REVIEW

Viruses as precipitants of asthma symptoms. I. Epidemiology

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Christopher Robin had wheezles and sneezles, they bundled him into his bed.
They gave him what goes with a cold in the nose, and some more for a cold in the head.
They wondered if wheezles could turn into measles, if measles would turn into mumps;
They examined his chest for a rash, and the rest of his body for swellings and lumps.
They sent for some doctors in sneezles and wheezles, to tell them what ought to be done.
All sorts and conditions of famous physicians came hurrying round at a run.
They all made a note of the state of his throat, they asked if he suffered from thirst;
They asked if the sneezles came *after* the wheezles, or if the first sneezle came first.
They said, 'If you teazle a sneezle or wheezle, a measle may easily grow.
But humour or pleazle the wheezle or sneezle, the measle will certainly go.'
They expounded the reazles for sneezles and wheezles, the manner of measles when new.
They said 'If he freezles in draughts and in breezles, then PHTHEEZLES may even
    ensue.'
Christopher Robin got up in the morning, the sneezles had vanished away.
And the look in his eye seemed to say to the sky, '*Now, how to amuse them today?*'

A. A. Milne, *Now We Are Six*, 1927.

Introduction

An association between respiratory infections and asthma attacks has been acknowledged for several decades. Patients suffering from an acute attack of asthma very often give a history of a cold and upper respiratory symptoms in the days *preceding* the onset of the exacerbation. Since 1957 evidence has accumulated that it is particularly viral infections that are associated with exacerbations of asthma. A direct causal link has therefore been inferred and various possible mechanisms have been explored. In this article we review the epidemiological evidence for such a link. Two further articles will review, firstly, physiological and experimental studies examining proposed cellular and biochemical mechanisms whereby attacks of asthma may be induced by virus infections, and secondly, recent developments in the molecular biology of rhinoviruses and their receptors, and will examine the potential for preventing or ameliorating attacks precipitated by viral infections.

Historical background

The laboratory identification of viruses dates from the observation of cytopathic effect in tissue culture in 1929 by Andrewes in the U.K. [1] and Rivers in the U.S.A. [2]. Influenza viruses were first isolated in 1933 [3] and discovery and culture of other respiratory viruses including parainfluenza viruses, enteroviruses, adenovirus, and respiratory syncytial virus (RSV), followed in the 1940s and 1950s. It was not until 1960 that Tyrrell and others [4] at the Common Cold Research Unit, Salisbury, discovered suitable conditions for culture of 'the common cold viruses' (rolled tube cultures of sensitive cell lines at 33°C and pH 7·0), and these viruses were named rhinoviruses in 1961 [5]. Another group of common cold viruses, the coronaviruses, were discovered in 1961–62 independently by Tyrrell and Bynoe [6] in the U.K.

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(reported 1965) and Hamre and Procknow [7] in the U.S.A. (reported 1966).

The aggravation of asthma during respiratory infections was regarded in the 1950s as a manifestation of bacterial allergy [8]. In 1959, Feingold [9] reviewed the role of infection in bronchial allergic disease and described two patterns. In the first pattern, syndromic infections such as pertussis, mumps, chickenpox and measles, caused a mild aggravation of allergic disease in their prodromal stage, followed by a remission of allergic symptoms during the acute phase, and then on recovery a recrudescence of allergy which persisted at a higher baseline than previously. In the second pattern (interpreted as being bacterial in origin), infection of the upper respiratory tract associated with a neutrophilia in the blood (which Feingold assumed was a sign of bacterial infection), aggravated the allergic disease in the acute stage, but this was followed by almost complete recovery, which was speeded by the use of antibacterials. We now know that neutrophilia is not a reliable sign of bacterial infection, and that the majority of upper respiratory infections are viral in origin, so that Feingold was probably unwittingly describing the aggravation of asthma by viral respiratory infections, with or without secondary bacterial involvement.

The remission (often long-term) of allergic symptoms including asthma during measles had been described in 1953 [10]. However, the first reports of asthma being aggravated by viral infection were in 1957 and 1958 when asthma attacks were observed in cases of influenza A during influenza epidemics which affected two large camp populations—one in the 4th National Boy Scouts Jamboree in Pennsylvania in July 1957 [11] (27 cases of asthma out of 616 cases of influenza), the other in the Centenary World Guide Camp in Ontario one month later [12] (seven cases of asthma out of 185 cases of influenza). At about the same time, an infectious agent cultured from chimpanzees with coryza was identified in the throat of infants with bronchiolitis and bronchopneumonia and was named respiratory syncytial virus [13]. By 1966 the main viruses thought to aggravate asthma or wheezing were thought to be influenza, parainfluenza and RSV [14]. The contribution of upper respiratory tract viruses to attacks of asthma or wheezing has only been studied in depth in the last 25 years.

Epidemiological studies

Epidemiological evidence for an association between virus infections and asthma exacerbations

There are several lines of evidence which associate virus infections with asthma attacks. Firstly the identification rate of viruses during exacerbations of asthma (10–50%,

see below) is similar to that generally found during respiratory infections, and more specifically so in studies that have investigated episodes of respiratory infection with and without asthma or wheezing (with *vs* without: 27·4% *vs* 33·5% [15]; 28·6% *vs* 29·5% [16]. This rate is much higher than the viral identification rate generally found during asymptomatic periods in asthmatics and non-asthmatics, which is usually around 3% [16–19] (Table 1). Other studies have confirmed this finding, although directly comparable figures were not given [20–23].

