

Viral infection in wheezy bronchitis and asthma in children

I. MITCHELL, H. INGLIS, and H. SIMPSON

From the Royal Hospital for Sick Children and City Hospital, Edinburgh

Mitchell, I., Inglis, H., and Simpson, H. (1976). *Archives of Disease in Childhood*, 51, 707. **Viral infection in wheezy bronchitis and asthma in children.** Virus isolation was attempted on 267 out of 360 patients with wheezy bronchitis or asthma admitted to hospital during a 3-year period. Viruses were isolated on 39 occasions, the most common being respiratory syncytial virus and rhinovirus. The peak months for virus isolation were February and August. Virus isolation was significantly more common in readmissions than in first admissions ($P < 0.01$). Viruses were isolated in both sexes throughout childhood and though the admission rate fell with increasing age, the isolation rate was unaffected. The possible significance of viral infection as a cause of acute attacks of wheezing in children is discussed.

Many factors, including bacterial and viral infections, are believed to precipitate attacks of wheezing in children. The evidence for bacterial infection is conflicting. Sanders and Norman (1968) failed to show an association between bacterial infection and episodes of wheezing in a study of hospital outpatients, whereas Eisen (1969) considered that bacterial infection was an important factor in precipitating exacerbations of wheeze. Reports of the relation of viral infections and wheezing have been concerned mainly with children strongly suspected of wheezing after upper respiratory tract infections and studies have generally been confined to the winter months (Freeman and Todd, 1962; Berkovich, Millian, and Snyder, 1970; McIntosh *et al.*, 1973; Minor *et al.*, 1974b). The most convincing evidence, showing a strong association between viral infection and wheezing in children, comes from a 5-year study in general practice (Horn *et al.*, 1975).

The present study was undertaken to determine the incidence, nature, and seasonal variation of viral infections in children admitted to hospital with wheezy bronchitis or asthma. Recent evidence suggests that both conditions are due to the same basic disorder (Williams and McNicol, 1969) and no attempt was made to separate them. The study was conducted without preconceived ideas about possible seasonal variation in viral infections, or

whether clinical features suggested that respiratory infection had precipitated an attack.

Patients and methods

From 1 November 1971 to 31 October 1974, 192 patients over one year of age were admitted with wheezy bronchitis or asthma to one 25-bed medical ward in the Royal Hospital for Sick Children, Edinburgh, on 360 occasions (Table I). The first admission refers to the

TABLE I
Number of admissions

	Boys	Girls	Total	Virus culture	
				No.	%
First admissions	126	66	192	141	73.4
Readmissions	98	70	168	126	75.0
Total admissions	224	136	360	267	74.1

study period though some had been admitted previously. Subsequent admissions are considered together as readmissions.

On the morning following admission throat and nasal swabs and, in the last year of the study, nasopharyngeal aspirates, were obtained and taken to the virus laboratory within one hour of collection. Specimens for virus culture were collected on 74.1% of all admissions and studies were performed irrespective of the duration of symptoms before admission. Omissions occurred mainly at the weekends. Virus cultures were carried out on

267 admissions, 75 of whom also had paired sera examined. Laboratory techniques have been described (Simpson *et al.*, 1974).

Age, sex, month of admission, age of onset of wheeziness, and family history were noted retrospectively from the case notes for each case. Investigations on each admission included haemoglobin, total and differential white count, chest *x*-ray, and bacterial culture of throat and nose swabs and sputum. Arterial or arterialized capillary blood gas analyses were performed in 71 (26.5%) admissions.

Hospital management usually included oral or inhaled salbutamol or intravenous aminophylline, 30–40% humidified oxygen, and sometimes antibiotics. The most severely affected cases were also treated with systemic corticosteroids and parenteral fluid therapy. Mechanical ventilation was employed in 2 patients because of severe ventilatory failure.

