

# Respiratory viral infection and wheezy bronchitis in childhood

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**ABSTRACT** The role of respiratory viral infection in wheezy bronchitis was studied in 163 children, aged 0-12 years, in a London general practice. Virological investigations were also performed when these same children had acute upper respiratory illness without wheeze. A virus was isolated in 146 (26.4%) of 554 episodes of wheezy bronchitis, rhinoviruses accounting for almost half of the isolations. The relative frequency with which individual viruses were isolated in wheezy bronchitis was similar to that in acute upper respiratory illness in 180 other children who had never had wheezy bronchitis. The large number of isolations of rhinoviruses in wheezy bronchitis is probably due to their numerous serotypes and the absence of cross-immunity between them. Our findings have confirmed that infection by respiratory viruses can provoke wheezy bronchitis in certain children, in whom host factors are an important predeterminant. In children with a previous history of wheezy bronchitis infection by rhinoviruses was associated significantly more often with such an episode than with upper respiratory illness. The maturation of protective mechanisms, including the acquisition of specific immunity to a progressively larger number of viruses, could explain the fall in the age-incidence of wheezy bronchitis.

In a survey of all forms of acute respiratory illness in children, aged 0-12 years, in a London general practice (Gregg, 1970, 1975; Horn *et al.*, 1975), one of our principal aims was to elucidate the role of viral infection in wheezy bronchitis. We have used this term to denote episodes of illness whose salient features are cough and the presence on auscultation of wheeze in addition to crackles. We used the term wheeze to signify an objective finding that we defined as a high-pitched sound, usually more pronounced during expiration, and audible over most parts of the chest.

Wheezy bronchitis is one of the most common forms of respiratory illness in childhood. Other terms used to describe these episodes, such as spastic bronchitis and bronchitis asthmatoïdes, testify to their close resemblance to asthma. Williams and McNicol (1969) considered wheezy bronchitis and asthma to be polar extremes of a single disorder with a common underlying abnormality, but most paediatricians and general practitioners prefer to make a distinction between

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them, on the ground that many children with wheezy bronchitis do not exhibit wheeze under any other circumstances. For the purposes of this paper we have not distinguished between episodes of wheezy bronchitis occurring in children whom we regarded as having asthma (because of their liability to wheeze under a variety of other circumstances) and episodes in other children in whom wheeze had been recorded only in association with bronchitis. Our findings with respect to skin test reactivity, family history, and response to exercise will be reported elsewhere.

This paper reports the virological findings in 554 episodes of wheezy bronchitis that occurred in 163 children during the five-year survey (October 1967 to December 1972). We have compared the findings with those made when these same children had acute upper respiratory illness and also with the findings in acute upper respiratory illness in a control group of 180 children who had never had wheezy bronchitis.

## Methods

Virological investigations were performed in any

child, aged less than 13 years, in whom symptoms of acute respiratory illness had begun within the previous five days. So far as possible all children who had wheezy bronchitis were investigated in every subsequent acute respiratory illness.

Swabs were taken from the nose and throat and the specimens were placed in transport medium (Hanks's BSS with bovine albumin) and chilled on icepacks until they were delivered to the laboratory. The three cell cultures used for the isolation of viruses were HEp-2, diploid human embryo lung fibroblasts (W1-38), and primary rhesus monkey kidney cells. A selective diphasic medium and supplemented Difco PPLO agar plates were used for the isolation of *Mycoplasma pneumoniae*. Rhinoviruses were serotyped at the Virus Reference Laboratory, Colindale.

In children old enough to co-operate, peak expiratory flow (PEF) was measured during episodes of wheezy bronchitis and after recovery. In a few children reversibility of airflow obstruction during episodes of wheezy bronchitis was assessed by noting the rise of PEF after inhalation of isoprenaline or salbutamol aerosol. The observed rise was expressed as a percentage of that which would have restored PEF to the highest value attained in remission.

