
SHORT REPORT

Timing of monoclonal antibody for seasonal RSV prophylaxis in the United Kingdom

N. L. GODDARD, M. C. COOKE, R. K. GUPTA AND J. S. NGUYEN-VAN-TAM*

Health Protection Agency Centre for Infections, London, UK

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SUMMARY

Respiratory syncytial virus (RSV) infection produces more severe disease and increased hospitalization rates in high-risk babies. The monoclonal antibody palivizumab offers protection against complications, and the first of five monthly doses should be administered before the onset of community RSV activity. However, the required real-time prediction of this onset is problematic. We attempted to identify seasonal RSV patterns by retrospectively examining 10 years of laboratory reports for RSV and clinical episode reports for certain respiratory presentations in both primary and secondary care. Analysis of hospital laboratory reports, incidence of acute bronchitis in primary care, and hospital admissions for acute bronchitis and bronchiolitis in young children revealed a consistent increase in RSV activity during week 43 each year. Promptly commencing prophylaxis during the second week of each October (week 42) would precede the onset of the RSV season in the United Kingdom, and provide coverage until its decline in mid-March.

Respiratory syncytial virus (RSV) is the most common cause of lower respiratory tract infection in young children; its manifestations include bronchiolitis in infants/young children, and acute bronchitis in older children [1, 2]. Approximately 80% of children are infected by 2 years of age, but re-infection can occur throughout life. RSV infection is the commonest cause of hospitalization in children aged <1 year [3], and it causes more severe disease in high-risk infants. Early data suggest a possible association between RSV infection in children with chronic lung disease who were born prematurely, and chronic respiratory morbidity [4]. The UK Joint Committee on Vaccination and Immunisation advises that the RSV-monoclonal antibody, palivizumab, should be offered prophylactically to babies under 2 years of age

with severe chronic lung disease, who are on home oxygen during the RSV season and on a case-by-case basis for babies with rare conditions such as multiple congenital abnormalities or severe immunodeficiency [5].

Thresholds for community influenza activity are used to trigger the use of neuraminidase inhibitors in high-risk patients [6, 7], although the intervention of choice in these patients remains prevention through vaccination. In contrast, RSV activity cannot be employed in the same way to trigger the use of palivizumab. Laboratory data are subject to reporting delays, and therefore cannot be used for real-time decision making. In addition, the first dose of palivizumab should be given prior to the onset of RSV activity and there are limited data to support its use beyond five doses at monthly intervals. Thus, waiting until laboratory data indicate that RSV is circulating risks starting therapy too late; conversely, starting therapy too far in advance of RSV activity risks giving

* Author for correspondence: Dr Jonathan Van-Tam, Respiratory Department, Centre for Infections, Health Protection Agency, 61 Colindale Avenue, London NW9 5EQ, UK.
(Email: jonathan.vantam@hpa.org.uk)

the fifth monthly dose too early to cover the end of the RSV season. Timing the use of palivizumab would be optimized by increasing clarity over the precise onset of the RSV season.

This retrospective study aimed to identify patterns in seasonal RSV activity by examining 10 years of laboratory data on RSV isolations, the incidence of acute bronchitis in primary care, and hospitalizations for bronchiolitis/bronchitis in children aged <5 years.

Virological data sources were as follows: laboratory reports of positive RSV detections made to the Health Protection Agency (HPA) from approximately 300 NHS/private hospital laboratories between 1994 and week 20 of 2004; laboratory reports of RSV from community-derived virological sampling undertaken by the Enteric, Respiratory and Neurological Virus Laboratory (ERNVL) between 1999 and 2004. Samples tested included nasopharyngeal aspirates, nose/throat swabs, and bronchoalveolar washings. Methods for RSV testing included antigen detection by immunofluorescence and nucleic acid detection by polymerase chain reaction (PCR) assays, but excluded viral culture. Denominators and, therefore, rates of confirmed RSV could not be calculated as criteria and thresholds for RSV testing vary between individual hospitals and individual GPs. It was, therefore, not possible to determine the proportion of symptomatic patients tested.

Clinical data sources comprised: Royal College of General Practitioners (RCGP) sentinel practice episode rates for influenza-like illness (ILI), acute bronchitis and total respiratory disease (TRD) between 1994 and 2004; NHS Direct total call rates, and percentage of calls assigned to 'colds/flu' or 'cough' algorithms between 2001 and 2004; hospital admissions based on age between 1993 and 2003 with a respiratory discharge diagnosis, obtained from Hospital Episode Statistics (HES). Notably, the RCGP episode rate did not include a specific category for bronchiolitis.

