ORIGINAL ARTICLE

Respiratory illness associated with influenza and respiratory syncytial virus infection

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Arch Dis Child 2005;90:741-746. doi: 10.1136/adc.2004.063461

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Accepted
18 February 2005
Published Online First
26 April 2005

Aims: To estimate excess morbidity during periods of influenza and respiratory syncytial virus (RSV) activity.

Methods: Retrospective analysis of a sentinel practice network database in active and non-active virus periods. Main outcome measures: clinical diagnoses of new episodes of influenza-like illness (ILI), acute bronchitis, asthma, and otitis media.

Results: The clinical diagnosis of ILI was consistent with influenza virus activity and acute bronchitis with RSV. During periods of virus activity, estimates of excess morbidity in children aged 1-4 and 5-14 years diagnosed as having acute otitis media exceeded those diagnosed with each of the other three conditions; in children <1 year estimates for acute bronchitis were highest. Using a *broad definition* of virus activity and summarising the data for all children diagnosed with ILI, 60% was attributable to influenza (40% RSV) as were 37% of episodes diagnosed as acute bronchitis, 9% of those with asthma and 48% of those with otitis media. Using a *narrow definition*, corresponding proportions were: for ILI diagnoses 77% (23% RSV), acute bronchitis 32%, asthma zero, and otitis media 45%. Acute bronchitis was diagnosed twice as frequently in association with RSV as with influenza in all age groups: excess asthma episodes were only evident in RSV active periods.

Conclusions: Except in relation to ILI, RSV caused more illness than the influenza virus in the respiratory diagnoses examined, emphasising the need for RSV prevention and treatment. Influenza was not associated with excess asthma episodes.

Preventive and prophylactic programmes for disease management require an understanding of the natural history and complications associated with the disease. In the United Kingdom annual vaccination against influenza is recommended for children at risk because of co-morbidity including those with asthma, diabetes, chronic cardiovascular or renal disease, and the immune compromised: there is no recommendation for universal vaccination. The evidence base for this policy is derived mainly from extrapolating to children, the results of studies of vaccine efficacy in adults.^{1 2} Palivizumab (a monoclonal antibody) is available for prophylaxis against respiratory syncytial virus (RSV), but it is very expensive and has limited clinical application.

Influenza and RSV cause lower respiratory tract infections in persons of all ages, though RSV infection impacts particularly in young children.^{3 4} Both viruses are prevalent in most winters, often at about the same time. Both mutate frequently and thus recurrent infections are common. Children infected with either virus commonly present with fever and cough, sometimes accompanied by wheeze, and some because of otitis media.⁵

RSV infection has been associated with the subsequent development of asthma, but conversely a lack of exposure to common virus infections has been suggested as a cause of asthma.⁶⁻⁹ The highest asthma attack rates in young children occur in December when the impact of RSV in the community is greatest.¹⁰ Many other viruses are known to be associated with asthma attacks.^{6 11-15}

The diagnosis of asthma in young children is difficult: it is usually made clinically when the child is seen in an attack and is based on the clinical history and presence of bronchospasm. Acute bronchitis is diagnosed much more frequently than asthma.¹⁶ Otitis media can also be difficult to diagnose, especially in young children (because of the absence of direct communication and the difficulty of getting

a good view of the eardrum). Incidence is strongly correlated at a weekly level with upper respiratory tract infections.¹⁷

We aimed to quantify the impact of influenza virus and RSV on clinical diagnoses of influenza-like illness (ILI), acute bronchitis, asthma, and otitis media by estimating the excess children reporting to general practitioners with these conditions during influenza and RSV active periods over the six winters 1994/95 to 1999/2000.

METHODS

The Weekly Returns Service (WRS) of the Royal College of General Practitioners has collected data on selected new episodes of illness since 1967.¹⁸ With increasing computerisation, data collection was extended in 1994 to include all diseases. General practitioners define the problems presented at each consultation in diagnostic terms where possible and distinguish between new episodes of illness and follow up consultations. Diagnosis is clinically based, though guidelines (not age specific) have been circulated to the recorders for selected conditions. As an example, the guidance for acute bronchitis (and bronchiolitis) specifies an acute illness with a cough and scattered or generalised abnormal chest signs including wheeze, and coarse or moist sounds. For asthma, a new episode is deemed to occur when a person consults because of an asthma attack or if his asthma is out of control. Weekly incidence rates (per 100 000 persons) for new episodes of ILI, acute bronchitis, asthma, and otitis media were assembled for the six winters. These were grouped by age (<1, 1-4, 5-14 years) and compared with viral isolates for influenza (A or B) and RSV confirmed cases reported to the Health Protection Agency (HPA).