By contrast, as also shown in Table 1, bacteria are found in the respiratory tract of asthmatics as commonly during asymptomatic and symptomatic periods [18,24]. A number of other studies have also for various reasons concluded that bacterial infections were not significantly involved in provoking exacerbations of asthma [22, 23,25–29]. Bacterial infection in cultures of transtracheal aspirates were not found to correlate with asthma exacerbations [30]. Chronic bacterial colonization has not been found to increase rates of asthma attacks [18], but chronic bacterial sinusitis may do so [31,32], probably via indirect effects such as loss of nasal conditioning of the inspired air [33]. Although it was once common practice to use antibacterials in acute asthma, antibiotics were not found to alter the course of acute asthma [27,34,35], and are no longer part of the routine management of acute asthma [36].

Secondly, there is a close temporal relationship between virus infections and asthma exacerbations, both at the individual and at the population level. A parallel between seasonal variations in wheezing episodes among asthmatic children and identification peaks of various viruses was noted by McIntosh *et al.* [24]. Henderson *et al.* [37] in a study over 11 years of 6165 lower respiratory illnesses (1851 with wheezing) occurring in children in a large paediatric practice, documented striking parallels between yearly peaks in wheezing-associated respiratory illness, and RSV outbreaks. There was a further parallel between age–sex distribution of the total number of respiratory illnesses and the wheezing-associated respiratory illnesses. A similar parallel was found between age-specific identification rates of individual viruses in children with 'wheezy bronchitis', and in children with purely upper respiratory tract illnesses [16].

Stronger evidence comes from prospective studies of individuals with asthma. The rate of virus identification decreases substantially after the acute stage of respiratory illness [15,27], which makes chance coincidence of virus identification with wheezing episodes inherently unlikely. In three separate studies in which monitoring was intensive and specimens were obtained on a regular basis between episodes, virus identifications in individuals

Table 1. Viral and bacterial identification rates during wheezing and during asymptomatic periods.

| 1st Author | Year | Identification rate (%) while subjects were: | | ID ratio A/B |
		Wheezy (A)	Asymptomatic (B)	
Viruses				
Mitchell [17]	1978	14·3	0·8	17·9
Horn [16]	1979	26·4	3·2	8·3
Hudgel [18]	1979	11·0	3·3	3·3
Jennings [19]	1987	18·6	3·3	5·6
Bacteria				
McIntosh [24]	1973			
Pneumococcus		26	24	1·1
H. influenzae		32	37	0·9
β-haemolytic streptococcus		6	7	0·9
Staphylococcus aureus		18	19	0·9
Enteric bacilli		26	21	1·2
Hudgel [18]	1979	9	9	1·0

clearly coincided in time with increases in asthma medication score [24], increases in asthma symptom score [22], and decreases in daily FEV_1 [23]. In each study the observed changes lasted from several days to a fortnight, a time course far more prolonged than the experimental late asthmatic response to allergen. In fact the time course of wheezing associated with infection has a characteristic pattern: Mertsola *et al.* [38] found that among 54 children aged 1–6 years, the wheezing started a mean (s.d.) of 43 (7) hours after the first symptoms of respiratory infection, and lasted for 3·8 (4.2) days in patients with positive virology. This pattern is consistent with observations in clinical practice, and again does not resemble the pattern of acute allergen challenge.

There have been few studies which have directly compared the importance of viruses and aero-allergens as provoking agents for severe asthma exacerbations. Potter *et al.* [39] in Cape Town studied 40 children consecutively admitted to hospital for asthma, and 40 well asthmatic children, and could find no relation between the admissions and meteorological changes, changes in pollen or spore counts, or known allergen exposure, but a strong association with symptoms and signs of respiratory infection. In a similar study Carlsen *et al.* [28], found little relation between the seasonal distribution of acute asthma attacks in 169 asthmatic children in Oslo, with the seasonal changes in central city counts of pollens to which the children were allergic. On the other hand there was both an individual and a population association of attacks with viral identifications.

The study of Storr and Lenney [40] offers indirect evidence, although no virological studies were performed. For each week of the year they obtained a 10 year average of the number of children hospitalized for asthma in Brighton. This process might be expected to even out random year to year variability in admission rates. However a distinctive pattern was evident in the averaged data, and had a striking relationship to school holiday periods, which were associated with troughs in admission rates, followed by a sharp rise to a peak after the beginning of each school term. The pattern was most striking in 4–10 year olds but was also seen in 0–3 year olds who do not attend school. This is even more significant considering that Brighton is a holiday resort and would experience a substantial increase in childhood population during holiday periods. The authors surmised that this pattern was unlikely to be explained by stress or by aeroallergen exposure (house dust mite levels are higher in the home than at school), and postulated that viruses were acquired from other localities by individuals during holiday travel and were then rapidly spread through a susceptible population, both at school and amongst younger siblings. If this speculation is correct, then it argues that viral infections have a major role in severe asthma exacerbations in children.

