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Respiratory viral infection in childhood. A survey in general practice, Roehampton 1967–1972

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SUMMARY

The role of viruses and *M. pneumoniae* in episodes of acute respiratory illness in childhood has been studied in a London general practice. The total isolation rate was 31·7%, but the rate varied from 32·6% in upper respiratory infections to 64·0% in pneumonia. The clinical features associated with infection were influenced not only by the type of agent but also by age and other host factors in the infected children. Rhinoviruses were more commonly isolated than any other agent and were frequently associated with wheezy bronchitis.

INTRODUCTION

Most early studies of respiratory viral infection in childhood were carried out in children who had been admitted to hospital with serious illnesses, such as bronchitis, pneumonia, or laryngotracheobronchitis. The role of viruses in the less severe but much more common episodes of acute respiratory illness treated at home by general practitioners has been studied in this country by the Medical Research Council (M.R.C. Report, 1965; Poole & Tobin, 1973), and in the U.S.A. by Glezen *et al.* (1971) and Maletsky *et al.* (1971). Some surveys have also been undertaken in nurseries and schools (Bell *et al.* 1961; Pereira, Andrews & Gardner, 1967; Beem 1969; and Loda, Glezen & Clyde, 1972). Much of this work has been reviewed by Channock & Parrott (1965), by Miller (1968) and by Gardner (1968).

The survey reported here was carried out in a single general practice in collaboration with the Department of Microbiology of the Brompton Hospital. Its principal aim was to investigate the role of viruses, *Mycoplasma pneumoniae* and bacteria, in episodes of acute respiratory illness in childhood. Since preliminary findings suggested that host factors were of importance in determining the clinical features of viral infection (Gregg, 1970), the objectives of the survey were extended to include an investigation of these factors, particularly in children who were subject to asthma and bronchitis.

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This paper presents the virological findings of the first five years of the survey (October 1967 to December 1972). The bacteriological findings, the association between viral infection and wheeze, and the investigation of host factors will be reported separately.

PATIENTS AND METHODS

The survey was undertaken in a National Health Service general practice in Roehampton, a residential suburb of south-west London, which has been a smoke-controlled zone for the last 15 years. The majority of patients live in three large council housing estates and belong to social classes III and IV. The number of patients who were registered with the practice in January 1971 was 4800, of whom 919 were children under the age of 13 years (male:female ratio, 1·1:1). Episodes of acute respiratory illness were classified according to the findings on physical examination, as follows:

Upper respiratory. Those with nasal discharge or obstruction, pharyngitis, tonsillitis or otitis media.

Middle respiratory. Laryngitis, tracheitis and croup.

Lower respiratory. Those in which auscultation revealed abnormal physical signs, whether or not they were accompanied by symptoms and signs in the upper respiratory tract. Bronchitis was diagnosed if medium crepitations or scattered rhonchi were heard and laryngotracheobronchitis if, in addition, the child had croup. The term 'wheezy bronchitis' was used to describe episodes of bronchitis associated with generalized wheeze, wheeze being defined as a high pitched musical sound heard throughout the lung fields and usually more marked on expiration. Hence the term 'wheeze' refers to an objective finding and not to the parents' description of symptoms. A diagnosis of pneumonia was made only when physical signs suggestive of consolidation were confirmed by a chest radiograph. The term 'bronchiolitis' was used to describe episodes occurring in infants who had rapid respiration, hyperinflation and respiratory difficulty, and in whom fine crepitations and wheeze were usually present. In some infants it was impossible to differentiate between bronchiolitis and severe wheezy bronchitis.

These categories of respiratory illnesses correspond closely to those of Miller (1973) except that we have distinguished between bronchitis and wheezy bronchitis. Cough was such a common feature of all types of respiratory illness that it was not classified separately.

In every episode the clinical history and date of onset of illness were recorded as well as the physical findings on examination. Specially designed cards were used for recording and analysing the data. For the purpose of analysis, the children were divided into four age groups – less than 1 year, 1–4 years, 5–8 years and 9–12 years.

Virological investigations were made in children under 13 years of age who had symptoms of respiratory illness of recent onset. Children who suffered recurrent episodes of bronchitis or wheezy bronchitis were, as far as possible, investigated during every episode of upper and lower respiratory illness.