These virological and clinical data were graphed against each other by year to identify associations which might predict the beginning and end of RSV activity each season.

Hospital RSV samples were highly skewed towards the very young (91% from children aged 0–4 years). In contrast, although 5000 community specimens were submitted during this time to ERNVL, only 8% were obtained from children aged <5 years. This was most probably due to difficulties in obtaining samples from this age group in general practice, and

consequently ERNVL data proved of no value for the study.

Associations were noted between hospital laboratory reports of RSV from patients aged 1 month to 4 years (by date of specimen) and both RCGP episode rates for acute bronchitis and the number of hospital admissions for acute bronchitis and bronchiolitis, among children aged 0–4 years (Fig.). Complete data from these three sources were available between 1998/99 and 2002/03 RSV seasons, and in each season RCGP acute bronchitis episode rates rose above 250/100 000 population during the same week that 100 or more positive detections of RSV were made. Hospital admissions rose rapidly 2–4 weeks after this point was reached (Table). Laboratory reports of RSV decreased below 50 per week after early March (week 10), but episode rates for acute bronchitis tended to fluctuate without the same obvious decline. No clear associations were apparent between episode rates for ILI, TRD or NHS Direct data and either community/hospital RSV laboratory reports (data not shown).

In order to appreciate the significance of the results presented in this study, it is necessary to be clear why laboratory data are unsuitable for making real-time decisions about the onset of RSV activity. The laboratory reports of RSV from private and NHS laboratories represent positive detections only, without denominators. Thus, it is not possible to assess the proportion of specimens positive in any given week, which is considered to be a more reliable indicator of increasing activity than the number of positive specimens alone. In addition, reporting delays of up to several weeks prevent these data being used for real-time decision making. Retrospective analyses by date of specimen, as described in this study, are possible and more accurately reflect the timing of clinical illness. By combining hospital laboratory data with community data on acute bronchitis in children aged 0–4 years, the study demonstrates that an obvious upsurge in RSV activity occurs during mid-October each year (week 43). The timing of this upsurge appears so consistent that we conclude it can be used to advise clinicians about starting palivizumab in high-risk babies and children.

If prophylaxis with palivizumab were to be started promptly during the second week in October each year (week 42), this would almost always be just before the onset of RSV activity in the United Kingdom. Subsequently, the last of five consecutive monthly doses would be administered in the second

Table. Timing of increase in weekly episode rates for acute bronchitis, laboratory reports of RSV and hospital admissions for bronchiolitis and bronchitis in children aged 0–4 years

Winter season	Episode rate: acute bronchitis (0–4 years)		RSV laboratory reports from 300 laboratories around the UK (1 month to 4 years)		UK NHS Hospital admissions: bronchitis and bronchiolitis (0–4 years)	
	Week no. (in which episode rate ≥ 250)	GP episode rate for acute bronchitis that week (per 100 000 population)	Week no. (in which reports > 100)	Cases of laboratory-confirmed RSV that week	Week no. (in which admissions > 100)	No. of UK NHS hospital admissions that week
1998/99	43	254	43	149	46	99
1999/00	42	293	42	144	45	125
2000/01	43	250	43	107	47	166
2001/02	45	271	45	133	47	104
2002/03	43	287	43	134	46	128
2003/04	43	251	47	143	n.a.	n.a.

n.a., Not available.

