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Contribution of RSV to bronchiolitis and pneumonia-associated hospitalizations in English children, April 1995–March 1998

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SUMMARY

Estimates of the number of hospitalizations attributable to specific pathogens are required to predict the potential impact of vaccination. All hospital admissions for lower respiratory tract infection (LRI) in children < 5 years in England in 1995–8 were reviewed. Most admissions (76·8%) were not associated with specific organisms. Seasonality in pathogens that cause bronchiolitis and pneumonia was used to predict the proportion of cases with unspecified aetiology attributable to different organisms using multiple linear regression. Of 12298 admissions for LRI, 17·5% were due to RSV infection. An estimated 74·8% (95% CI, 72·0–77·7%) of 'unspecified bronchiolitis' admissions and 16·3% (95% CI, 13·7–18·8%) of 'unspecified pneumonia' admissions were RSV related. The total mean annual incidence of hospital admissions attributable to RSV is 28·3/1000 children < 1 year of age, and 1·3/1000 children 1–4 years old. The greater burden of RSV infection than indicated through discharge data is revealed through applying simple statistical methods.

INTRODUCTION

Respiratory syncytial virus (RSV) is the most common cause of lower respiratory tract infection (LRI) in infants and children worldwide. Epidemics occur yearly during winter and early spring in temperate climates. RSV has a variety of clinical and epidemiological manifestations in different age groups. Despite the presence of maternal antibodies, severe clinical manifestations (typically pneumonia and bronchiolitis) often resulting in hospitalization most commonly occur among infants aged less than 6 months. The risk of serious RSV disease is markedly increased for children born prematurely or with underlying chronic lung disease such as bronchopulmonary dysplasia [1]. Nearly all children are infected by 2 years of age. However, since the virus induces poor protective immunity, reinfection throughout life is common. Thus RSV is increasingly recognized as an important cause of otitis media in older children [2] and of serious respiratory disease in the elderly and immunocompromised individuals [3–5].

There have been a number of recent potential therapeutic developments: immunoprophylaxis with RSV specific immune globulin or monoclonal antibodies targeted at high-risk infants. After the failure of a formalin-inactivated vaccine in the early 1960s, which induced an exaggerated clinical response to wild type RSV infection in infants, there are currently no safe and effective vaccines licensed. However, two approaches are being evaluated in clinical trials: subunit vaccines for immunization of older children

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with underlying chronic lung disease and the elderly, and live attenuated vaccines for infants [6].

In the United Kingdom, Sims et al. [7] reported over 25 years ago that the risk of hospital admission with RSV in the first year of life in northeast England was 20 per 1000 per year. More recent UK studies have been undertaken in cohorts of pre-term infants and those with underlying chronic lung disease to determine the potential impact of immunoprophylaxis. They reported an annual incidence of hospitalization for confirmed RSV infection of 36–41 admissions per 1000 at risk infants [8, 9]. However, serious RSV disease and consequently hospitalization can occur in otherwise healthy infants as well as in high-risk children. With recent advances in vaccine development it is crucial to obtain an update of the burden of RSV in both groups to determine the most appropriate vaccination strategy.

In this study we examine all hospitalizations for LRI in England over a 3-year period to try and determine hospitalization rates in those under 5 years of age. However, in common with most surveillance data, which rely on clinical reports for which laboratory data are not complete, a large number of hospitalizations are recorded at the syndromic level (e.g. unspecified pneumonia). This poses a problem when trying to ascertain the burden of particular aetiological agents. Previous authors have often used rather crude assumptions; such as all bronchiolitis cases are due to RSV. In this paper we use a simple statistical technique to estimate what proportion of these hospitalizations of young children with LRI can be attributed to specific aetiological agents, thereby providing a baseline for an evaluation of the potential health and economic impact of RSV vaccination as new vaccines become available.