Numerous studies have documented an association between the severity of the wheezing illness and the viral identification rate. Horn *et al.* [27] isolated viruses in 49% of all episodes of wheezy bronchitis in children, and in 64% of severe episodes requiring corticosteroids. Simi-

larly Beasley *et al.* [41] identified viruses in adult asthmatics in 10% of exacerbations and 36% of severe exacerbations of asthma. Minor *et al.* [22] and Roldaan and Masural [23] found that asthma occurred more frequently in severe than in mild viral infections, and Mitchell *et al.* [42] studying children who had attacks of wheezy bronchitis or asthma, documented more severe blood gas abnormalities in those with positive viral findings than in those with negative findings.

The associations listed above of virus identifications with wheezing attacks versus asymptomatic periods, with severe attacks versus mild attacks, and the close temporal associations, in which viral infections *precede* the onset of wheezing illness, argue strongly for a causal link, although they cannot prove it. Final proof will require experimental studies on volunteers, detailed mechanistic studies and controlled trials in acute asthma attacks of therapies specifically developed against respiratory viruses.

Difficulties involved in identification of respiratory viruses

Before examining viral identification rates in asthma, it is pertinent to look at the considerable difficulties involved in isolating respiratory viruses [15,27]. Identification rates will depend on the organisms prevalent during the study, which will vary seasonally and from year to year, and with the age of subjects studied. They will also depend on the quality and intensity of prospective follow-up—whether regular investigations between symptomatic episodes are performed, the criteria for investigation of symptomatic episodes, and the time elapsed between notification and investigation of a symptomatic episode. Technical problems include the difficulties of obtaining a satisfactory clinical specimen, of transporting and storing it in adequate conditions to preserve identifiable virus, and of availability of sensitive cell lines for screening. In addition, laboratories vary considerably in their experience and success rate in culture of specific viruses. Certain of the respiratory viruses are particularly difficult—coronaviruses because they require organ or animal cultures (sensitive cell lines and antigens for serology have limited availability), rhinoviruses because of their fastidiousness for certain cells and culture conditions and the fact that the large number of serotypes precludes serology for screening, respiratory syncytial virus because of its sensitivity to freezing and thawing, and parainfluenza viruses because they will only culture satisfactorily on primary cell lines. These difficulties mean that there is a very low false positive rate for identification of respiratory viruses as a group, but the false negative rate for the above viruses is likely to be significant, particularly so for rhinoviruses.

Virus identification rates in exacerbations of asthma and wheezing (Table 2)

A number of studies since 1960 have investigated viral respiratory infections in relation to wheezy illness, the majority looking at children. A summary of those studies which were informative for rates of viral identification during wheezy illnesses is presented in Table 2. The studies are divided into two main groups. Section A (incidental studies) lists studies in which the episodes selected for investigation were respiratory infections or wheezing illnesses in children as they presented to a clinic or to a hospital for admission. They are generally based on large subject populations and can be regarded as cross-sectional studies extending over a period of time. Section B (prospective studies) lists studies in which a relatively small group of children (upper portion) or adults (lower portion) with asthma or 'wheezy bronchitis' were followed, some with symptom or medication diaries, for periods of 3 to 30 months, and were investigated during respiratory infections (which they were usually requested to report), as well as on a regular basis in some studies. In both sections, the denominator for total and specific viral identification rates is the number of episodes of wheezing illness investigated. Some of these are explicitly stated to be asthma attacks, others are described as respiratory tract infection with wheezing, wheezy bronchitis, or bronchitis/bronchiolitis. Studies in the latter category were only included if the definition given of bronchitis or bronchiolitis was not restricted to infancy, and included the features of wheezing or airtrapping (some studies in the 1970s appeared to apply the label of 'bronchiolitis' to any wheeze associated respiratory infection in childhood [37,44]). Blanks in the viral identification section of the table may mean that the virus was looked for but not found, or that it was not looked for. In many studies it is not clear which of these is the case, but where the authors reported finding a virus in another part of the paper but not specifically among wheezy subjects, the rate is listed as zero. It can be generally assumed that blanks under enteroviruses and adenoviruses mean that the virus was looked for and not found, as these viruses will grow readily in most culture systems, whereas for coronaviruses, the studies that did not report them generally did not look for them. In the case of the other viruses, the situation is not clear.

The incidental studies (Section a, Table 2) show overall viral identification rates of 9·8–48·6%, and when these are weighted by the number of episodes studied, and averaged, an overall identification rate of 24·0% of 4896 episodes were positive. At least some of the variability between studies is understandable in terms of the populations studied and methods used. There were only three