Results

There were no deaths in the present series. Table II shows that there were 39 virus isolates from 38 admissions, an infection rate of 14.2%. Rhinovirus and respiratory syncytial (RS) virus were the commonest viruses cultured. Table III

TABLE II
Virus isolations from 38 admissions

Viruses cultured	No. of occasions
Rhinovirus (various serotypes)	16
Respiratory syncytial virus	6
Adenovirus (various serotypes)	5
Herpes simplex	4
Echo 15 and 18	2
Influenza A	1
Influenza B	1
Parainfluenza 1	1
Parainfluenza 3	1
Coxsackie B ₄	1
Mumps	1

shows that there was serological evidence of infection on 12 occasions (RS virus in 6), in 8 of which culture was negative.

Fig. 1 shows aggregate data of patients admitted and investigated and the virus isolates for each month of the year. Results for each month of the study (Fig. 2) showed that admissions were least common in the winter months. There was a slight month-to-month variation in the number investigated and in the virus isolation rate, February and August being peak months for virus isolation. Fig. 3 shows the seasonal variation in the two most commonly isolated viruses. Rhinoviruses were found throughout the year, whereas RS virus isolation was confined to the winter months.

TABLE III
Serology results

Virus	No. of occasions	Complement fixation tests (expressed as the reciprocal of the serum dilution)
Respiratory syncytial virus	6	256 (1 specimen) 128→256* 2→64 16→128* 16→256 256→64† 256→16‡
Adenovirus	3	<16→128 1024→512
<i>Coxiella burnetii</i>	1	<16→64
Influenza A	1	<8→256
Parainfluenza 1	1	<16→64

* Virus also identified by culture or fluorescent antibody technique.

† Rhinovirus cultured on same admission.

‡ Influenza A virus cultured on same admission.

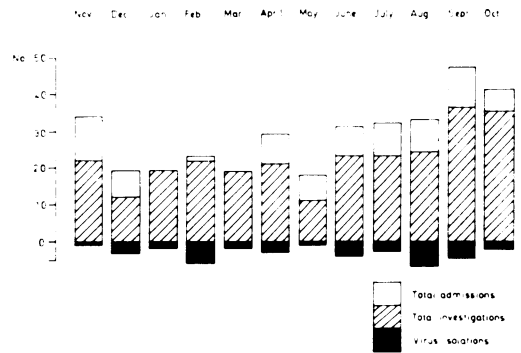


FIG. 1.—Admissions and viral isolations: aggregate data.

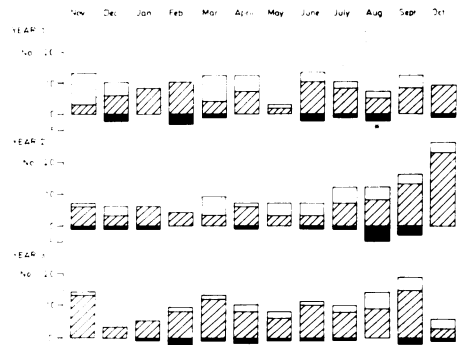


FIG. 2.—Admissions and viral isolations for each month.
* Two viruses isolated from one patient.

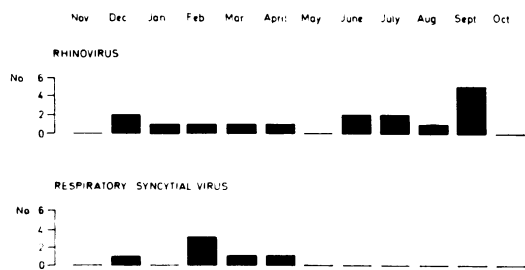


FIG. 3.—Seasonal variation in virus isolation.

Fig. 4 shows that virus isolation was significantly higher in readmissions than in first admission ($P < 0.01$). The 26 positive viral cultures in readmissions occurred in 16 patients, 3 of whom had positive viral cultures on three occasions, 4 on two, and the remaining 9 on one only. Boys predominated in both first and subsequent admissions.