Abbreviations: HPA, Health Protection Agency; ILI, influenza-like illness; RSV, respiratory syncytial virus; WRS, Weekly Returns Service

Table 1 Influenza and RSV active periods by week number (weeks duration)

Influenza (A and B)			RSV		
Year	Broad definition	Narrow definition	Year	Broad definition	Narrow definition
1994/95	1–14 (14)	4–10 (7)	1994/95	45–4 (12)	49–1 (5)
1995/96	45–3 (11)	47–1 (7)	1995/96	46–6 (13)	50–4 (7)
1996/97	49–9 (13)	2–6 (5)	1996/97	47–9 (15)	47–1 (7)
1997/98	6–14 (9)	9–15 (7)	1997/98	44–3 (12)	48–52 (5)
1998/99	51–7 (9)	51–5 (7)	1998/99	45–3 (11)	47–51 (5)
1999/00	50–5 (8)	51–3 (5)	1999/00	44–1 (10)	46–50 (5)

For each winter, diagnosis, and age group, we calculated the mean weekly incidence rate in virus active periods and the excess over a baseline rate formed from the remaining winter weeks (week 40 of one year to week 20 of the next). This excess was multiplied by the number of weeks in which the virus was active to estimate the cumulative winter excess. The calculation was initially performed for a combined RSV and influenza active period, then repeated for the two viruses separately. This combined cumulative winter excess rate was allotted to RSV and influenza in the same proportion as the separate virus estimates.

Active periods were defined (*broad definition*) from the clinical incidence of ILI as previously described¹⁹ and from weekly RSV reports to the HPA exceeding 200 in children <1 year old. Week 52 was treated as active if reports in both weeks 51 and 01 exceeded 200, because laboratory investigation routines are limited during the Christmas and New Year period. The sensitivity of the definition of the active periods was explored in a *narrow definition* based solely on viral isolates (influenza) and virological reports (RSV). Examination of weekly virus counts revealed that, although the magnitude of peaks varied between age bands for both influenza and RSV, a similar time trend was evident in all ages. Hence, the active periods were defined by incorporating sufficient weeks, around the peak week to include 40% of all influenza isolates and 50% of all RSV reports for the entire winter (table 1). This definition was chosen to provide maximum separation of influenza virus and RS virus active periods. Further definitions embracing greater proportions were explored. The relative proportions of excess diagnoses attributable to influenza and RSV were compared for each definition.

RESULTS

The cumulative population (person-weeks) on which this study is based is detailed in table 2. Periods of virus activity (influenza and RSV combined) and the respective populations are here defined by the *broad definition*. The *narrow definition* included 67 active weeks altogether; populations in virus active weeks were approximately one third less.

Weekly clinical incidence data for ILI in children in the three age groups during each winter are compared with virus report data in fig 1A. In the winters in which RSV and influenza virus were best separated (1994/95 and 1997/98), reported incidence of ILI was more clearly evident in the influenza active period than in the RSV active period. The same tendency, though less obvious, was observed in 1998/99 and 1999/00. In 1995/96 and 1996/97 there was very little differentiation between influenza and RSV active periods.

A similar comparison is made for acute bronchitis (fig 1B), which is reported five times as frequently as ILI. Clinical incidence aligns very closely with RSV active periods, though a secondary less obvious incidence surge is evident in those winters in which influenza follows RSV. The results for asthma (fig 1C) are less clear; incidence surges were found in four of the six RSV active periods (exceptions 1995/96 and 1996/97). There were no particular surges during influenza virus activity, and surges were found when neither virus was circulating. The incidence of otitis media (fig 1D) is evident over both RSV and influenza active periods.

Figure 1 also shows differences between age groups. For ILI, incidence rates were similar in all age groups. For acute bronchitis, incidence in children <1 year was much higher than that in older age groups, though for asthma it was less. In the age group 5–14 years, for acute bronchitis, asthma, and otitis media, incidence was less than in younger age groups: the impact during RSV periods was generally less than that seen in younger children.

Table 3 summarises the average weekly baseline incidence in non-virus active periods for each winter, diagnosis, and age group. For ILI, baseline rates were around 25 per 100 000: for otitis media and acute bronchitis, rates were much higher than those for ILI and asthma. For each of these diagnoses, rates were less in 1999/00 than in 1994/95. In children <1 year, background rates of asthma were about a tenth of those for acute bronchitis; in age group 1–4 years, half; and 5–14 years, roughly equal.

