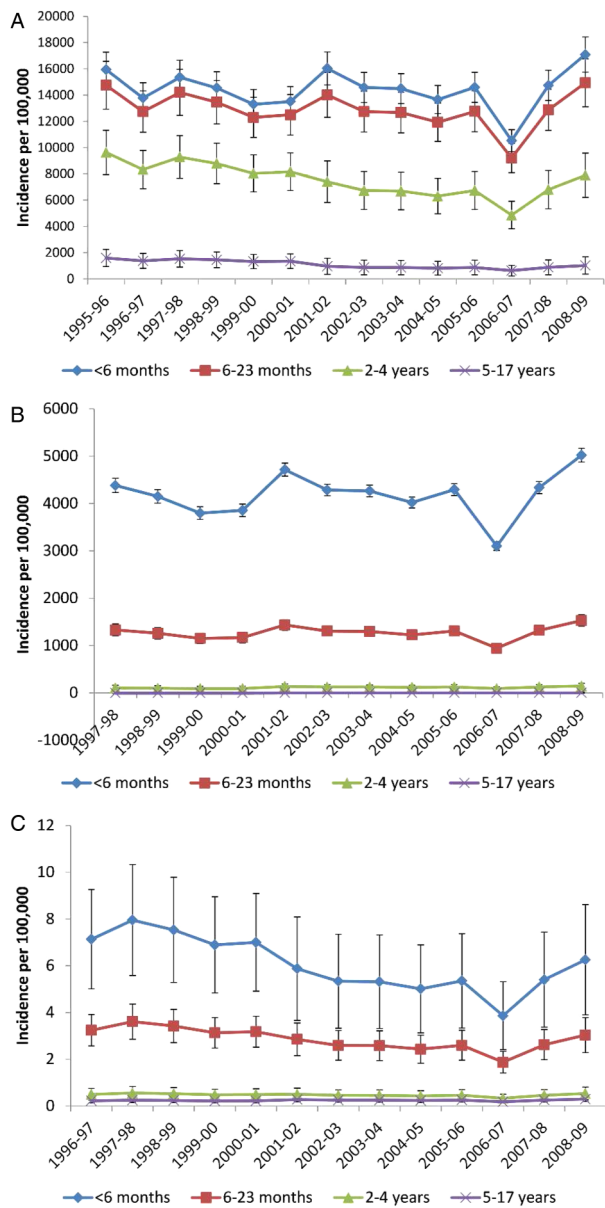
Figure 1 Seasonal incidence (per 100 000) of general practice episodes (A), hospitalisations (B) and deaths (C) due to respiratory syncytial virus-attributable respiratory disease (broadly defined) by age. Vertical lines=95% CIs.

burden, and thus provides a strong case for increasing efforts to prevent RSV in the age group up to 4 years.

The strengths of our study include the extended study period (14 seasons) and the availability of individual patient data for defined outcomes recorded in large, nationally representative databases, which reduced the risk of sampling error. Additionally, we employed a broad definition of respiratory disease to improve the sensitivity in capturing the full RSV-attributable disease burden, while retaining specificity. Finally, we report novel data on antibiotic prescribing attributable to RSV.

We adopted a conservative approach to reduce the possibility of overestimating the burden of RSV, using a seasonal (sine/cosine pair) adjustment in the model to control for a number of seasonal confounders for which data are not available, including other important winter seasonal pathogens such as human rhinoviruses, enteroviruses, human bocovirus, human metapneumovirus and coronaviruses.[15] The cyclic component of the model was highly collinear with RSV seasonality, and less so with influenza. The cyclic components therefore took a greater portion of the burden of RSV than they took from the burden of influenza. Thus, inclusion of the cyclic terms in the model may have caused the burden of RSV to be underestimated; in any event, their inclusion substantially reduced the risk that the study overestimates RSV burden. This is because RSV infections follow regular seasonal cycles in temperate climates, and the seasonal terms do not necessarily adjust for temporal autocorrelation in the time series. This is a limitation of most studies on disease burden that make use of epidemiological time series because there is not currently a technique that can satisfactorily ensure temporal and spatial independence in the structure of the time-series data, and simultaneously yield biologically meaningful estimates of disease burden. The best approach in such cases is to recognise the exploratory nature of this type of study and avoid an excessive reliance on p values and CIs (which are determined based on the assumption of independence). When developing the model, we ran variants with shorter period cyclical terms, and found that adding these terms did not explain any more of the variability.

Potential limitations inherent in the regression model therefore include the assumption that the pathogen is responsible for the majority of the increase in disease during a period of virus circulation, and the assumption of a constant seasonal baseline and a sinusoidal pattern of seasonal outcomes. There is also the potential for bias linked to heteroscedasticity, for which the impact on the estimated rates is difficult to assess and also difficult to resolve, for example, by attributing weights (1/var) to the observed weekly counts. This is a general limitation of all the models based on count data (ie, log-linear Poisson, negative binomial and linear regression models) and not specific to the model we used.