Most specimens were taken during the first 5 days of illness. Separate swabs

Table 1. *The number and types of respiratory illness investigated in children of different ages*

Respiratory illness	Age in years: < 1	1	2	3	4	5	6	7	8	9	10	11	12	All ages
Upper	73	108	108	80	84	97	103	72	64	60	55	43	33	980
Middle														
Laryngitis, Tracheitis, Croup	8	11	11	11	6	13	5	4	2	4	1	4	4	84
Lower														
Laryngotracheo-bronchitis	3	4	1	6	6	2	4	3	1	2	2	1	2	37
Bronchitis (without wheeze)	29	34	37	24	22	34	27	7	9	8	10	3	0	244
Wheezy bronchitis	29	20	30	40	58	65	52	61	58	47	46	27	21	554
Bronchiolitis	5	2	0	0	0	0	0	0	0	0	0	0	0	7
Pneumonia	2	3	3	1	4	3	3	1	4	0	3	1	0	28
Total	149	182	190	162	180	214	194	148	138	121	117	79	60	1934

were taken from the nose and throat, the child being encouraged to cough during the latter procedure. Both were broken off into a bottle containing Hanks's BSS and bovine albumen which was then chilled on freeze packs. The specimens were usually delivered to the laboratory within 6 hr., otherwise they were stored overnight at 4° C. In only a few instances were single or paired specimens of serum taken for diagnosis by complement fixation.

LABORATORY METHODS

The bottle of medium was well shaken to liberate cells from the swabs and the suspension was inoculated into cell cultures of primary rhesus monkey kidney, diploid human embryo lung fibroblasts (WI-38), and HEp2. Monkey kidney cultures were tested for haemadsorption using guinea-pig erythrocytes twice weekly. If no virus had been isolated from monkey kidney and HEp2 cells after 3 weeks, a blind passage was made into similar cell cultures for a further week. If no cytopathic effect was seen in inoculated WI-38 cultures within 2 weeks, they were discarded. Only those isolations which were confirmed by neutralization tests were included in the positive results. Rhinoviruses and Coxsackie viruses were serotyped.

M. pneumoniae was cultured in a selective medium similar to that described by Chanock *et al.* (1967) and on supplemented Difco PPLO agar (Andrews, 1968). Typing was done by the disk growth inhibition test using specific rabbit antisera (Clyde, 1964).

RESULTS

During the 5-year period, 4984 episodes of respiratory illness were seen and treated, of which 1934 were investigated (1229 in boys and 705 in girls). Almost half (44·9%) of the episodes investigated involved the lower respiratory tract:

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Table 2. *Agents isolated in* 1934 *episodes of illness*

Agent	Number isolated		Isolation rate (%)
Rhinoviruses	162		8·4
Parainfluenza 1	31		
Parainfluenza 2	28		
Parainfluenza 3	42	111	5·7
Parainfluenza 4A	1		
Parainfluenza 4B	9		
Respiratory syncytial virus	56		2·9
Influenza A	61		3·2
Influenza B	28		1·4
Enteroviruses			
Coxsackie A	24		
Coxsackie B	36	66	3·4
Echoviruses	5		
Poliovirus 2	1		
Adenoviruses	45		2·3
Mumps	3		0·2
Herpes simplex	17		0·9
Mycoplasma pneumoniae	37		1·9
Psittacosis (serological diagnosis)	1		
Double isolations	27 (54 agents)		1·4
Total	614		31·7

Table 3. *Double isolations of agents*

Coxsackie A	+parainfluenza (4), +adenovirus (1), +rhinovirus (1), +other types of Coxsackie A (2), +Coxsackie B (1)
M. pneumoniae	+rhinovirus (1), +parainfluenza (1), +RS virus (1), +influenza A (2), +influenza B (1), +Coxsackie B (1)
Parainfluenza	+rhinovirus (5), +adenovirus (1), +echovirus (1), +Coxsackie B (2)
Rhinovirus	+Coxsachie B (1), +adenovirus (1)

Table 4. *Serotypes of viruses (including those in double isolations) in order of frequency: the numbers of each are shown in parentheses*

Rhinoviruses	15 (24), 26 (17), 4 (16) 1B (12), 30 (10), 13 (9), 5, 8, 31 (8), 3 (7), 22 (6), 12 (4), 2, 32 (3), 6, 10, 14, 23, 29 (2), 1A, 7, 12, 17, 18, 19, 37, 39, 44 (1), not yet typed (15)
Coxsackie A viruses	4 (15), 2, 9 (5), 5, 8, 10, 16 (2)
Coxsackie B viruses	5 (12), 2 (10), 1, 4 (8), 3 (4), not yet typed (1)
Echoviruses	9 (2), 17 (2), 2 (1), 20 (1)
Adenoviruses	2 (19), 1 (12), 5 (6), 3 (5), 7 (2), 26 (1), not yet typed (1)

of these 4·3% were laryngotracheobronchitis, 28·0% bronchitis, 63·7% wheezy bronchitis and only 4·0% pneumonia or bronchiolitis.