METHODS

Data source

The details of patients admitted to hospital with a diagnosis of LRI (definition given below) were obtained from the hospital episodes statistic (HES) database from April 1995 through March 1998. HES contained personal, medical and administrative details of all patients admitted to NHS hospitals in England, a population of approximately 49 million people. HES records included information on patient's age, sex, dates of admission/discharge, number of bed days, and outcome. As data also contain personal identifiers such as date of birth and postal code, duplicates could be identified and excluded. Hospitalization rates were calculated using denominators derived from the annual resident population estimates based on the projections of the 1991 UK census (Office for National Statistics).

All admissions with an International Classification of Diseases 10th Revision (ICD-10) code associated with LRI in any of the seven diagnostic fields for each record were included in the analysis. The following codes were used to cover all causes of LRI: pneumonia (J12–18), acute bronchitis (J20), acute bronchiolitis (J21), unspecified acute lower respiratory infection (J22), bronchitis, not specified as acute or chronic (J40), influenza (J10, J11), other chronic obstructive pulmonary disease with acute lower respiratory tract infection/acute exacerbation, unspecified (J44), whooping cough (A37), Legionnaires' disease (A48), *Chlamydia psittaci* infection (A70), and congenital pneumonia (infective) (P23).

To determine the proportion of patients hospitalized due to RSV who were in 'high risk', premature birth and underlying chronic respiratory disease categories were specifically ascertained among the hospitalized children under 5 years of age. The following ICD-10 codes were used to define HES records associated with high-risk status: gestation before 37th week (P07), respiratory distress of newborn (P22), congenital pneumonia (P23), neonatal aspiration syndromes (P24), respiratory disease originating in the perinatal period (which includes bronchopulmonary dysplasia) (P27/P28), congenital malformations of trachea, bronchus, lung (Q32/Q33), chronic obstructive pulmonary disease (J44), and cystic lung disease (J98.4). For ease of presentation the term 'low risk' is used for patients who did not have one of the above codes recorded.

Statistical analysis

No aetiological cause was recorded for a large number of LRI admissions (termed here 'unspecified LRI'). Multiple linear regression analysis was used to estimate the contribution of RSV and other aetiological agents of lower respiratory tract illnesses to hospital admissions in children coded as 'unspecified LRI', following the method of Ryan et al. [10]. The technique uses the observed temporal variation in potential causative agents of the clinical outcome (in this case pneumonia and bronchiolitis of unspecific aetiological cause) to estimate the level of underdiagnosis for each of these causes.

Because there are two clinical syndromes with differing patterns of possible infectious cause, two

Table 1. *Number and diagnosis of lower respiratory tract infection (LRI)-associated hospitalizations in children < 5 years of age England, 4/95–3/98*

Diagnosis	No. of admissions	%
Unspecified LRI, of those:	97783	76·8
Pneumonia	52107	
Bronchiolitis	42350	
Bronchitis	2673	
Influenza (virus not identified)	620	
Chronic obstructive pulmonary disease	8	
Mixed (> 1 unspecified LRI)	25	
RSV	22229	17·5
Bordetella spp.	3155	2·5
Streptococcus pneumoniae	915	0·7
Mycoplasma pneumoniae	691	0·5
Parainfluenza	434	0·3
Influenza	275	0·2
Dual infections	163	0·1
Haemophilus influenzae	158	0·1
Other (allergic asthma, *Chlamydia* spp., enterovirus, *Klebsiella pneumoniae*, staphylococcus, streptococcus group B)	1495	1·2
Total	127298	100·0

Table 2. *Children hospitalized with reported RSV infection who are classed as 'high-risk' patients*

	< 1 year ($n = 20310$)	1–4 years ($n = 1919$)
'High risk' of those	382 (1·9%)	77 (4·2%)
Preterm	133 (35%)	8 (10%)
Underlying chronic respiratory disease	249 (65%)	69 (90%)

models were developed for the regression analysis using different dependent variables; model 1, for unspecified bronchiolitis (ICD-10: J21.9) and model 2 for unspecified pneumonia (ICD-10: J12.8/9; J15.8/9; J18. Both models used the weekly number of admissions in children under 5 years of age for the respective ICD-10 diagnoses. The independent variables were the weekly numbers of the following recorded causes of LRI-associated hospital admissions:

- RSV (ICD-10: J12.1; J20.5; J21.0)
- *Streptococcus pneumoniae* (ICD-10; J13)
- Influenza (ICD-10: J10)
- Parainfluenza (ICD-10: J12.2; J20.4; J05.0)
- *Bordetella species* (ICD-10: A37)
- *Haemophilus influenzae* (ICD-10: J14; J20.1)
- *Mycoplasma pneumoniae* (ICD-10: J15; J 20.0)

We also defined a variable named 'other' which included LRI-associated admissions due to pathogens or diseases for which either the total number of admissions was under 100 (*Klebsiella pneumoniae*, staphylococci, streptococci group B, chlamydial pneumonia, Legionnaires' disease, rhinovirus) or were too heterogeneous to analyse them separately (allergic asthma, nonallergic asthma, mixed asthma). Patients of all age groups were combined for the independent variables, as there was no difference in seasonal patterns between younger and older age groups and using all ages made the seasonal trends more distinct.

A backward stepwise regression was performed to remove variables that did not contribute to the model using SPSS 10.0 for Windows (SPSS Inc., Chicago, IL, USA). In a step-by-step procedure single variables that reduced R^2 by the smallest increment were removed from the equation if the resulting decrease was not statistically significant by the F test (significance level of F value $< 0{\cdot}05$). The procedure was continued until the removal of a variable caused a significant reduction in R^2. Analysis of residual plots was performed to assess the validity of the model and evidence for autocorrelation. The likely impact of possible model misspecification was investigated by examining the changes in coefficients of the final model to sequential deletion of significant variables.

Differences in the length of stay (number of bed days) between the 'high risk' RSV patients and RSV

Table 3. *Spell duration of 'high risk' and 'low risk' children hospitalized with reported RSV infection*

	< 1 year		1–4 years	
	'High risk' ($n = 382$)	'Low risk' ($n = 19928$)	'High risk' ($n = 77$)	'Low risk' ($n = 1842$)
Known spell duration	90%	98%	94%	99%
Median (mean) no. of days	8 (16)	3 (4)	7 (20)	3 (4)
Range	0–243	0–305	0–560	0–478

patients with no code for high risk ('low risk') were compared by using the Wilcoxon rank sum test. We used the Fisher's exact test to assess whether there was a difference in mortality between the two groups.

RESULTS

LRI admissions in children

Between April 1995 and March 1998, 127298 children under 5 years of age were admitted to hospital with a diagnosis of LRI in England. Of these, 17·5% of the hospital admissions were coded as 'LRI due to RSV', 76·8% as 'LRI due to unspecified organism' and the remaining 5·7% were due to other specified causes. Table 1 shows the numbers and diagnosis of the hospitalized children. Of the 97783 children under 5 years of age admitted due to an unspecified LRI, 53·3% were diagnosed with pneumonia, 43·3% with bronchiolitis, 2·7% with bronchitis, and 0·6% with influenza (virus not identified). Less than one percent of the children was diagnosed with more than one unspecified LRI, and unspecified chronic obstructive pulmonary disease, respectively. Sixty-four percent of all hospitalizations were in children younger than 1 year. The sex distribution was 58% male, 41% female and 1% non-reported.

RSV admissions in children

Of the 22229 hospital admissions coded as due to RSV infection during the 3-year study period, 91·3% ($n = 20310$) were children younger than 1 year and 65·9% ($n = 14639$) were under 6 months of age. Ninety-seven percent ($n = 21554$) of all RSV patients were diagnosed with bronchiolitis, 1·9% ($n = 416$) with bronchitis, and 1·1% ($n = 243$) with pneumonia.