Table 2. Identification rates of viruses and *M. pneumoniae* in wheezy episodes

(a) Incidental studies of unsolicited presentations with RTI/asthma

1st Author	Year	Number	Age (years)	Source of cases	Presenting condition (n)	Study period (months)	Description given	n	Spec.	Culture	Serum	Ag-D	Any virus	Rhin	Cor	RSV	Par	Inf	Ad	Ent	Myc	H.S.	Other	Dual
Tyrrell [43]	1965	1888	0–17+	Home/admissions	RTI (1888)	36	Bronchitis/iolitis c. wheeze	225	12	abdeg	lm		28·4	3·1		8·0	3·6	0·0	4·0	5·3		0·9	0·9	
Disney [25]	1971	51	?0–14	Admissions	Asthma	12	Asthma attacks	51	12	dh			9·8			2·0	5·9		0·0				2·0	
Glezen [44]	1971	2000	0–15+	Paed. practice	LRTI (3000)	66	Bronchiolitis c. wheeze	855	12	degk			25·1	1·8		8·8	8·3	1·1	1·8	0·7	2·8		0·4	
Horn [15]	1975	919	0–13	General practice	RTI (1934)	60	Wheezy bronchitis/iolitis	561	12	dehk			27·6	12·1		2·7	3·2	2·0	0·9	3·0	1·6	1·1		1·1
Mitchell [42]	1976	192	1–12	Admissions	Asthma/wheezy bronchitis	36	Asthma/wheezy bronchitis	267	125	d'eh	?lm		17·2	6·0		3·7	1·1	1·1	3·0	2·2		1·5	0·7	1·1
Henderson [37]	1979	3–6000	0–15	Paed. practice	LRTI (6165)	132	Wheeze-associated RTI	1851	2	deghk			21·4	1·3		7·3	5·7		2·3	2·2	2·5			
Horn [16]	1979	163	0–12	General practice	Wheezy bronchitis	62	Wheezy bronchitis	554	12	dehk			26·4	12·6		2·2	4·0	2·0	0·9	4·0	1·8	1·8		1·1
Horn [27]	1979	22	5–15	General practice	Wheezy bronchitis	16	Wheezy bronchitis	72	123	d/g'hk			48·6	31·9		1·4	4·2	11·1	1·4		1·4			
Carlsen [28]	1984	169	2–15	Paed. clinic/adm's	Asthma	24	Asthma attacks	256	5	gg'j	mo	x	28·5	12·9	1·6	5·5	3·9	1·6	3·1					
Jennings [19]	1987	204	0–12	Admissions	Asthma	12	Asthma attacks	204	125	dehij	mn	x	18·6	1·5		6·4	0·5	2·9	2·0	5·4				
Totals/weighted average ID rate†						10 studies		4896				1173+ve	24·0	5·3	(1·6)	6·0	5·0	1·1	2·0	1·5	(2·3)			

† Figures in parentheses for each virus calculated from only those studies which used methods to identify that virus.

(b) Prospective studies of subjects with asthma

1st Author	Year	Number	Age (years)	Source of cases	Entry condition	Study period (m)	Description given	n	Spec.	Culture	Serum	Ag-D	Any virus	Rhin	Cor	RSV	Par	Inf	Ad	Ent	Myc	H.S.	Other	Dual‡
Children																								
Berkovich [34]	1970	84	0·5–16	Paed. clinic	Asthma	6	Wheezing episodes	108	16	bcde	?lm		22·2			2·8	6·5	10·2	0·9		4·6			
Lambert [45]	1970	2	7–25	?General practice	Asthma	24	Exacerbations	11	123	bde	m		45·0	27·0			18·0	9·0						
McIntosh [24]	1973	32	1–7	Hospital	Asthma	15	RTI with wheezing	139	12	dehk	lm		41·7		9·4	17·3	14·4	0·7	4·3	0·7				(7·2)
Minor [22]	1974	16	3–11	Allergy clinic	Asthma	7	Exacerbations	61	12	dehk	?lm		37·7	24·6			9·8					3·3		
Minor [46]	1976	49	3–60	General practice	Asthma	8	Asthma episodes	71	12	deh	l		23·9	9·9		2·8	1·4	5·6	1·4		2·2			2·8
Mitchell [17]	1978	16	2–6	Paed. resp. clinic	Asthma	12	Wheezing episodes	91	12	d'eh	?m		14·3	5·5		1·1	1·1		2·2	4·4				
Roldaan [23]	1982	32	9–16	Asthma resort	Asthma	3–30	Exacerbations	45		eg'	lm		48·9			2·2	4·4	37·8	2·2		2·2			
Mertsola [38]	1991	54	1–6	Hospital	Wheezy bronchitis	3	Wheezing episodes	76	5	eg'	o	y	39·5	10·5	11·8	6·8	6·6	1·3	1·3		1·3	3·3		6·6
Totals/weighted average ID rate†							8 studies of children	602				192+ve	31·9	12·3	10·2		7·0	8·0	2·4	4·4	2·2	3·3		
Adults																								
Huhti [47]	1974	63	15–77	Admission	Asthma	12	Asthma admission	142			m		19·0			4·2	4·2	7·7	0·7		3·5	0·7		3·5
Hudgel [18]	1979	19	24–67	O/P/private pract.	Asthma	8–19	Exacerbations	76	4	deh	lm		10·5	2·6		1·3	2·6	3·9						
Beasley [41]	1988	31	15–56	O/P Clinic	Asthma	11	Asthma	178	5	dee	lm	xz	10·0	2·2		4·5	1·7	1·1				0·6		
Totals/weighted average ID ratio†							3 studies of adults	396				53+ve	13·3	2·4		3·8	2·8	4·0	0·7	0	3·5	0·7		(2·8)

† Figures for each virus calculated from only those studies which identified that virus.

‡ Figure in parentheses for the dual infections indicate that the viruses concerned are also included under the individual virus rates. RTI, respiratory tract infection; LRTI, lower RTI; ID, identification; O/P, outpatient; Rhin, rhinovirus; Cor, coronavirus; RSV, respiratory syncytial virus; Par, parainfluenza virus; Inf, influenza virus; Ad, adenovirus; Ent, enterovirus; Myc, *Mycoplasma pneumoniae*; HS, herpes simplex.