Variation in virus isolation with age and sex is shown in Fig. 5. Viruses were isolated in both sexes throughout childhood and though the admission rate fell with increasing age, isolation rate was

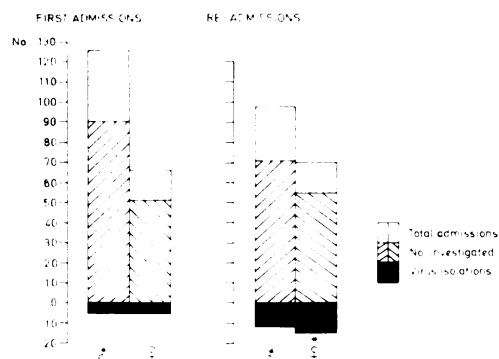


FIG. 4.—Virus isolation in first admissions and readmissions. *Two viruses isolated from one patient.

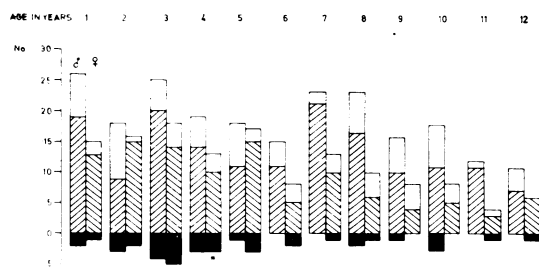


FIG. 5.—Variation in virus isolation with age and sex. *Two viruses isolated from one patient.

unaffected. Infection was commoner in girls over the age of 5 years than in boys of the same age ($P < 0.05$).

The number of patients in whom arterial or arterialized capillary blood gas analysis was performed—56 (24.5%) of the virus-negative admissions and 15 (38.5%) of virus-positive admissions—provides a measure of clinical severity, as do the results themselves. The mean (\pm SD) $Paco_2$ in those with positive viral cultures was 41.7 ± 21.6 mmHg and in those with negative viral culture 36.9 ± 9.5 mmHg. Hydrogen ion concentrations were 47.86 ± 14.59 and 44.67 ± 8.70 nmol/l (pH 7.32 ± 0.08 and 7.35 ± 0.06) respectively. Of the 7 patients with $Paco_2 > 50$ mmHg, 3, including the 2 patients in whom ventilation was assisted, had positive viral cultures.

The majority of patients, whether viral positive or negative, had started to wheeze before the age of 2. There was a history of asthma, eczema, hay fever, or urticaria in first-degree relatives in 65 (49.2%) of the 132 patients with negative viral cultures and in 16 (57.1%) of the 28 patients with positive viral cultures. 25 of the latter group have continued to wheeze periodically for one year.

Discussion

We have isolated viruses from the upper respiratory tract in 14.2% of children investigated after admission to hospital with acute attacks of wheezing. The infection rate is increased to 17.2% when serological and cultural results are combined. Because of differences mainly in design and patient selection, our findings cannot readily be compared with others reported previously, but they do confirm the association of viral infection and wheezing attacks. They also present an opportunity to comment on the seasonal variation of virus infection and the possible relation of virus isolation to the age, sex, and atopic background of the affected child, as well as to severity of illness.

Berkovich *et al.* (1970) showed viral or *Mycoplasma pneumoniae* infection serologically in about one-third of 84 children (from an initial group of 136 children) during attacks of wheezing associated with upper respiratory tract infection. In a study over two winters McIntosh *et al.* (1973) showed viral infection in 33% of wheezing attacks in the first winter and in 50% in the second. Minor *et al.* (1974a) studied 16 patients during 58 episodes of wheezing. 24 were associated with viral infection, and in 35 no viruses were detected. The above studies were confined to the winter months. Horn *et al.* (1975) found an isolation rate of viruses

and *M. pneumoniae* of 27.4% in 544 episodes of wheezy bronchitis in general practice. The investigation was confined to wheezy children with upper respiratory tract symptoms for less than 5 days, which may explain the higher rate of isolation than in the present series. In a hospital-based study (Disney, Matthews, and Williams, 1971) comparable to ours but limited to one year, only three viruses were cultured during 51 episodes of wheeze. The conclusion, that viruses are not implicated in acute attacks of wheezing in children, must be interpreted with caution for epidemics of viral illness may be missed unless studies are conducted over several consecutive years.