Our model could not account for patients who did not seek care, nor the quality of diagnoses recorded in the databases or changes in coding systems or practices over time. We did not evaluate the effect of influenza or pneumococcal conjugate vaccination on outcomes. Finally, we did not consider specific RSV risk criteria in young children (prematurity, chronic lung disease, congenital heart disease and immune suppression) that have been defined within the context of prophylaxis with the monoclonal antibody palivizumab.[16] Further investigation of additional paediatric age groups and strata related to RSV-related risk factors would help to refine our estimates.

Population-based approaches have been used to assess the disease burden attributable to RSV less frequently than for influenza. Relatively few studies of influenza

Table 3 Average seasonal RSV-attributable burden of hospitalisations* (HES) in the UK (1997–2009), by outcome and age

Respiratory outcome*	Age	N	Episodes/100 000 population (range)	Per cent of all events attributable to RSV†	RSV: influenza ratio‡
Respiratory disease	<6 months	13 862	4184 (3099–5019)	42.2	21.1:1
	6–23 months	12 862	1272 (943–1528)	19.5	9.3:1
	2–4 years	2436	114 (90–145)	5.1	1.9:1
	5–17 years	0§	0§	0§	0:1
Pneumonia and influenza	<6 months	198	60 (44–71)	26.9	3.2:1
	6–23 months	1086	107 (80–130)	27.8	4.5:1
	2–4 years	1033	48 (37–59)	25.7	7.8:1
	5–17 years	429	4 (3–5)	12.3	1.2:1
Bronchitis and bronchiolitis	<6 months	12 458	3760 (2775–4494)	79.3	43.3:1
	6–23 months	7598	752 (547–886)	58.7	70.2:1
	2–4 years	1260	59 (46–75)	29.8	7.2:1
	5–17 years	269	3 (2–4)	9.1	1.1:1

*Outcomes refer to the 'primary' cause for hospitalisation for HES.
†Per cent of RSV-attributable events among all events due to outcome.
†Ratio of proportions/100 000 RSV/(influenza A+B).
§On-statistically significant negative estimates (95% CIs included 0) suppressed and expressed as 0.
N=average seasonal number of specified RSV-attributable events for each outcome.
Range=range of estimates per season.
HES, hospital episode statistics; RSV, respiratory syncytial virus.

burden have included information on RSV circulation in their models, and many used laboratory-confirmed RSV time series only as a control variable or did not investigate disease outcomes known to be specific to RSV infections.[17] Our approach estimated the RSV-attributable burden in primary care by exploring outcomes known to be specifically associated with RSV, such as bronchitis and bronchiolitis. We showed that most RSV infections in children were captured by a diagnosis of bronchitis and bronchiolitis. While other groups have modelled even broader diagnostic ranges (cardiorespiratory, or all-cause),[18 19] we found that using multiple cause diagnoses ('any mention' for HES and ONS data) and a broad respiratory definition (respiratory disease broadly defined, all databases), consistently captured the RSV burden in all settings. Negative outcome controls may be useful to detect confounding.[20] The expected absence of attributions for urinary tract infection and accidents supports the modelling methodology employed.

A European multicountry study that used CPRD data (2002–2008) in a similar approach to assess influenza-like illness due to influenza or RSV estimated an average seasonal consultation rate for influenza-like illness due to RSV of 83/100 000 in 0–4 years old and 43/100 000 for 5–14 years old.[21] These estimates are markedly lower

Table 4 Average seasonal RSV-attributable burden of deaths (ONS) with a respiratory disease cause in the UK (1996–2009) by age and outcome

Respiratory outcome*	Age	N	Episodes/100 000 population (range)	Per cent of all events attributable to RSV†	RSV: influenza ratio‡
Respiratory disease	<6 months	20	6 (4–8)	12.0	2.8:1
	6–23 months	29	3 (2–4)	17.6	5.5:1
	2–4 years	10	0 (0–1)	10.0	1.6:1
	5–17 years	24	0 (0–0)	8.6	1.5:1
Pneumonia and influenza	<6 months	8	2 (2–3)	15.5	2.3:1
	6–23 months	13	1 (1–2)	20.8	3.2:1
	2–4 years	6	0 (0–0)	12.4	1.9:1
	5–17 years	10	0 (0–0)	8.0	1.0:1
Bronchitis and bronchiolitis	<6 months	8	2 (1–3)	47.1	12.4:1
	6–23 months	10	1 (1–1)	61.3	5.4:1
	2–4 years	2	0 (0–0)	39.1	1.9:1
	5–17 years	1	0 (0–0)	11.3	0.8:1

*Outcomes refer to the 'any mention cause of death for ONS'.
†Per cent of RSV-attributable events among all events due to outcome.
‡Ratio of proportions/100 000 RSV/(influenza A+B).
N=average seasonal number of specified RSV-attributable events for each outcome.
Range=range of estimates per season.
ONS, office of national statistics; RSV, respiratory syncytial virus.

than our findings for RSV-attributable GP office visits using a broader respiratory disease definition, illustrating the need to include a wide range of respiratory syndromes in order to capture all RSV disease.