* Methods: spec (specimen): 1 = nose swab; 2 = throat swab; 3 = sputum; 4 = nasal washings; 5 = nasal aspirate; 6 = rectal swab.
Culture (cell line): a = embryonated egg; b = human embryonic kidney; c = human amniotic cells; d/d' = 1°/2° monkey kidney; e = human embryonic lung (incl W138); f = MRC-5; g = Hela; g' = Ohio Hela; h = Hep-2; i = MDCK; LLC-MK2; k = mycoplasma culture.
Serum: l = haemagglutination inhibition; m = complement fixation; n = neutralization; o = Ab-enzyme immunoassay.
Ag-D (Antigen detection): x = immunofluorescent microscopy; y = Ag-enzyme immunoassay; z = electron microscopy.

studies with identification rates less than 20% [19,25,42], and these rates were obtained from children admitted to hospital with asthma, whereas the other studies all included outpatients, and the highest rates were obtained from studies in primary care. This probably reflects the time delay between initial respiratory symptoms, and viral investigation. As mentioned above, respiratory symptoms precede the onset of wheezing often by several days, and further time may elapse before a patient is admitted to hospital. This explanation is consistent with the finding of Horn *et al.* [15] that 33% of specimens obtained in the first 5 days of illness were positive, whereas only 18% of specimens obtained after 5 days were positive.

When we examine the individual viruses identified, weighted averages indicate rhinoviruses, RSV and parainfluenza viruses to be the predominant organisms. All the studies found RSV and parainfluenza viruses, and all but one found rhinoviruses and adenoviruses. The exception was the study of Disney *et al.* [25], which only used two cell lines, neither of which was sensitive to rhinovirus, and had the lowest overall identification rate. Among the viruses the rate of rhinovirus identification was the most variable between studies, as might be expected from the difficulty of isolating this virus, and the four studies [15,16,27,28] (three of which were from the same group) with the highest rhinovirus rates, also had high overall identification rates. In three studies [37,43,44] with high overall rates but low rhinovirus rates, RSV and parainfluenza viruses were the predominant organisms. This might be due to different expertise with different viruses in the individual laboratories, or it might reflect the phenomenon of interference, whereby high or epidemic infection rates of one virus result in lower infection rates with other viruses [44] (as with parainfluenza type 1 and 2 infections which alternate in predominance from year to year). Identification rates for other viruses, were, with a few exceptions, lower and less variable between studies. *Mycoplasma pneumoniae* was only identified in studies that used appropriate methods, and only one study [28] used methods specifically for coronavirus.

The prospective studies (Section b, Table 2) in children show a higher weighted average identification rate (31·9%). This is likely to be due to the earlier reporting and investigation of episodes in a follow-up study. Again rhinovirus identification was the most variable between studies and the study with the lowest overall rate [17] (14·3%) had a low rate of rhinoviruses identified although rhinoviruses were the predominant organisms. From the description given of the virology [48] it does not appear that this low rate was due to inadequate methods, but again a slightly higher rate (17%) was reported from specimens taken within 48 hr of symptom onset. Two

studies with high overall isolation rate [23,24] did not attempt to identify rhinoviruses at all. Both of these studies involved very close monitoring of the children by physicians who kept daily records. In one [24], the children were observed in hospital over a period of months: RSV, parainfluenza viruses and coronaviruses were predominant. In the other [23] (which in spite of using only serology had the highest overall identification rate) children were in an Alpine asthma resort over a period of months and had daily physician examinations and spirometry: influenza viruses accounted for the majority of identifications. These studies serve to emphasize that intense observation and early investigation are important and productive in identifying viruses. Weighted average identification rates again indicate rhinoviruses, RSV and parainfluenza viruses to be important, but influenza viruses were also prominent, as were coronaviruses in the two studies which looked for them.

The overall identification rate in the three adult studies (13·3%) is less than half of that in children. The study of Huhti *et al.* [47] looked only at hospital admissions and some subjects lived at a great distance from the investigation centre, in addition only serology was used. In the other two studies, methods appear to have been adequate. Adults have a lower incidence of upper respiratory infection than children [49], and this might mean that viruses are a less important trigger of asthma than in children. However, there is a paucity of data in adults and further studies are required to confirm this. Two studies in adults have been deliberately omitted from the list. In a study of 111 exacerbations of asthma in 51 adults over 18 months, Clarke [50] isolated viruses in only four exacerbations and found seroconversions in another four, and concluded that respiratory infection was not contributory to asthma exacerbations. However, culture specimens were only obtained in 27 exacerbations, and paired sera in 102. Weighting by these figures gives an estimated overall identification rate of 18·7% [(4/27) + (4/102)]. Tarlo *et al.* [51] followed 19 asthmatics and their normal spouses over 12 months, and stated that less than 10% of exacerbations were associated with respiratory infection; however, the actual viral identification rate during episodes is difficult to obtain from the data presented. In the three studies shown in the table, there was little difference in average rates of identifying rhinoviruses, RSV, parainfluenza viruses, influenza viruses or *Mycoplasma pneumoniae*, which were in general lower than for the same viruses in children; this was particularly so for rhinoviruses.