The proportion of reported 'high-risk' patients was 4% ($n = 77$) among the RSV-associated hospitalized children aged 1 to 4 years, whereas for children under 1 year, 1·9% ($n = 382$) met the criteria for 'high-risk' patients (Table 2). The number of bed days was significantly higher at $P < 0·001$ (Wilcoxon rank sum test) in 'high-risk' patients in both age groups (8 bed days for children < 1 year and 7 for children aged 1–4 years) compared with the corresponding 'low risk' patients (3 and 3 bed days respectively) (Table 3). The proportion of 'high risk' RSV infants who died was significantly higher compared to 'low risk' (3·3% *vs.* 0·2%) (proportions $P < 0·001$, Fisher's exact test). There was evidence for increased mortality amongst 'high risk' patients aged 1–4 years, though the difference was not significant at the 5% level ($P = 0·093$) (Table 4).

Temporal trends in LRI admissions

The models we constructed used the patterns of seasonal variation in the weekly number of admissions for each known cause of LRI. Figure 1 shows the seasonal variation of weekly admissions due to RSV, influenza, *S. pneumoniae*, *H. influenzae*, *M. pneumoniae*, 'other', *Bordetella* spp., and parainfluenza in all age groups during the 3-year study period.

The weekly number of RSV admissions peaked sharply annually during the winter months. Admissions due to influenza and *S. pneumoniae* also peaked clearly in winter but their peaks varied more than that of RSV over the study period, and a large number of hospitalization due to *S. pneumoniae* occurred in spring and early summer. Admissions associated with *H. influenzae* and *M. pneumoniae* and 'other' also peaked in winter but did not show such distinct seasonal patterns. *Bordetella* spp. has 3–4 year epidemic cycles and reports increased steadily to a peak in 1998 but also with annual peaks in late summer/autumn. Parainfluenza showed no clear seasonal variation.

Estimated hospitalization rates

Using our final models, the weekly number of unspecified bronchiolitis and unspecified pneumonia hospitalizations due to RSV and the other respiratory

Table 4. *Mortality of 'high risk' and 'low risk' children hospitalized with reported RSV infection*

	< 1 year		1–4 years	
	'High risk' ($n = 382$)	'Low risk' ($n = 19928$)	'High risk' ($n = 77$)	'Low risk' ($n = 1842$)
Known method of discharge	96%	99%	97%	99%
Died	12 (3·3%)	38 (0·2%)	2 (2·7%)	11 (0·6%)