Table 1 shows the frequency of different types of illness investigated according to age. Whereas the number of upper respiratory illnesses investigated fell after the age of 6 years, that of lower respiratory illnesses was maintained until the age of 10 years because of the frequency of wheezy bronchitis in older children.

Diagnosis of infection by viruses and M. pneumoniae

The isolation rate for the 5-year period was 31·7%, the relative frequency of

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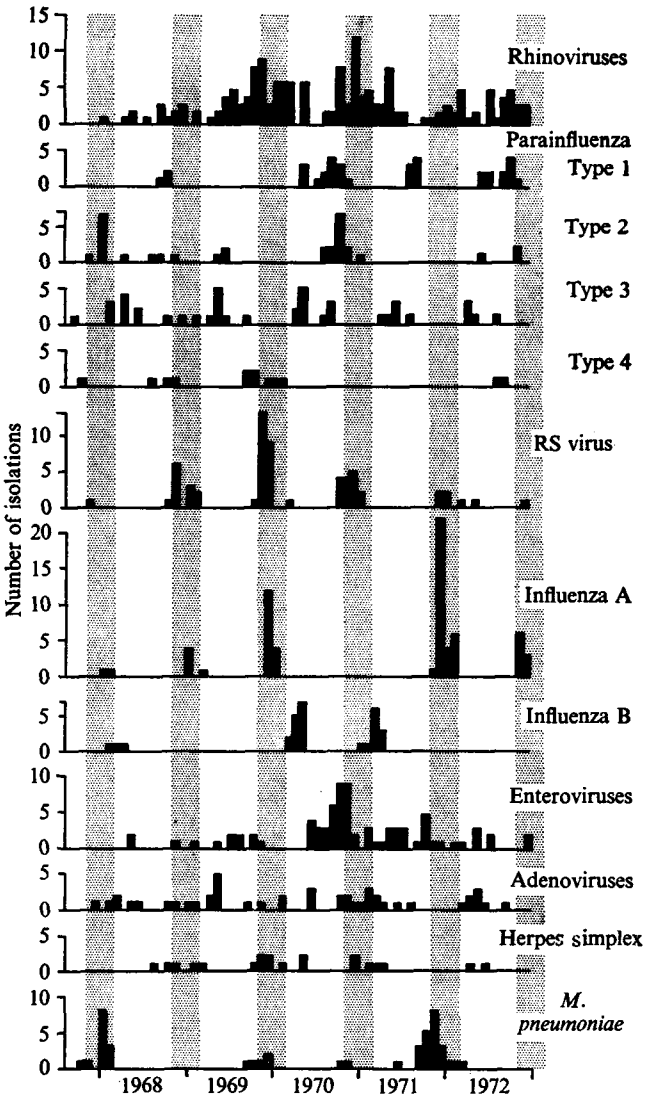

Fig. 1. Seasonal incidence of viruses and *M. pneumoniae*. (Shading indicates winter months: Nov.-Feb.)

each agent being shown in Table 2. In 27 episodes two agents were isolated: in 20 of these two types of virus were found, and in the remainder a virus was associated with *M. pneumoniae* (Table 3). The serotypes of viruses isolated are shown in order of frequency in Table 4.

Seasonal incidence

In each year of the survey a fall in isolation rate occurred during some months especially February, March and April, although there was no reduction in the number of episodes investigated (Fig. 1). Influenza A virus was isolated only when there was an epidemic in the community. *M. pneumoniae* was cultured during the