The cumulative winter excess rates of ILI, acute bronchitis, asthma, and otitis media reported during RSV and influenza active periods based on the *broad definition* are summarised for each winter in fig 2. It shows considerable variation between

Table 2 Cumulative population (person-weeks) in combined influenza and RSV active period and number of active weeks according to broad definition

Year	Active weeks			Inactive weeks			No. of active weeks
	<1 year	1–4 years	5–14 years	<1 year	1–4 years	5–14 years	
1994/95	80491	393072	958342	41924	208262	509486	22
1995/96	55445	274699	685557	76674	376913	947064	14
1996/97	67700	313479	803187	82850	380626	982392	15
1997/98	98911	459805	1237457	55730	261737	703763	21
1998/99	80727	366577	995012	101877	457277	1249411	15
1999/00	75169	349196	955037	109955	511910	1403246	14
Total	458443	2156828	5634592	469010	2196725	5795362	101

Figure 1 Weekly incidence rate per 100 000 persons of (A) influenza-like illness, (B) acute bronchitis, (C) asthma, and (D) otitis media compared with influenza virus isolates and respiratory syncytial virus (RSV) reports: three week moving average by age over years 1994 to 2000.

years and in the relative impact of each virus. For ILI, in each of the age groups, estimates for the influenza period exceed those in the RSV period in 1994/95, 1997/98 (except children <1 year), and 1998/99: rates were similar in remaining winters. For acute bronchitis (except 1995/96 and 1996/97), the estimates attributed to RSV are substantially higher than to influenza. For asthma, only in 1995/96 and 1997/98 was there any evidence of excess during influenza active periods. There were several negative estimates in the influenza active period, and taken as an average over the six winters, the incidence of asthma did not increase during influenza active periods. There were however substantial excesses of asthma in RSV periods every winter. For otitis media, cumulative winter excess rates in children 1–4 years were slightly higher in RSV than in influenza virus active periods, but in other age groups they were similar.

In table 4 we report the relative proportions of excess diagnoses in each age group averaged over the six winters in the respective influenza virus and RS virus active periods, as calculated in the *broad* and *narrow* definitions of virus active period. For ILI in children less than 1 year (as an example), allocation of the estimate of excess ILI cases according to the *broad definition* ($n = 30\,352$ over the six winters) was 54% to influenza and 46% to RSV, but based on the *narrow definition* ($n = 23\,990$), the excess was distributed more towards influenza (66%/34%). As expected, the numerical estimates derived from the *narrow definition* were less than those derived from the *broad definition* (mostly 25–50% less, data not presented). Using the *narrow definition*, the proportion of ILI attributed to influenza increased from 60% to 77%, for acute bronchitis it decreased from 37% to 32%, for asthma from 9% to 0%, and for otitis media from 48% to 45%. The *narrow*

Table 3 Average weekly baseline incidence (per 100 000) in virus non-active periods by diagnosis and age group

Year	ILI			Acute bronchitis			Asthma			Otitis media		
	<1	1–4	5–14	<1	1–4	5–14	<1	1–4	5–14	<1	1–4	5–14
94/95	24	36	20	596	258	77	100	150	92	664	605	180
95/96	34	44	33	600	282	83	98	132	73	699	698	214
96/97	21	27	19	590	253	71	74	128	71	565	529	157
97/98	13	28	21	474	236	73	54	103	73	528	551	155
98/99	20	20	18	361	147	49	39	90	58	379	382	114
99/00	10	11	10	410	165	42	43	79	47	387	388	111

Figure 2 Cumulative excess incidence per 100 000 of (A) influenza-like illness, (B) acute bronchitis, (C) asthma, and (D) otitis media, allotted to influenza and respiratory syncytial virus (RSV) active periods for age bands <1, 1-4, and 5-14 years over winters 1994/95 to 1999/00.

definition increases the relative importance of RSV for all conditions except ILI. The estimates derived by using other definitions of virus active periods, including greater proportions of virus reports, were similar to those found for the *broad definition*.

DISCUSSION

The findings of this study suggest:

- The overall impact of RSV on respiratory illnesses in children of all ages exceeds that due to influenza.
- ILI is diagnosed more frequently in periods subsequently established as influenza active than those established as RSV active. However, there remain substantial numbers of

cases of ILI reported in RSV active periods in all age groups.

- Excess incidence of acute bronchitis during periods of RSV activity in age groups <1, and 1-4 years is twice that seen during influenza active periods: in children 5-14 years the excess incidence rates were similar.
- Asthma episodes occur much less frequently than acute bronchitis and are not increased during most influenza periods, whereas they are substantially increased in RSV periods in all three age groups.
- Otitis media is increased equally during RSV and influenza active periods. In children 1-4 and 5-14 years, excess incidence exceeded that for each of the other diagnoses.