## Results

In January 1971 919 children aged 0-12 years were registered with the practice. During the survey 163 children (111 boys and 52 girls) were investigated in one or more episodes of wheezy bronchitis. The seasonal incidence was highest from September to December. Of the 554 episodes investigated, 372 occurred in boys and 182 in girls (MF ratio 2:1). Most episodes (42%) occurred in children aged 4-7 years, 34% in children aged 0-4, and 24% in children aged 8-12.

The number of episodes investigated per child ranged from one in 41·7% to four or more in 28·9% of the children. The strong tendency of wheezy bronchitis to recur was shown by the finding that 480 (86·5%) of the 554 episodes occurred in children who had had at least one previous episode, while of the 74 children investigated during their first episode, 58 (78·4%) had at least one subsequent episode.

The severity of episodes varied greatly, from those in which wheeze was not accompanied by dyspnoea to those in which there was severe respiratory distress. Only one child was admitted to hospital with wheezy bronchitis during the survey: two infants, who later became subject to

wheezy bronchitis, were admitted, one with bronchiolitis and one with pneumonia.

A virus was isolated in 146 of the 554 episodes of wheezy bronchitis (table 1). On 31 occasions children with a history of wheezy bronchitis were investigated when they had no symptoms, only one isolation being made (table 1). There was a highly significant difference ( $\chi^2=8.35$ ,  $P<0.005$ ) between the isolation rate in remission (3·2%) and that in wheezy bronchitis (26·4%).

The number and relative frequency of individual viruses isolated in wheezy bronchitis are shown in table 2. Rhinoviruses were isolated far more often than any other virus in children of all ages (fig 1): of the 28 serotypes identified, only four (types 1B, 4, 15, and 31) were isolated in five or more episodes.

Of the 163 children investigated in an episode of wheezy bronchitis, 105 children were also investigated when they had an upper respiratory illness without wheeze. The relative frequency

Table 1 Isolations of viruses and *M pneumoniae* in wheezy bronchitis and in remission

	No of episodes investigated	No of episodes in which isolations were made			Isolation rate
		Single	Double	Total	
Wheezy bronchitis	554	140	6	146	26·4%
Remission	31	1	0	1	3·2%

Table 2 Relative frequency of viruses isolated in wheezy bronchitis (including double isolations)

Viruses	No of isolations	Relative frequency
Rhinoviruses	70	46·1%
Parainfluenza viruses		
Type 1	7	
2	2	
3	6	
4a	1	
4b	6	
Enteroviruses	22	14·5%
Coxsackie A	9	
Coxsackie B	12	
Echovirus	1	
Respiratory syncytial virus	12	7·9%
Influenza A virus	8	5·2%
Influenza B virus	3	1·9%
Adeno viruses	5	3·3%
<i>Mycoplasma pneumoniae</i>	10	6·6%
	152	100·00%
<i>Double isolations</i>		
Rhinovirus and parainfluenza virus 4b	(2)	
Coxsackie virus A and parainfluenza virus 1	(1)	
Coxsackie virus A and parainfluenza virus 3	(1)	
Coxsackie virus A and Coxsackie B	(1)	
Coxsackie virus B and <i>M pneumoniae</i>	(1)	