In overview these studies demonstrate some common features. All of the respiratory viruses and *Mycoplasma pneumoniae* have been associated with asthma exacerbations, including herpes simplex virus, although it is hard to know whether this is solely an oral/perioral contami-

·nant. Owing to technical difficulties (which have been acknowledged by authors of all of the above studies), there is great variability in the identification of rhino-viruses and few studies have looked at coronavirus, although these are the two predominant viral species in the common cold [49]. Several studies have implicated two different organisms in the same episode on a few occasions: in the majority of cases this is due to seroconversion to two viruses, or simultaneously with culture of another virus, and rarely due to culture of two organisms [24]. None of the studies has a 'full house' of organisms, again emphasizing individual, seasonal and laboratory variation, and the difficulties of identifying viruses. The frequency of different viruses corresponds broadly to the frequency of the viruses in respiratory illness in the age group studied [16]. However, when hospital admissions for respiratory illness *without* wheeze are considered, rhinoviruses are less commonly found, and RSV more commonly found, than in acute asthma [19,43]. This does not mean that rhinoviruses are not an important cause of hospitalization [52], but that severe lower respiratory disease due to rhinoviruses commonly consists of exacerbation of asthma rather than other pathological conditions. The same may be true of coronaviruses, but little information exists.

Rates of wheezing/asthma in viral respiratory infections (Table 3)

The proportions of subjects who wheeze with an identified respiratory virus have been listed in studies informative in this regard in Table 3. Studies which were not informative were those where investigations were only performed during episodes of wheezing. The table is again divided into incidental studies, where the denominator for the per cent wheezing is all episodes of respiratory tract infection positive to any or specific viruses in extended cross-sectional studies of children, and prospective studies (five in children and one in adults), where the denominator is the number of virus-positive episodes of RTI in asthmatic subjects followed for varying periods. In some studies the numerator was the number of episodes of bronchitis or bronchiolitis, when these were defined in the study as conditions with wheeze and signs of obstruction or air-trapping.

In the incidental studies, the overall rate of wheezing observed during virus-positive illnesses is quite variable (12·5% to 56·4%, weighted average 31·3%), which is also reflected in the variability of wheezing with individual viruses (Fig. 1), and probably represents differences in the groups studied or in the priority given to the identification of wheeze. Rhinovirus and RSV have the two highest rates of wheezing (57% and 77% respectively),

both figures coming from the same study [55] in which 'bronchopulmonary obstruction' is the numerator. The authors defined this as at least three of the signs of '. . . wheezing, expiratory stridor, respiratory chest recessions, rapid respiration rate and audible rales, rhonchi and sibilating rhonchi. . .'. This may have been a broader numerator than in the other studies. In most of the studies, influenza viruses gave generally lower rates of wheezing than the other viruses, which is somewhat paradoxical, considering that this virus is the one most often characterized by infection of the lower respiratory tract in the general population. This might add strength to the argument (discussed in more detail in the second article in this series) that the wheezing arises as an indirect effect of upper respiratory infection.

In the prospective studies of asthmatics, overall wheezing rates were generally higher, as would be expected, and were very consistent at 50–60%, including the single informative study of adults. Further, there was somewhat more consistency both between studies and between the rhinoviruses, coronaviruses, RSV and parainfluenza viruses, in the propensity to be associated with wheezing (Fig. 2). However, influenza viruses had more variability, with wheezing rates varying from 7 to 86%. Adenoviruses and enteroviruses were associated with lower rates of wheezing than the other viruses, but the numbers of enteroviruses and *Mycoplasma pneumoniae* were too small to make adequate judgements.

Do children with asthma get more viral respiratory infections than other children?

Subjects with asthma, particularly in childhood, appear to have frequent respiratory infections, and this is often evidenced by a long history of recurrent antibiotic courses before the diagnosis of asthma is made. However, it is not clear whether they are more susceptible to respiratory infection than those without asthma, or whether they manifest infection more obviously with the development of wheezing or coughing, making subclinical infection less likely. Minor *et al.* [26] found a greater incidence of identifiable viral infections in asthmatic children compared to their non-asthmatic siblings, attributable mostly to an excess of rhinovirus infections. On the other hand, Horn and Gregg [56] found a higher overall incidence of symptoms among asthmatic children with rhinovirus infection than occurred with rhinovirus infection in other groups, including the group defined as having recurrent 'wheezy bronchitis'. In addition, among asthmatics with rhinovirus infection, bronchitis with wheeze was the most common condition, whereas among other groups pure upper respiratory symptoms were predominant. With parainfluenza virus infection the results were more vari-

Table 3. The proportion of viral identifications associated with wheezing episodes