Table 4 Ratio % of mean winter estimate of excess GP episodes allotted to influenza and RSV active periods as defined *broad* or *narrow*

		Influenza/RSV % of total			
		<1 years	1-4 years	5-14 years	All ages
Influenza-like illness	Broad	54/46	58/42	62/38	60/40
	Narrow	66/34	72/28	80/20	77/23
Acute bronchitis	Broad	32/68	32/68	49/51	37/63
	Narrow	26/74	26/74	48/52	32/68
Asthma	Broad	0/100*	12/88	12/88	9/91
	Narrow	0/100*	0/100*	0/100*	0/100*
Otitis media	Broad	45/55	45/55	52/48	48/52
	Narrow	43/57	41/59	51/49	45/55

*Negative values are entered as zero.

What is already known on this topic

- Influenza and respiratory syncytial virus are well recognised causes of regular winter respiratory infections
  - The relative impact of each is unclear
- The incidence of respiratory infections during winter outside the periods of influenza and RSV activity declined over the six winters as has been reported previously from WRS data based on all ages.²⁰ Influenza and RS viruses are highly variable from year to year and these cannot usefully be evaluated for trend in a limited six winter period.

The conclusions relating to the impact of influenza and RS virus are reinforced by the analysis using the *narrow definition* of active periods to try and separate their impact. The implications of these findings can be considered in two areas: clinical diagnosis and vaccination policy.

Clinical diagnosis

There is always considerable variability in operational research using general practice diagnoses unsubstantiated in individual cases by virological investigation. However, this study is comparing the effects of RSV and influenza in a clinical environment in which there is no selective bias in favour of one organism or the other. It was of particular interest to note the relative precision of the diagnosis of ILI during influenza active periods and of acute bronchitis during RSV active periods. The importance of lower respiratory tract clinical signs in the diagnosis of these two conditions could perhaps be exploited to greater clinical effect in routine clinical practice, though the distinction can never be regarded as absolute. Influenza and RSV active periods were least separable in winters 1995/96 and 1996/97, creating the maximum difficulty for allotting excesses to each of the conditions separately. This fact probably affected the results for asthma: in the remaining winters excess incidence was more clearly associated with RSV active periods. In a study of elderly hospitalisations, Falsey *et al* noted increased likelihood of wheeze in RSV as opposed to influenza infection.²¹ Furthermore the well recognised syndrome of bronchiolitis in young children is associated with lower respiratory tract clinical signs and mostly due to RSV.

In the analysis based on the *broad definition* of influenza virus and RS virus active periods, the cumulative excess incidence of all diagnoses attributed to both influenza and RSV exceeded those based on the *narrow definition*. Using either definition, estimates of excess incidence of otitis media in age groups 1–4 and 5–14 years slightly exceeded those for acute bronchitis and both substantially exceeded those for ILI and asthma. In children <1 year, estimates of the excess incidence of acute bronchitis exceeded the others.

Vaccination policy

These results emphasise the need for effective vaccines and treatments against disease caused by RSV. They further strongly support the inclusion of otitis media and of acute bronchitis as important end points in the evaluation of vaccine efficacy and effectiveness studies for interventions involving both viruses.^{22–24} Current NHS policy in the UK recommends that asthmatic children aged 2 years and over should be vaccinated against influenza. The basis of this policy stems largely from the accumulated evidence from adults with asthma and chronic obstructive pulmonary

What this study adds

- RSV is more important than influenza as a cause of respiratory infection in children <1 year and 1–4 years
- In children 5–14 years the overall impact of each virus was virtually the same
- Excess morbidity diagnosed as asthma was found solely in RSV periods
- There were more excess episodes of otitis media during active virus periods than each of the other conditions, and almost equal proportions were attributable to influenza and RSV

disease.² Viral respiratory infections, generally though not influenza specifically, are recognised as a major cause of exacerbation of asthma.^{12–13} Our findings challenge the need for routine vaccination of healthy children because of the risk of asthma attacks occurring as a complication of influenza infection. This is not to be confused with the vaccination of asthmatic children; though, with no increased asthma detected during influenza active periods there would appear little likelihood of increased asthma attacks in asthmatic children. Seasonal patterns of episodes of asthma in children presenting to general practitioners as reported in the WRS are very similar to patterns of hospital admission for asthma.¹⁰ Our results accord with the findings of Bueving *et al* who studied asthma in a randomised trial of influenza vaccine in asthmatic children aged 6–18 years in 1999/00 and 2000/01; and with the Cochrane review of the benefits of influenza vaccination in childhood asthmatics.^{1–25}

ACKNOWLEDGEMENTS

We gratefully acknowledge the contribution of the WRS sentinel practices and their staff to providing the GP episode data. The Birmingham Research Unit of the Royal College of General Practitioners is funded by the Department of Health.

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Competing interests: none

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