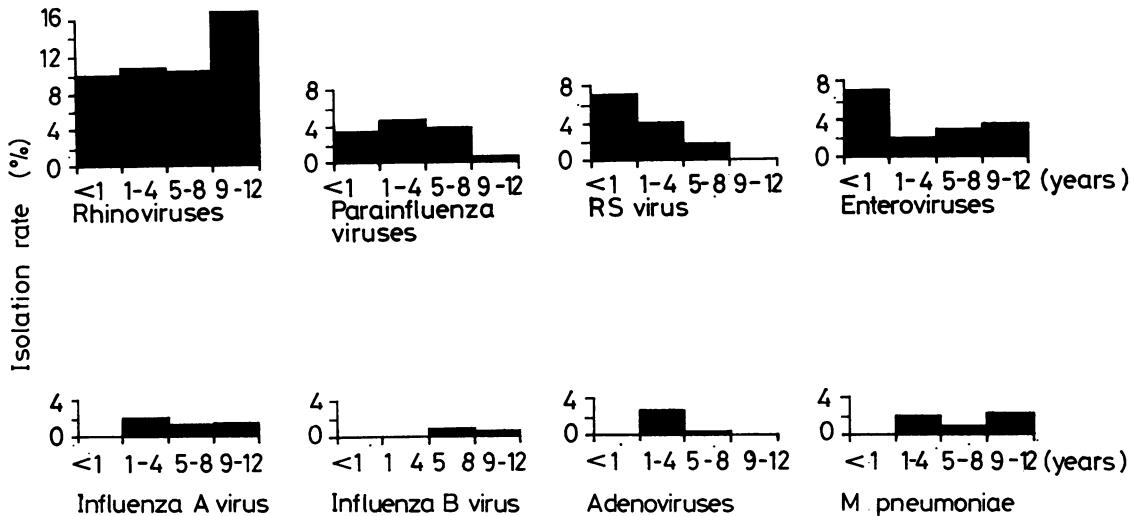


Fig 1 Age-distribution of infection by individual agents in wheezy bronchitis.

with which individual viruses were isolated in the two forms of illness was compared. Some children had been investigated in many more episodes of wheezy bronchitis or upper respiratory illness, or both, than others, but this source of bias was eliminated by randomly selecting one episode of each form of illness from every child. The isolation rates so obtained were almost identical (28.6% in wheezy bronchitis and 29.5% in upper respiratory illness). Highly significant differences were found, however, in the frequency with which rhinoviruses and parainfluenza viruses were isolated in the two forms of illness. The former were isolated far more often in wheezy bronchitis than in upper respiratory illness ( $\chi^2=11.36$ ,  $P<0.001$ ), whereas parainfluenza viruses were isolated more often in upper respiratory illness ( $\chi^2=6.03$ ,  $P<0.02$ ).

Despite the frequency with which children subject to wheezy bronchitis were investigated in all forms of acute respiratory illness, a given virus (or serotype) was isolated more than once in the same child on only 12 occasions, in 11 of which the length of time separating the isolations suggested reinfection rather than carriage. In five of these children, four of whom were reinfected by rhinoviruses, wheezy bronchitis occurred with the first episode of infection but not with reinfection. In two other children, also reinfected by rhinoviruses, wheezy bronchitis occurred with both the first and subsequent episodes of infection but in each case reinfection was associated with a clinically less severe episode than had occurred with the previous infection.

The age-incidence of infection by individual viruses in wheezy bronchitis (fig 1) was compared with that in acute upper respiratory illness in the control group of children (fig 2). No major differences emerged. The distribution of rhinovirus serotypes was similar in the two forms of illness.

In 38 episodes of wheezy bronchitis the mean rise of PEF after inhalation of a bronchodilator aerosol was only 35.1% (SD 21.4) of that which would have restored it to the highest value attained during remission.

## Discussion

An association between respiratory viral infection and wheezy bronchitis in children has been reported by many other investigators (Gardner *et al*, 1960; Freeman and Todd, 1962; Reilly *et al*, 1962; Holzel *et al*, 1963; Berkovich *et al*, 1970; Glezen *et al*, 1971; Jacobs *et al*, 1971; Maletzky *et al*, 1971; McIntosh *et al*, 1973; Minor *et al*, 1974a; Minor *et al*, 1976; Mitchell *et al*, 1976). There are good grounds, which we have discussed elsewhere (Horn and Yealland, 1974; Horn *et al*, 1975), for believing that the isolation of a virus in an episode of acute respiratory illness generally indicates a causal association. Although in the present study a virus was isolated in only 26.4% of episodes of wheezy bronchitis, this does not preclude the possibility of viral infection having occurred in the remainder. Several technical factors reduce the chances of isolation, such as obtaining insufficient infected epithelial cells during swabbing, the failure of viruses to survive during