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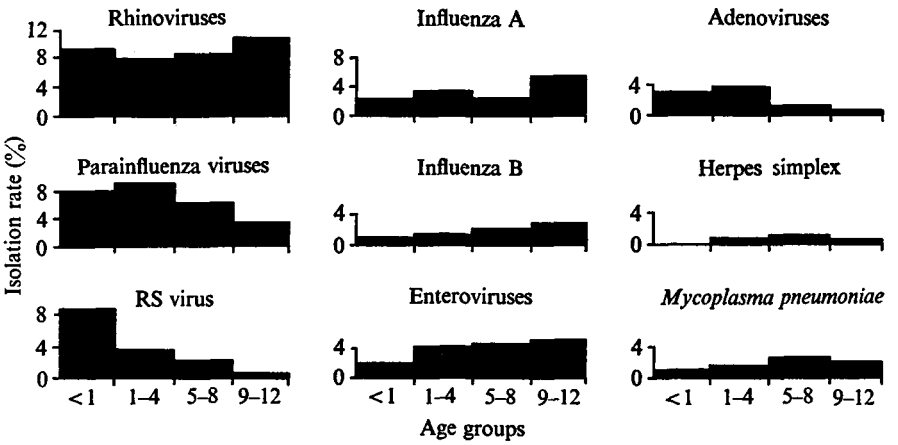

Fig. 2. Age distribution of viruses and *M. pneumoniae*.

winters of 1967–8 and 1971–2 but seldom between these two outbreaks. Respiratory syncytial (RS) virus was isolated almost exclusively during winter months. During each outbreak of parainfluenza viruses, several serotypes were isolated but one or two usually predominated (Fig. 1) and similarly in the case of rhino- and Coxsackie viruses.

Age distribution

Eighty-one per cent of all isolations were made from patients under the age of 8 years, reflecting the larger number of episodes which were investigated in younger children (Fig. 2). RS virus, parainfluenza viruses and adenoviruses were more commonly isolated from children under the age of 4 years, whereas influenza viruses, enteroviruses and *M. pneumoniae* were isolated more frequently in older children. Rhinoviruses were isolated with equal frequency in children of all ages.

Factors influencing isolation rate

Two factors which might influence the isolation rate were examined – the interval between the onset of illness and taking the swabs, and the effect of storage overnight of specimens. Viruses were isolated from 33% of specimens taken within 5 days of the onset of illness and from only 18% of those taken later. Storage overnight did not reduce the isolation rate which, in 111 such specimens, was found to be 37%.

Association between clinical findings and agent identified

The isolation rate was found to vary with the type of illness (Table 5). The types of illness which occurred in association with each agent are shown in Table 6, in which the salient associations are emphasized by bold type.

Nasopharyngeal symptoms and signs and cough were commonly associated with all agents. Otitis media was frequently associated with influenza B, RS virus, and adenovirus infections. Most children from whom influenza viruses were isolated

Table 5. *Isolation of agents in different types of respiratory illness*

Respiratory illness	No. of episodes investigated	No. in which one or more agents were isolated	Isolation rate (%)
Upper	980	320	32·6
Middle			
Laryngitis, Tracheitis, Croup	84	31	36·9
Lower			
Laryngotracheobronchitis	37	19	51·4
Bronchitis (without wheeze)	244	71	29·0
Wheezy bronchitis	554	152	27·4
Bronchiolitis	7	3	42·9
Pneumonia	28	18	64·3
Total	1934	614	31·7

had febrile upper respiratory illnesses and influenza-like symptoms were milder than in adults. Parainfluenza viruses predominated in middle respiratory infections. Lower respiratory illnesses occurred in association with all agents but it can be seen that the high rates of isolation in pneumonia, bronchiolitis, wheezy bronchitis and laryngotracheobronchitis (Table 5), were due to *M. pneumoniae*, RS virus, rhinoviruses and parainfluenza viruses respectively (Table 6).

M. pneumoniae was the commonest cause of pneumonia. Episodes in which this agent was isolated usually began with mild upper respiratory symptoms, but persistent cough was the most common presenting feature. The illness tended to be more prolonged than those associated with viral infection and the children were often pale, anorexic and easily fatigued for several weeks afterwards. RS virus was the only agent which was isolated in episodes of bronchiolitis.

Respiratory viruses were isolated from 12 children during the prodromal phase of an acute infectious disease. Three parainfluenza viruses, one rhinovirus, one influenza A and one Coxsackie virus were isolated during the early stages of illnesses which were subsequently diagnosed clinically as measles. One influenza A and one parainfluenza virus were found in two children who later developed mumps, and one adenovirus and 3 parainfluenza viruses were isolated from children with the 'whooping cough' syndrome. Parainfluenza viruses were also obtained from 5 children who had non-specific morbilliform rashes. Mumps virus was isolated from 3 children who had no salivary gland enlargement.