(a) *Incidental studies of unsolicited presentations with RTI*

Author	Year	Number	Age (years)	Source of cases	Presenting condition	RTIs	Study period (months)	Methods* Spec	Culture	Serum	Ag-D	Virus IDs n	% of RTIs	Episodes studied: Description given	% n	Any virus	Rhin	Cor	RSV	Par	Inf	Ad	Ent	Myc	H.S.	Other
Gardner [53]	1960	146	0–5+	Admissions	RTI	146	6	2	adg	m		36	25	Bronchitis c. wheeze	5	13·9					22					
Freeman [54]	1962	357	0–5+	Admissions	RTI	?	36	12	dh	lmn		357	—	Wheeze	96	27·0			52	21	14	13				
Tyrrell [43]	1965	1888	0–17+	Home/admissions	RTI	1888	36	12	abdeg			479	25	Wheeze	60	12·5	10		17	14	3	10	23			16
Glezen [44]	1971	2000	0–15+	Paed. practice	LRTI	3115	66	12	degk			863	28	Bronchiolitis c. wheeze	215	24·9	50		35	20	14	13	24			15
Horn [15]	1975	919	0–13	General practice	RTI	1934	60	12	dchk			614	32	Wheezy bronchitis/iolitis	156	25·4	42		27	16	12	18		35		
Henderson [37]	1979	3–6000	0–15	Paed. practice	LRTI	6165	132	2	deghk			1324	21	Wheeze-associated RTI	396	30·0	49		38	21	11	25	19			
Carlsen [55]	1984	873	0–5+	Admissions	RTI	?	84	5	degh	m	x	873	—	Bronch-pulm-obstruction	492	56·4	57		77	34	16	36				
Kellner [52]	1989	519	0–3	O/P & adm's	RTI	519	20	5	g'		y	227	44	Wheezing			22		25			15				
Totals/weighted average wheezing rate								8 studies				4546			1452	31·3										

(b) *Prospective studies of RTIs in asthmatics*

Author	Year	Number	Age (years)	Source of cases	Entry condition	RTIs	Study period (months)	Methods* Spec	Culture	Serum	Ag-D	Virus IDs n	% of RTIs	Episodes studied: Description given	% n	Any virus	Rhin	Cor	RSV	Par	Inf	Ad	Ent	Myc	H.S.	Other
Children																										
McIntosh [24]	1973	32	1–7	Hospital	Asthma	?	15	12	dehk	lm		102	—	RTI with wheezing	58	56·9		63	96	51	7	35		1/1		
Minor [22]	1974	16	3–11	Allergy O/P	Asthma	71	7	12	dchk	?lm		35	49	Exacerbations	23	58·9	58			0/3	86	0/4	0/1	0/1		
Minor [46]	1976	49	3–60	General practice	Asthma	128	8	12	deh	l		33	26	Asthma	17	51·5	47		67	50	80	33	0/2			
Roldaan [23]	1982	32	9–16	Asthma resort	Asthma	59	3–30	5	eg	lm	o	39†	32	Exacerbations	22	56·4			1/2	2/5	57	1/2		1/1		
Mertsola [38]	1991	54	1–6	Hospital	Wheezy bronchitis	115	3	5	eg	o	y	52	45	Wheezing episodes	30	57·7		69		71	25	20		50		
Totals/weighted average wheezing rate								6 studies of children				261			150	57·5										
Adults																										
Beasley [41]	1988	31	15–56	O/P Clinic	Asthma	251	11	5	dee	lm	xz	30†	10	Exacerbations	18	60·0	68		57	60	1/1	0/1	0/1	1/1		67

† Number includes identifications in episodes of wheeze without symptomatic RTI. ID rate calculated from identifications in symptomatic RTI.

RTI, respiratory tract infection; LRTI, lower RTI; O/P, outpatient; ID, identifications; Rhin, rhinovirus; Cor, coronavirus; RSV, respiratory syncytial virus; Par, parainfluenza virus; Inf, influenza virus; Ad, adenovirus; Ent, enterovirus; Myc, *Mycoplasma pneumoniae*; HS, herpes simplex.

* Methods: Spec (Specimen): 1 = nose swab; 2 = throat swab; 3 = sputum; 4 = nasal washings; 5 = nasal aspirate.
Culture (cell line): a = embryonated egg; b = human embryonic kidney; c = human amniotic cells; d/d = 1°/2° monkey kidney; e = human embryonic lung (incl W138); f = MRC-5; g = Hela; g' = Ohio Hela; h = Hep-2; i = MDCK; j = LLC-MK2; k = mycoplasma culture.
Serum: 1 = haemagglutination inhibition; m = complement fixation; n = neutralization; o = Ab-enzyme immunoassay.
Ag-D (Antigen detection): x = immunofluorescence microscopy; y = Ag-enzyme immunoassay; z = electron microscopy.
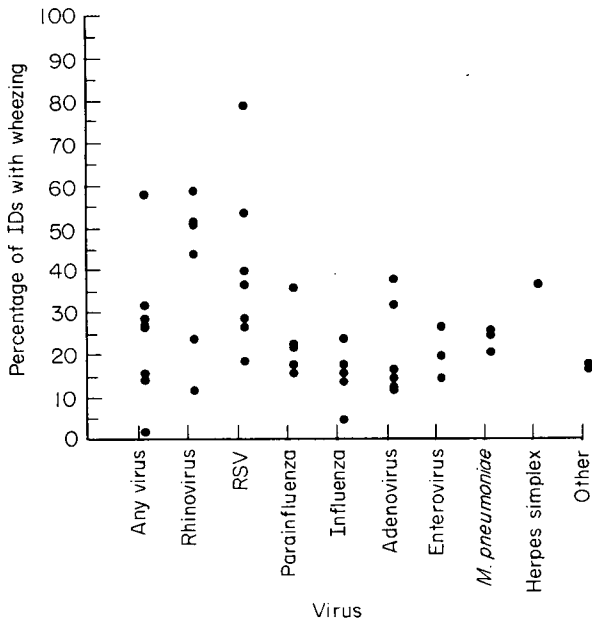
Fig. 1. Wheezing as a per cent of identifications (IDs): incidental studies.
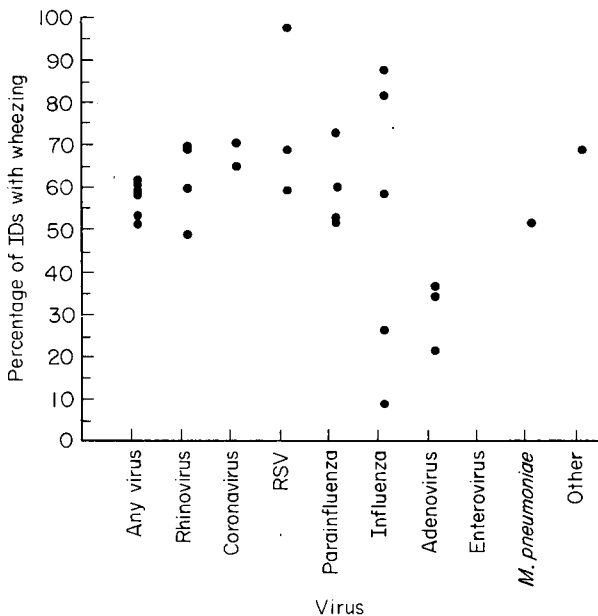