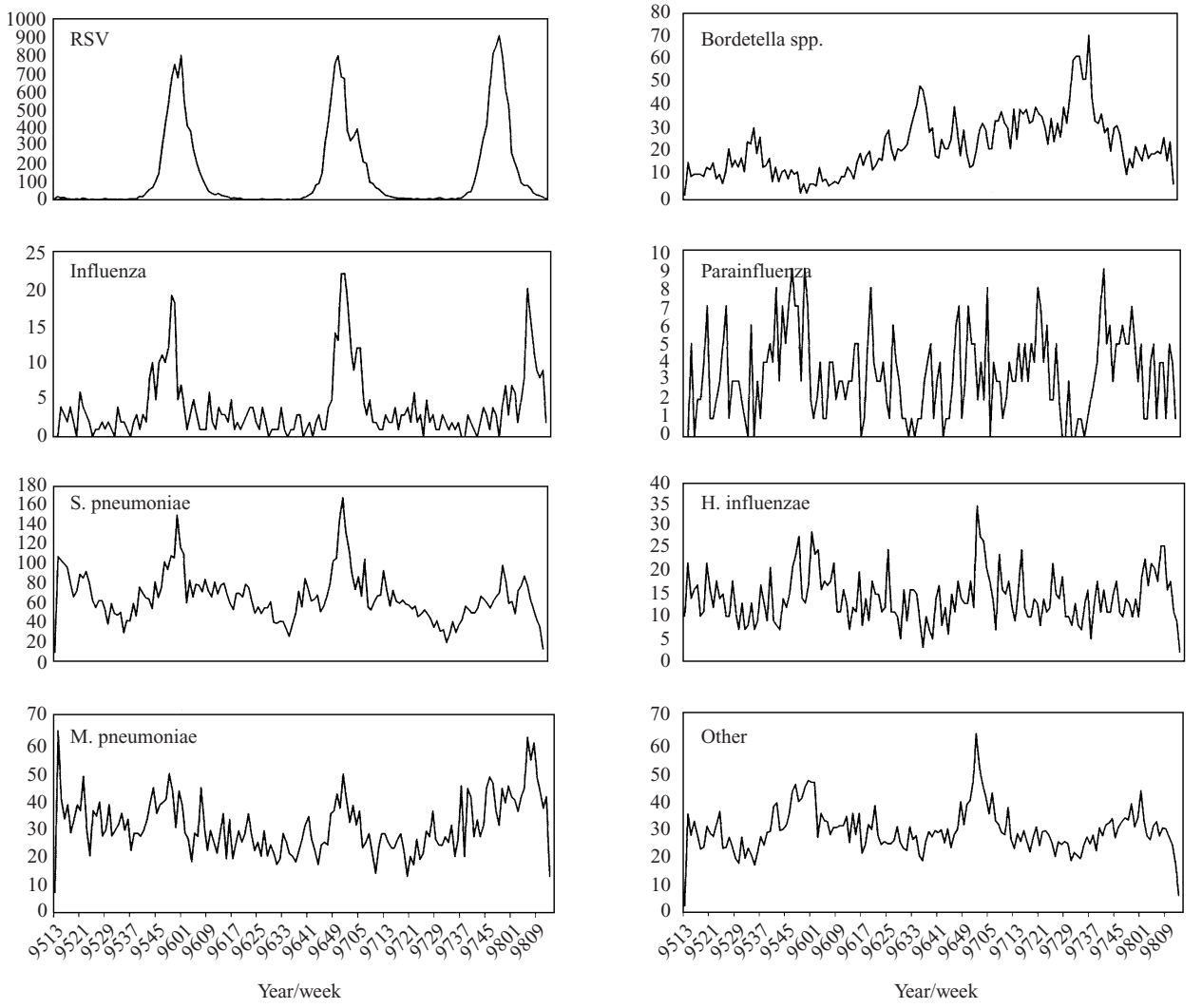

Fig. 1. Seasonality of weekly hospital admissions in all patients for LRI due to RSV, influenza, *S. pneumoniae*, *M. pneumoniae*, *Bordetella* spp., parainfluenza, *H. influenzae*, and 'other', England, April 1995–March 1998.

pathogens were estimated. Figures 2 and 3 show that these estimates correspond closely with the observed weekly numbers. Derived from these estimates the proportion of unspecified bronchiolitis and unspecified pneumonia accounted for by these organisms were calculated (Tables 5, 6).

Seventy-five percent (95% CI, 72·0–77·7%) of the 'unspecified bronchiolitis' admissions and 16·3% (95% CI, 13·7–18·8%) of the 'unspecified pneumonia' admissions in children younger than 5 years of age were RSV related. This results in a total (observed + expected) mean annual incidence of hospital admissions attributable to RSV of 1·3 per 1000 among children aged 1–4 years, and of 28·3 per 1000 for children under 1 year of age during the 3-year study period.

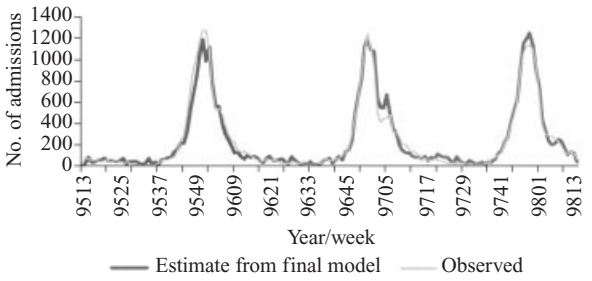

Fig. 2. Comparison of observed weekly number of unspecified bronchiolitis hospitalizations in children < 5 years of age with estimated weekly number due to RSV, influenza, and parainfluenza based on the final model$_{\text{bronchiolitis}}$ shown in Table 5.