Double isolations were more common in children under the age of 8 years than in older children. No association was found between any two types of virus or between any one virus and *M. pneumoniae*. In no case was the illness of greater severity than might have been caused by either agent acting singly.

Reinfection

The same virus serotype was isolated more than once from 22 children. There were also 5 repeat isolations of *M. pneumoniae* but 3 of these were made within

Table 6. *Relationship between clinical features and agents (frequency %)*

Clinical features	Rhino-viruses 162	Para-influenza viruses 111	RS virus 56	Influenza A_2 61	Influenza B 28	Entero-viruses 66	Adeno-viruses 45	Herpes simplex 17	*Mycoplasma pneumoniae* 37	Double isolates 27
Respiratory										
Upper										
Nasal	87·0	61·5	86·0	65·9	60·9	48·6	64·4	82·5	48·9	66·5
Pharyngitis	49·0	49·5	57·0	59·1	53·8	56·0	64·4	58·7	32·5	55·8
Otitis media	8·0	12·6	**28·5**	8·2	**43·0**	18·3	**24·4**	17·7	16·2	26·0
Cough	73·5	81·0	75·0	77·1	64·1	50·0	48·8	76·2	78·5	74·1
Middle										
Croup / Laryngitis / Tracheitis	4·9	**12·6**	3·6	1·6	3·6	—	2·2	5·9	2·7	7·4
Lower										
Laryngotracheobronchitis	4·3	7·2	1·8	—	—	1·5	2·2	5·9	—	—
Bronchitis without wheeze	6·2	12·6	23·2	19·7	14·3	4·5	6·6	—	16·2	22·2
Bronchitis with wheeze	**42·0**	16·2	21·3	13·2	10·7	25·8	11·2	35·3	24·3	22·2
Bronchiolitis	—	—	**5·4**	—	—	—	—	—	—	—
Pneumonia	—	1·8	3·6	3·3		—	2·2	—	**27·1**	—
Non-respiratory										
Fever	12·4	22·4	19·6	**47·5**	**50·0**	33·3	40·0	23·5	19·0	11·1
Headache	—	—	1·8	8·2	3·6	10·6	6·6	5·9	2·7	—
Myalgia	1·8	0·9	—	**16·5**	3·6	—	2·2	—	—	—
Rashes	0·6	7·2	1·8	1·6	7·1	1·5	4·4	11·8	5·4	3·7
Generalized lymphadenopathy	—	8·2	1·8	4·9	3·6	6·1	13·4	5·9	2·5	—
Conjunctivitis	3·7	4·5	1·8	4·9	—	3·0	—	—	2·7	—
Gastrointestinal	4·3	8·2	7·2	11·5	10·7	**21·2**	6·6	11·8	10·8	—

4 weeks of the first, suggesting persistence rather than reinfection. On the other hand, the repeat isolations of viruses and the remaining 2 of *M. pneumoniae* were considered to be reinfections, either because over a year separated the initial from the repeat isolation, or because other agents or a negative result were recorded during the intervening period.

In most cases, the illness associated with reinfection was of no greater severity than the initial infection. Reinfection by RS virus occurred in 4 children in successive winter seasons, one of whom had 3 episodes: in none was the subsequent illness more serious than that of the first infection. In 4 children, however, the episode of reinfection was more severe than the initial illness. In one of these an initial infection by adenovirus type I was associated with pharyngitis, fever and marked enlargement of cervical glands: when reinfected 6 months later, the child had similar symptoms with bronchopneumonia. A second child had a herpes simplex infection with coryza and cough on the first occasion and bronchitis on reinfection 7 months later. In the other 2 children reinfection by *M. pneumoniae* occurred after intervals of 37 and 45 months: both had an upper respiratory illness on the first occasion and one had bronchitis and the other pneumonia on reinfection.

DISCUSSION

Several facts suggest that, in most instances, the isolation of a virus or *M. pneumoniae* during an acute episode of respiratory illness is of aetiological significance. First, other studies in which symptom-free patients or 'controls' were investigated have shown that viruses are more frequently isolated from those who have respiratory symptoms than from those who are symptom-free (M.R.C. Report, 1965; Hurrell, Sturdy, Frood & Gardner, 1971; Lambert & Stern, 1972; Poole & Tobin, 1973; Horn & Yealland, 1974). Secondly, in this survey, as in the two large surveys of the Medical Research Council (M.R.C. Report, 1965; Poole & Tobin, 1973), the chance of isolating an agent was greatest during the first few days of an illness; only in the case of adenoviruses (Brandt *et al.* 1969) and *M. pneumoniae* (Foy *et al.* 1966) has it been shown that isolations can be made for long periods after the initial infection. Thirdly, some viruses tend to be associated with distinctive clinical illnesses.