Fig. 2. Wheezing as a per cent of identifications (IDs): prospective studies.

able, and with RSV, the overall incidence of symptoms was lowest in asthmatics, and highest in those children with no history of respiratory illness, although asthmatics exhibited a higher rate of wheeze. Roldaan and Masural [23] found that an asthma exacerbation occurred in six of 21 episodes of seroconversion (three influenza, two parainfluenza type 3, one adenovirus) with mild or absent upper respiratory symptoms, suggesting that the asthma may have been the only manifestation of the viral infection in these six episodes. In a study of 30 preschool children presenting with recurrent respiratory infection, Isaacs *et al.* [57] found that in comparison to a control group of children, the index children had both a higher rate of viral infections and a higher incidence of lower respiratory disease (predominantly wheeze), during proven viral infections. Thus both mechanisms may be contributory: asthmatic children may get more virus infections and more obvious lower respiratory tract symptoms during them, than other children. The situation is less clear in adults with asthma, among whom, again, there is little data regarding viral infections. Tarlo *et al.* [51] found that asthmatic adults reported more symptomatic respiratory infections than their non-asthmatic spouses, but had a lower viral identification rate. Beasley *et al.* [41] reported a similar viral identification rate in asthmatics and non-asthmatics, although the rate for the latter was not given.

Although asthma in children appears to be a risk factor for more symptomatic viral infections, atopy or allergy in itself does not, whether this is measured by skin test positivity or by total IgE [27,28,38,47,57,58]. Several studies have reported that males with asthma or wheezy bronchitis have a higher incidence of viral respiratory infections than females, with male/female ratios between 1·2 and 2·0 [37,42,44,45]. In addition, the age may be important in the total number of infections, and in the predominant viruses. Most studies report that RSV infections are highest in the first year of life and decrease in incidence thereafter (although they still occur in adults [41]), whereas influenza and *Mycoplasma pneumoniae* infections (and in some studies rhinovirus infections), become more common in late childhood [15,16,37,44]. Most studies have found an overall decrease in the prevalence of proven virus-associated wheezing episodes with age [15,19,42,46,48], although Mitchell *et al.* (1976) found that the total viral identification rate during episodes did not alter with age [42].

Summary

The epidemiological studies cited have indicated that viruses are commonly associated with wheezing illnesses

in populations, in individuals, and in time, but, unlike bacteria, are rarely found during asymptomatic periods. Viruses have been identified in up to 50% of wheezing illnesses and asthma exacerbations occurring in childhood, and in up to 20% of those in adults. In childhood the predominant organisms identified have been rhinoviruses, RSV and parainfluenza viruses, but coronaviruses have not been studied adequately. Wheezing appears to be more common during rhinovirus and RSV than other virus infections in children spontaneously presenting with respiratory infections to medical care, but all virus groups have been incriminated, and in general, wheezing occurs in upwards of 50% of viral infections in asthmatics followed prospectively. The few adult studies available show little difference between viruses in identification rates during wheezing, or propensity to result in wheezing. The predominant viruses change with age, and children with asthma seem to be more prone to symptomatic virus infections than other children, although the presence of atopy alone does not appear to be important.

There are important gaps in our knowledge of the epidemiology of virus-associated wheezing attacks, and further prospective studies are required, using early investigation and sensitive methods for identifying rhinoviruses and coronaviruses, to study severe asthma in children and adults. It is hoped that the use of nucleic acid hybridization and newer antigen-detection techniques will improve the ability to identify difficult viruses such as coronaviruses and rhinoviruses in the future. The ability to identify subclinical infections and compare the ratio of subclinical to clinical infections in normal and asthmatic children would be useful but would require intense monitoring of both groups for an extended period (minimum 12 months to cover seasonal variation) with full virological studies every 2–4 weeks—a difficult and expensive task. Another important line of study would be to prospectively document indoor aeroallergen exposure and virus infections in the same individuals, and compare their importance as precipitants of acute severe asthma attacks. With a clearer understanding of the groups at risk for asthma attacks, and the factors which put them at risk and precipitate their attacks, effective preventive strategies will become more feasible.

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