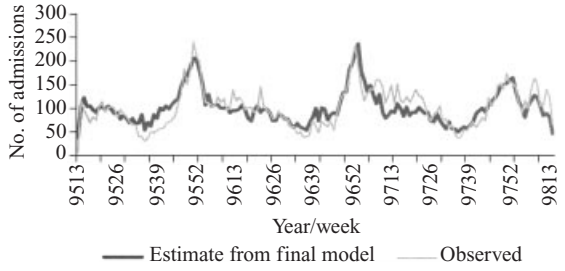

Fig. 3. Comparison of observed weekly number of unspecified pneumonia hospitalizations in children < 5 years of age with estimated weekly number due to RSV, influenza, and parainfluenza, *S. pneumoniae*, and *M. pneumoniae* based on the final model$_{\text{pneumonia}}$ shown in Table 6.

Table 5. *Estimates of the proportion* (%) *of unspecified bronchiolitis hospitalizations in children < 5 years of age due to specific respiratory pathogens and sensitivity of results to model specification*

Pathogen	Final model Model $1_{\text{bronchiolitis}}$	Model $2_{\text{bronchiolitis}}$
RSV	74·8	79·9
Influenza	10·1	—
Parainfluenza	12·7	—
Intercept	2·4	20·1
Adjusted R^2	0·965	0·955

The adjusted R^2s of both final models indicate that 97% and 80% of the variation in the weekly number of unspecified cases was explained by model $1_{\text{bronchiolitis}}$ and by model $1_{\text{pneumonia}}$ respectively. Furthermore, we checked model $1_{\text{bronchiolitis}}$ for confounding (Table 5) as RSV and influenza have quite similar seasonality and parainfluenza showed no clear seasonal pattern. Any possible bias seemed to be negligible as dropping the two significant variables from the model $1_{\text{bronchiolitis}}$ lead to only 5% increase in the estimated proportion of RSV (model $2_{\text{bronchiolitis}}$). In model $1_{\text{pneumonia}}$ (Table 6) *M. pneumoniae* accounted for 17·5% of the unspecified pneumonia admissions – more than expected, consequently '*Mycoplasma pneumoniae*' was dropped to check the robustness of the estimates (model $2_{\text{pneumonia}}$). There was little change in the remaining estimated proportions and the model fit was no better. In a third model (model $3_{\text{pneumonia}}$), we excluded the intercept to determine if we could obtain a better model fit. There was a large increase in the estimated proportion due to *S. pneumoniae* and *M. pneumoniae*. However, a slight decrease in the adjusted R^2 value was observed, suggesting poorer fit. Consequently, model $1_{\text{pneumonia}}$ was used to obtain the estimated hospitalization rates.

DISCUSSION

Our study estimates the annual incidence of hospital admissions attributable to RSV and other causes of LRI in children using a regression modelling approach. This technique uses the observed temporal trends in potential causative agents of LRI to estimate the contribution of each of these agents to 'unspecified' hospitalizations. These estimates of hospitalizations due to RSV together with the cases actually coded as RSV-associated hospitalizations represent 49% of all annual LRI admissions in children under 5 years of age in England. As expected for an illness with most severe manifestations in infants the estimated incidence of RSV-associated hospitalization was higher in children under 1 year of age accounting for 65% of all annual LRI admissions in England in this age group. There is a greater burden of RSV infection than indicated through current routine data (HES) in England. The findings suggest that in many cases RSV is not identified despite the availability of ICD10 codes in hospital records for RSV, and thus the illness is assigned a non-specific code for LRI.

Our results are in accordance with findings in a descriptive analysis of US National Discharge Survey data from 1980 through 1996 [11]. All discharge records from children younger than 5 years of age with an ICD-9 code (ICD-10 codes were not introduced until April 1995) for any respiratory illness among the diagnoses listed were selected for this study. Due to lack of a specific ICD-9 code for RSV-associated disease, the authors were forced to use the proportion of bronchiolitis from November through April as a rather crude proxy for RSV-associated

Table 6. *Estimates of the proportion* (%) *of unspecified pneumonia hospitalizations in children < 5 years of age due to specific respiratory pathogens and sensitivity of results to model specification*