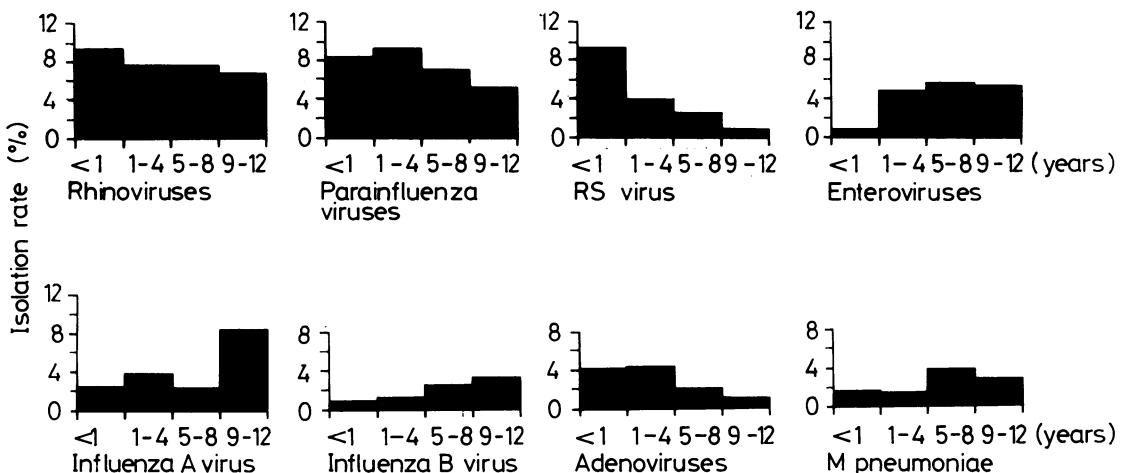


Fig 2 Age-distribution of infection by individual agents in upper respiratory illness in control children.

transport to the laboratory, and insensitivity of cell cultures, particularly those used for the isolation of rhinoviruses (Brown and Tyrrell, 1964).

The mechanisms underlying the provocation of wheezy bronchitis by viral infection remain obscure. Probably, however, they depend on the presence of viral infection in the bronchi themselves. Evidence in support of this proposition has come from a subsequent study, to be reported elsewhere, in which a virus was isolated from sputum in 43% of 72 episodes of wheezy bronchitis.

We found no evidence to support the hypothesis that previously acquired hypersensitivity to viral antigen is an aetiological factor in wheezy bronchitis. Possibly, of course, some of the episodes of wheezy bronchitis which we observed were, unknown to us, instances of reinfection. Of those few episodes of proved reinfection, however, which occurred in children with a previous history of wheezy bronchitis, almost all were associated with merely upper respiratory illness. Thus our findings suggest that immunity to a given virus, acquired at the time of primary infection, usually suffices to prevent the occurrence of wheezy bronchitis on subsequent infection by that virus.

Our finding, which accords with those of other investigators, that a wide variety of respiratory viruses were isolated in wheezy bronchitis suggests that the provocation of these episodes is a non-specific effect of viral infection. There were striking differences, however, between individual viruses in the relative frequency with which they were isolated. Two factors could account for these

differences. Firstly, certain viruses may be encountered more often than others and, secondly, viruses may differ in their inherent capacity to provoke wheezy bronchitis.

The broad similarity between the age-distribution of individual viruses in wheezy bronchitis and that in upper respiratory illness in control children (figs 1 and 2) suggests that the relative frequency with which they provoke wheezy bronchitis is a reflection of the relative frequency with which they infect all children of a given age. On the other hand, the striking difference between rhinoviruses and parainfluenza viruses in the form of illness that ensued when they infected children with a previous history of wheezy bronchitis might appear at first sight to be evidence of a difference in their propensity to provoke wheezy bronchitis. This finding, however, could have arisen if most rhinovirus isolations had been cases of primary infection and if most parainfluenza virus isolations had been cases of re-infection (and, therefore, less likely to provoke wheezy bronchitis). The likelihood of infection by a rhinovirus being primary must be greater than in the case of infection by a parainfluenza virus, especially in older children. Whereas there are only five parainfluenza virus serotypes, more than a hundred serotypes of rhinoviruses have now been classified (Melnick *et al*, 1974). Some rhinovirus serotypes are isolated much more commonly than others, but this does not necessarily imply that there are true differences in their prevalence, since it may be due merely to the greater ease with which some serotypes can be grown in tissue culture (Roebuck, 1976). Epidemiological studies in

nursery schoolchildren (Beem, 1969), military recruits (Rosenbaum *et al*, 1971) and families (Minor *et al*, 1974b) suggest that infection by one serotype does not generally confer cross-immunity against others.