Our estimate of a large RSV-attributable burden of hospitalisation among infants is in agreement with the only RSV surveillance study to date with laboratory confirmation of infection that has provided population-based estimates of RSV-related hospitalisations among young infants in the UK.[5] In this study, 3.6% of all <6 months old in one UK county were hospitalised with RSV-related lower RTI (primarily bronchiolitis) during 1996–1999,[5] compared with our roughly equivalent estimate of 3.8% for hospitalisation for RSV-related bronchitis/bronchiolitis between 1997 and 2009. Our finding that more deaths in young children were attributable to RSV than to influenza is in line with previous surveillance of childhood RSV and influenza deaths in the UK between 1989 and 2000, and in the USA between 1990 and 1999, in which RSV deaths predominated in children <1 year of age and were lower, or roughly equal, to that of influenza in 1–4 years old.[7 18] We estimated around 340 000 RSV-attributable GP episodes per average season in children <5 years of age. This compares with 246 000 estimated by a previous modelling study that used the same database but over a single season.[6] Our study considered a longer and more contemporary time period and more refined age stratification.

Other US studies of the RSV hospitalisation burden have given lower estimates than those of our study. A survey of hospitalisations coded as RSV under ICD-9 in the USA (1997–2006) estimated a RSV hospitalisation rate of 3860/100 000 among children <6 months of age and 80/100 000 in 2–4 years old, compared with a somewhat higher average seasonal burden of 4184/100 000 and 114/100 000, respectively, in our study.[22] A prospective study of laboratory-confirmed RSV acute RTI reported even lower annual rates of hospitalisation: 1240–2170/100 000 in <6 months old between 2000 and 2004 versus 3856–4714/100 000 for comparable seasons in our study, and 20–50/100 000 in 2–4 years old versus 91–136/100 000 in our study.[23] These estimates could reflect differences in admission practices between the two countries, or real differences in disease burden, but the greater specificity of the diagnostic criteria used in those studies compared with our broader definition of respiratory disease likely accounts for much of the observed variation.

By contrast, estimates of annual rates of prospectively identified, laboratory-confirmed physician office visits for acute RTI in the USA were similar to our study using the respiratory broad definition: 10 800–15 700/100 000 office visits in <6 months old between 2002 and 2004 versus 14 581–14 498/100 000 for comparable seasons in our study, and 3100–7700/100 000 in 2–4 years old versus 6694–6732/100 000.[23] Although using different age strata, our results also appear comparable to a

prospective German study of laboratory-confirmed RSV lower RTI in children 0–3 years of age (1999–2001), in which the estimated incidence of office visits was 7700/100 000 (95% CI 6 to 700; 8900) annually.[24]

There was a temporary decrease in incidences of RSV-associated respiratory outcomes in the 2006/2007 season that was apparent across all three databases. This decrease was also apparent in antibiotic attributions for RSV (data not shown) and was also evident for RSV-attributable respiratory disease in adults.[25] We have no way of knowing whether this decrease is within normal long-term RSV seasonal variability—although in the other seasons studied, the burden of RSV was remarkably consistent—or if other factors such as climatic conditions or other circulating viruses may have played a role.

CONCLUSION

The burden of disease attributable to RSV in children exceeds that of influenza. RSV was estimated to contribute substantially to the burden of GP office visits for a range of respiratory illnesses. Effective antiviral treatments and preventive vaccines are urgently needed for the management of RSV infection in children. Unlike influenza, RSV displays generally consistent seasonality and therefore predictability of the annual RSV epidemic. This information could be used by policymakers in terms of the timing of possible preventative strategies, but also in planning and preparing for peaks in healthcare use during RSV epidemics.

Analytica, LLC; he also discloses having received consultancy fees from Sage Analytica, LLC outside the submitted work.

DMF declares having received support for travel to international scientific meeting from the GSK group of companies and that he provided consultancy services to Sage Analytica, LLC, acting thereby as a co-researcher for the present project, for which the funding source was GlaxoSmithKline Biologicals SA. DMF also discloses the following conflicts of interest outside of submitted work: board membership received from the GSK group of companies and Novartis, consultancy services in relation to the IBGP project directed from Open Rome Paris and funded by the GSK group of companies, payment for lectures including service on speakers bureaus from Crucell Laboratories and money to his institution received from the Nivel Institute from the Netherlands (Collaborator Institution in the European Paediatric Influenza project supported by unconditional grant from Astra Zeneca).

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