Viruses associated with wheezing have varied in different studies. McIntosh *et al.* (1973) found RS virus to be the commonest, whereas others, (Berkovich *et al.*, 1970; Minor *et al.*, 1974a; Horn *et al.*, 1975) found associations between other viruses and wheeziness. Minor *et al.* (1974a) cultured rhinoviruses on 15 occasions out of 24 in which virus infection was associated with wheeze, and Horn *et al.* (1975) isolated rhinoviruses on 64 occasions out of 152 episodes of wheezy bronchitis with positive viral culture. RS virus and rhinovirus were the most common viruses isolated in our patients. RS virus isolation tended to occur during annual epidemics, whereas rhinovirus was a precipitant of wheeze throughout the year. Parainfluenzae and influenza A and B viruses have also been isolated from wheezy children but the association has been less constant than with RS virus and rhinovirus.

The rate of virus isolation was higher in children admitted on more than one occasion. This may suggest that viral infection occurs more commonly in children with an asthmatic tendency, and Minor *et al.* (1974b) have produced evidence to support this view. We found an atopic background (a common marker of an asthmatic tendency) in approximately half of the patients in both the virus-positive and virus-negative groups. The higher rate of isolation of viruses in readmissions was not due to the skewing effect of a few highly susceptible children as no child in the series had more than three infections. Moreover, 7 children, each with 5 or more admissions (45 admissions), had 10 isolations (22%), which is only slightly greater than the overall isolation rate.

In this study the rate of virus isolation in wheezing attacks did not change significantly with age though the incidence of viral infection was much higher in preschool children. This finding is not unexpected as the incidence of wheezing tends to fall throughout childhood. Any decrease in susceptibility to

wheeze by the time of school entry is possibly offset by greater exposure to viruses in overcrowded classrooms. If this were so, it would be surprising if the rate of virus isolation in wheezy children fell at least during the early years at school. Virus infection is also commoner in girls over the age of 5 than in boys of the same age ($P < 0.05$). Although significant, this finding may well not be relevant in view of the small numbers of patients and isolates in each group.

The role of virus infection in the natural history of wheezy bronchitis and asthma is not clear. In our series the proportion of children with a history of atopy in first-degree relatives was no different in the virus-positive and virus-negative groups. Horn *et al.* (1975) have shown that wheezy children with positive virology tend to wheeze also in response to exercise, inhaled allergens, and emotional upsets which suggest that host susceptibility is important. This view is strengthened by the finding that viruses associated with wheezing in some children may be associated with upper respiratory tract infection without wheeze in others. Most of these observations have been uncontrolled, but it is usually inferred that there is a relation between the child's atopic background and susceptibility to wheeze with certain viral infections. Nevertheless it is not known whether some children wheeze only with viral infection. In acute bronchiolitis due to respiratory syncytial virus it has been suggested that susceptibility both to bronchiolitis and subsequent wheeziness is greater in infants with a history of atopy in first-degree relatives than in controls of the same age (Rooney and Williams, 1971).

Our results suggest that wheezing attacks are more severe when associated with viral infection. The question of host susceptibility again arises, however, and our retrospective data do not allow precise definition of the relative roles of virus infections and atopy in determining severity. Indeed the many questions relating to virus/host interaction remain unanswered, but we are attempting in a prospective study to define further the interaction of virus infection, atopic background, and immunological status in wheezy children.

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Correspondence to Dr. Ian Mitchell, Royal Hospital for Sick Children, Sciennes Road, Edinburgh EH9 1LF.