Other investigators have reported an association between rhinovirus infection and wheeze in children and adults (Jacobs *et al*, 1971; Lambert and Stern, 1972; Minor *et al*, 1974a; Minor *et al*, 1976; Mitchell *et al*, 1976) but the number of episodes that they investigated was far smaller than in the present study.

Although all children are infected by respiratory viruses, wheezy bronchitis occurs in only a minority, in whom there is a pronounced tendency for episodes to recur. These considerations suggest the agency of host factors, as does the higher incidence of episodes in boys. One such host factor may be a defect in the protective mechanisms of the lower respiratory tract against viral infection. Minor *et al* (1974c) carried out a longitudinal study in 16 children with asthma and 15 of their non-asthmatic siblings and showed that the former had a higher incidence of infection by rhinoviruses, which generally precipitated an attack of asthma. The maturation with increasing age of the defence mechanisms of the lower respiratory tract against viral infection could explain the decline in age-incidence of wheezy bronchitis, a further contributory factor being the acquisition of specific immunity to an increasingly large number of respiratory viruses.

We found that only a small part of airflow obstruction in wheezy bronchitis was reversible by bronchodilators. A similar finding has been reported by Rutter *et al* (1975) who considered that mucosal oedema and mucus secretions were responsible for the refractory airflow obstruction. This would be consistent with our observation that in severe episodes steroid treatment brought about a more rapid reduction in the severity and duration of airflow obstruction than occurred in less severe episodes that were not so treated.

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## References

- Beem, M O (1969). Acute respiratory illness in nursery schoolchildren: a longitudinal study of the occurrence of illness and respiratory viruses. *American Journal of Epidemiology*, **90**, 30-44.
- Berkovich, S, Millian, S J, and Snyder, R D (1970). The association of viral and mycoplasma infections with recurrence of wheezing in the asthmatic child. *Annals of Allergy*, **28**, 43-49.
- Brown, P K, and Tyrrell, D A J (1964). Experiments on the sensitivity of strains of human fibroblasts to infection with rhinoviruses. *British Journal of Experimental Pathology*, **45**, 571-578.
- Freeman, G L, and Todd, R H (1962). The role of allergy in viral respiratory tract infections. *American Journal of Diseases in Children*, **104**, 330-334.
- Gardner, P S, Stanfield, J P, Wright, A E, Court, S D M, and Green, C A (1960). Viruses, bacteria, and respiratory disease in children. *British Medical Journal*, **1**, 1077-1081.
- Gelezen, W P, Loda, F A, Clyde, W A, Senior, R J, Sheaffer, C I, Conley, W G and Denny, F W (1971). Epidemiologic patterns of acute lower respiratory disease of children in a pediatric group practice. *Journal of Pediatrics*, **78**, 397-406.
- Gregg, I (1970). A study of recurrent bronchitis in childhood. *Respiration*, **27** suppl, 133-138.
- Gregg, I (1975). The role of viral infection in asthma and bronchitis. In *Symposium on Viral Diseases*, edited by A T Proudfoot, pp 82-98. *Royal College of Physicians of Edinburgh*.
- Holzel, A, Parker, L, Paterson, W H, White, L L R, Thompson, K M, and Tobin J O'H (1963). The isolation of respiratory syncytial virus from children with acute respiratory disease. *Lancet*, **1**, 295-298.
- Horn, M E C, Brain, E, Gregg, I, Yealland, S J, and Inglis, J M (1975). Respiratory viral infection in childhood. A survey in general practice. *Roe-hampton 1967-72. Journal of Hygiene*, **74**, 157-168.
- Horn, M E C, and Yealland, S J (1974). Significance of respiratory virus isolations. A study in primary schoolchildren. *Archives of Disease in Childhood*, **49**, 516-519.
- Jacobs, J W, Peacock, D B, Corner, B D, Caul, E O, and Clarke, S K R (1971). Respiratory syncytial and other viruses associated with respiratory disease in infants. *Lancet*, **1**, 871-876.
- Lambert, H P, and Stern, H (1972). Infective factors in exacerbations of bronchitis and asthma. *British Medical Journal*, **3**, 323-327.
- Maletzky, A J, Cooney, M K, Luce, R, Kenny, G E, and Grayston, J T (1971). Epidemiology of viral and mycoplasmal agents associated with childhood lower respiratory illness in a civilian population. *Journal of Pediatrics*, **78**, 407-414.
- McIntosh, K, Ellis, E F, Hoffman, L S, Lybass, T G, Eller, J J, and Fulginiti, V A (1973). The association of viral and bacterial respiratory infections with exacerbations of wheezing in young asthmatic children. *Journal of Pediatrics*, **82**, 578-590.