Pathogen	Final model Model $1_{pneumonia}$	Model $2_{pneumonia}$	Model $3^{a}_{pneumonia}$
RSV	16·3	16·5	15·1
Influenza	7·0	8·3	4·8
Parainfluenza	12·9	14·0	14·8
S. pneumoniae	19·8	23·0	33·5
M. pneumoniae	17·5	—	31·8
Intercept	26·6	38·2	—
Adjusted R^2	0·799	0·789	0·774

[a] Regression through the origin (no-intercept model).

hospitalizations. This study suggested RSV was responsible for 50–80% of annual LRI hospitalizations among children younger than 1 year. We have used specific ICD-10 codes for RSV-associated hospitalizations. Furthermore, our regression analysis made use of the temporal patterns of all of the most important respiratory pathogens over the entire 3-year study period, which makes our estimates more robust.

The hospitalization rate of 20 per 1000 per year in children younger than 1 year of age found in 1975 [7] by taking specimens from all children admitted to a paediatric ward with a respiratory tract illness in north-east England is approximately 50% lower than the rate derived from our estimates. However, a substantial increase in rates of hospitalization of infants with bronchiolitis during 1980–96 was also seen in an American study [11]. Furthermore, attendance at a child-care centre is considered to be an independent risk factor for LRI hospitalization in children under 2 years of age [12]. Thus the trend toward earlier enrolment in nurseries may lead to initial RSV infection at a younger age when severe disease and consequently hospitalization is more likely. Improved survival rates of premature infants may also have contributed to increases in RSV hospitalization rates over the last 20 years.

Previous studies have suggested that 'high risk' infants are the most important target group for intervention strategies [13–15]. Our data suggest that the majority (98%) of children under 1 year of age hospitalized with reported RSV infection are not 'high risk' (i.e. concurrently diagnosed with prematurity or underlying chronic lung disease). Our data show that spell duration and mortality is significantly higher in 'high risk' RSV patients but the major caseload of RSV occurred in otherwise healthy children. However, it is very likely that the information needed for defining patients as 'high risk' (gestation age, underlying medical conditions) were underreported in the HES records and we thus underestimate the proportion of 'high-risk' patients. Buck et al. (16) report that ex-preterm infants under 6 months of age and those with bronchopulmonary dysplasia accounted for 8% and 10% respectively of RSV positive admissions to the paediatric department in Cambridge, England, during the winters 1998/9 and 1999/2000.

Our method has potential limitations. As the regression models relied on the temporal pattern of in potential causative agents of LRI, a proportion of cases could be attributed to other pathogens with similar patterns, which we did not consider as variables in the models. Van den Hoogen et al. [17] described recently the characterization of a new member in the *Paramyxoviridae* family, isolated from 28 children with LRI over a period of 20 years. The clinical symptoms were reminiscent of those caused by RSV infection, although the seasonal pattern is still unclear. However, we examined all the major known infectious and non-infectious causes of respiratory illness in children. Secondly, RSV-associated hospitalizations may have been underestimated, because we were not able to estimate the proportion of 'unspecified bronchitis' hospitalizations related to RSV due to lack of data and consequently no clear seasonal pattern. Yet these represent a minority of LRI admissions in young children. Also, only admissions associated with LRI were included in the analysis, as RSV is not thought to cause any non-LRI syndromes in children unlike other causes of LRI such as influenza or *S. pneumoniae*. Estimates for hospital-

izations due to the latter organisms must take diagnoses such as febrile illnesses, septicaemia etc. in account.

In summary, our data suggest a large burden of LRI is due to RSV in young children and that the introduction of a safe and effective RSV vaccine could greatly reduce the number of hospitalizations. To determine which vaccination strategy (a high risk, targeted approach or a general population approach) should potentially be implemented, the possible contribution of underlying conditions, including premature birth, to the incidence of RSV hospitalizations in children needs to be more fully ascertained.

We have shown that data on hospital admissions can be analysed in a simple regression model to get a better estimate of the incidence of RSV-associated hospitalization in children and that this method is a useful tool to estimate the level of under-diagnosis of potential aetiological causes in non-specific clinical outcomes.

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