The isolation rate of viruses and *M. pneumoniae* in this survey is similar to that found by most other workers. Failure to isolate a virus during an acute episode of illness which is clinically typical of a viral infection, could be due to poor technique in taking the specimen, non-survival of the virus during transport, or technical difficulties in the laboratory. In addition, the fall in isolation rate during certain months of the year suggests that some illnesses may be caused by agents such as coronaviruses, which cannot readily be isolated by routine laboratory methods, by viruses which have not yet been identified, or by non-viral agents such as bacteria or allergens.

Development of immunity to viral infection

The fact that RS virus, parainfluenza viruses and adenoviruses were seldom isolated in older children (Fig. 2) suggests that immunity to these agents is usually acquired in early childhood and, although reinfection may occur in older children, it causes illness which is not severe enough to be brought to the doctor's notice. On the other hand, rhinoviruses, enteroviruses, *M. pneumoniae* and influenza viruses were isolated as frequently in older as in younger children (Fig. 2). The later development of immunity to rhinoviruses and enteroviruses might be explained by their large number of serotypes to which cross-immunity probably does not occur (Stott & Tyrrell, 1971). The higher frequency of isolations of *M. pneumoniae* and influenza viruses in older children could be due to their less frequent occurrence in the community and to antigenic variation in the case of influenza viruses.

A similar age distribution of viral infection in childhood has been reported by the Medical Research Council (1965), Chanock *et al.* (1967), Pereira *et al.* (1967), Glezen *et al.* (1971), and Poole & Tobin (1973). The evidence suggests that children, as they grow older, acquire progressively wider immunity to the many agents which can infect the respiratory tract. However, some children may be infected several times by a given agent before they attain clinical immunity. In general, illnesses associated with reinfection were less severe than those occurring with an initial infection. This was particularly noted with reinfection by RS virus, a finding also reported by Beem (1967).

Relations between agents and clinical features

While all agents were found to be associated with upper respiratory illnesses, some showed a tendency to cause particular clinical manifestations. For instance, RS virus and influenza A and B viruses were associated with otitis media, influenza A virus with fever and myalgia, and enteroviruses with gastroenteritis. More specific associations were found between RS virus and bronchiolitis, parainfluenza viruses and croup, *M. pneumoniae* and pneumonia, and rhinoviruses and wheezy bronchitis (Table 6).

The association between RS virus and bronchiolitis in infancy is now well recognized. However, in the present survey, most infants infected with RS virus had only a mild upper respiratory illness, suggesting that factors other than the nature of the virus and the age of the child are concerned in the development of bronchiolitis. The heightened response to infection in children who had previously received inactivated RS vaccine (Kapikian *et al.* 1969) and the demonstration of immune complexes in the lungs of fatal cases of bronchiolitis (Gardner, McQuillin & Court, 1970) suggest an immunological mechanism.

The relatively small proportion of children infected by parainfluenza viruses and *M. pneumoniae* who had laryngotracheobronchitis and pneumonia respectively, also suggests that unknown host factors modify the response to infection by these agents.

This survey differs from others in the large number of rhinoviruses which were isolated. Thirty-two serotypes were identified but there was no obvious difference

in the clinical features or severity of illness which they caused. Forty-two per cent of all rhinovirus infections were associated with acute wheezy bronchitis, whereas this virus was not isolated in any episode of pneumonia or bronchiolitis.

Most episodes of wheezy bronchitis occurred in children who were known to be predisposed to wheeze. In some children wheeze occurred only in association with infection while in others, who were considered to have asthma, it also occurred on exercise, on exposure to allergens or with emotional disturbance. Although all types of virus appeared to be capable of provoking wheezy bronchitis, rhinoviruses were isolated more frequently than any other agent, especially in older children. The role of viral infection in children with wheezy bronchitis and asthma will be discussed more fully in a later paper.

This survey has demonstrated the importance of viral infection as a cause of acute respiratory illness in children attending a general practice and has shown that respiratory viruses are responsible for many of the more severe forms of illness treated at home by the general practitioner.

The findings suggest that the clinical response to respiratory viral infection is determined not only by the nature of the virus but also by host factors in the child, such as age, immune status, and the predisposition to wheeze.

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