- Melnick, J L, Agol, V L, Bachrach, H L, Brown, F, Cooper, P D, Fiers, W, Gard, S, Gear, J H S, Ghendon, Y, Kasza, L, La Placa, M, Mandel, B, McGregor, S, Mohanty, S B, Plummer, G, Rueckert, R R, Schaffer, F L, Tagaya, I, Tyrrell, D A J, Voroshilova, M, and Wenner, H A (1974). Picornaviridae. *Intervirology*, **4**, 303-316.
- Minor, T E, Dick, E C, DeMeo, A N, Ouellette, J J, Cohen, M, and Reed, C E (1974a). Viruses as precipitants of asthmatic attacks in children. *Journal of the American Medical Association*, **227**, 292-298.
- Minor, T E, Dick, E C, Peterson, J A, and Docherty, D E (1974b). Failure of naturally acquired rhinovirus infections to produce temporal immunity to heterologous serotypes. *Infection and Immunity*, **10**, 1192-1193.
- Minor, T E, Baker, J W, Dick, E C, DeMeo, A N, Ouellette, J J, Cohen, M, and Reed, C E (1974c). Greater frequency of viral respiratory infections in asthmatic children as compared with their non-asthmatic siblings. *Journal of Pediatrics*, **85**, 472-477.
- Minor, T E, Dick, E C, Baker, J W, Ouellette, J J, Cohen, M, and Reed, C E (1976). Rhinoviruses and influenza type A infections as precipitants of asthma. *American Review of Respiratory Disease*, **113**, 149-153.
- Mitchell, I, Inglis, H, and Simpson, H (1976). Viral infection in wheezy bronchitis and asthma in children. *Archives of Disease in Childhood*, **51**, 707-711.
- Reilly, C M, Hoch, S M, Stokes, J, McClelland, L, Hamparian, V V, Ketler, A, and Hillman, M R (1962). Clinical and laboratory findings in cases of respiratory illness caused by coryzaviruses. *Annals of Internal Medicine*, **57**, 515-525.
- Roebuck, M O (1976). Rhinoviruses in Britain 1963-1973. *Journal of Hygiene*, **76**, 137-146.
- Rosenbaum, M J, De Berry, P, Sullivan, E J, Pierce, W E, Mueller, R E, and Peckinpaugh, R O (1971). Epidemiology of the common cold in military recruits with emphasis on infections by rhinovirus types 1A, 2 and two unclassified rhinoviruses. *American Journal of Epidemiology*, **93**, 183-193.
- Rutter, N, Milner, A D, and Hiller, E J (1975). Effect of bronchodilators on respiratory resistance in infants and young children with bronchiolitis and wheezy bronchitis. *Archives of Disease in Childhood*, **50**, 719-722.
- Williams, H E, and McNicol, K N (1969). Prevalence, natural history, and relationship of wheezy bronchitis and asthma in children. An epidemiological study. *British Medical Journal*, **4**, 321-325.

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