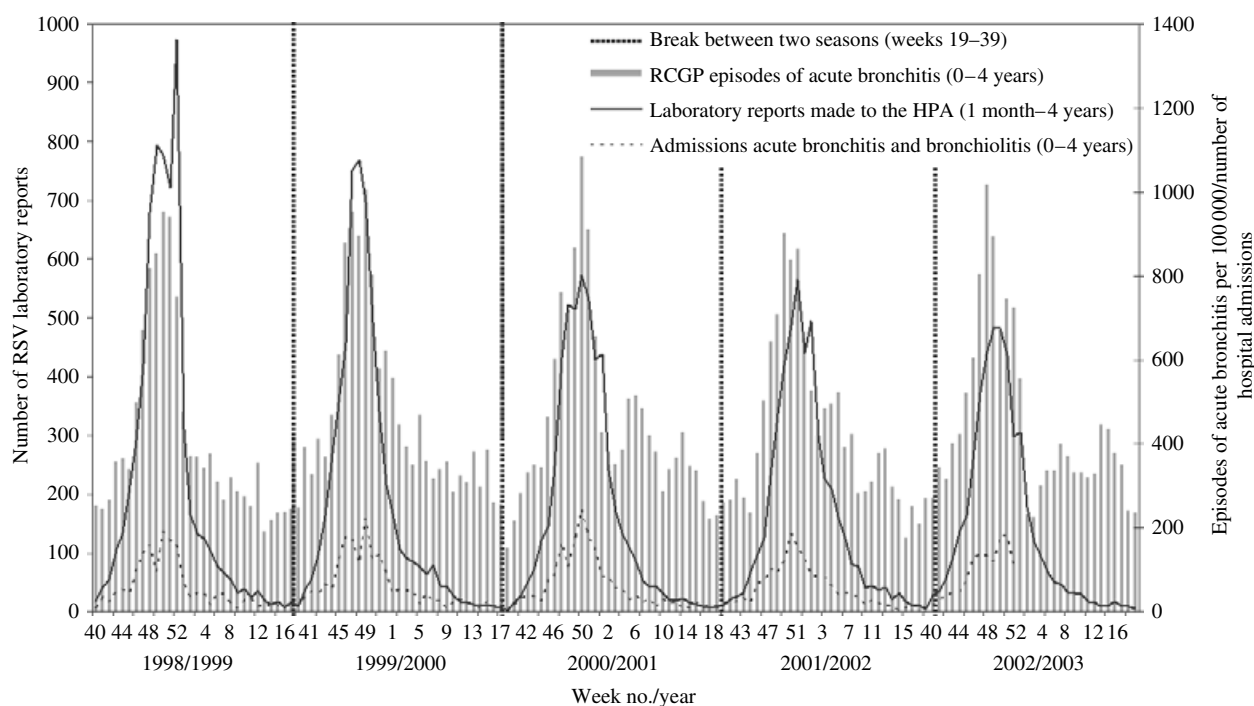


Fig. RCGP episode rates for acute bronchitis, laboratory reports of RSV received by HPA Centre for Infections, and hospital admissions between 1998/1999 and 2002/2003.

week of February (week 6). This would provide coverage until mid-March, by which time RSV detections tend to have fallen back to low levels with hospital admissions for acute bronchitis and bronchiolitis declining substantially. There remains only a small risk of infections outside the peak period associated with low levels of background activity. Finally, it should be borne in mind that our findings

apply to the United Kingdom and that parallel analyses would be needed in order to correctly time palivizumab prophylaxis in other countries.

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DECLARATION OF INTEREST

None.

REFERENCES

1. **Crowcroft NS, et al.** Respiratory syncytial virus: an underestimated cause of respiratory infection, with prospects for a vaccine. *Communicable Disease and Public Health* 1999; **2**: 234–241.
2. **Fleming DM, et al.** *A Winter's Tale: coming to terms with winter respiratory illnesses*. London: Health Protection Agency, 2005.
3. **Müller-Pebody B, et al.** Contribution of RSV to bronchiolitis and pneumonia-associated hospitalizations in English children, April 1995–March 1998. *Epidemiology and Infection* 2002; **129**: 99–106.
4. **Greenough A, et al.** Health care utilisation of prematurely born, preschool children related to hospitalisation for RSV infection. *Archives of Disease in Childhood* 2004; **89**: 673–678.
5. **Joint Committee on Immunisation and Vaccination.** Meeting minutes, 1 November 2002. London, UK. (<http://www.advisorybodies.doh.gov.uk/jcvi/mins01nov02.htm>). Accessed 1 April 2006.
6. **Goddard NL, et al.** Appropriateness of thresholds currently used to describe influenza activity in England 2003. *Communicable Disease and Public Health* 2003; **6**: 238–245.
7. **National Institute for Clinical Excellence.** Technology Appraisal No. 58: Guidance on the use of zanamivir, oseltamivir and amantadine for the treatment of influenza. London: National Institute for Clinical Excellence, 2003. (http://www.nice.org.uk/pdf/58_Flu_fullguidance.pdf). Accessed 1 April 2006.