A FAMILY STUDY OF RESPIRATORY ILLNESS

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RECENT investigations suggest that about one-third of all episodes of minor respiratory illness can be attributed to infection with known viruses (Medical Research Council, 1965). The following investigation attempts to outline the role of virus and bacterial infection in the aetiology of such illness in a specific community. It consisted of an epidemiological survey of a group of families with microbiological study of individual respiratory illnesses.

Methods

The participants in the study were asked to report by telephone whenever a cough or cold showed signs of spreading through their families. Once such a message had been received, the families were visited on the same day and often upon the three following days. All members were examined, particular attention being paid to the respiratory tract, and nose and throat swabs were taken from all, whether well or ill. These specimens were inoculated into a range of tissue culture systems described elsewhere (Medical Research Council, 1965). Other episodes of respiratory illness, notified to us by general practitioners or observed in laboratory staff were similarly investigated. These groups and the families from whom specimens were taken were designated 'investigated families'. Sera were obtained from military and civilian personnel and were tested against a range of respiratory viruses (Influenza A, B, C, adenovirus and Coxsackie A21).

In some of the families, specimens were not available but details of illnesses, recorded on cards and subsequently analysed as de-

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scribed elsewhere (Sutton 1961, 1965), yielded epidemiological information. These families were designated 'survey families'. Many of the investigated families also completed the record cards and so the two groups overlapped considerably.

An estimate of the trend of morbidity in the local population was obtained from analysis of the numbers of first claims to sickness benefit received at local National Insurance offices during the period November 1962 to June 1964. With all the errors implicit in these figures, it is nevertheless probable that the monthly variations reflect similar variations in respiratory illness incidence.

Results

In figure 1, the periodicity of first claims to sickness benefit (A)

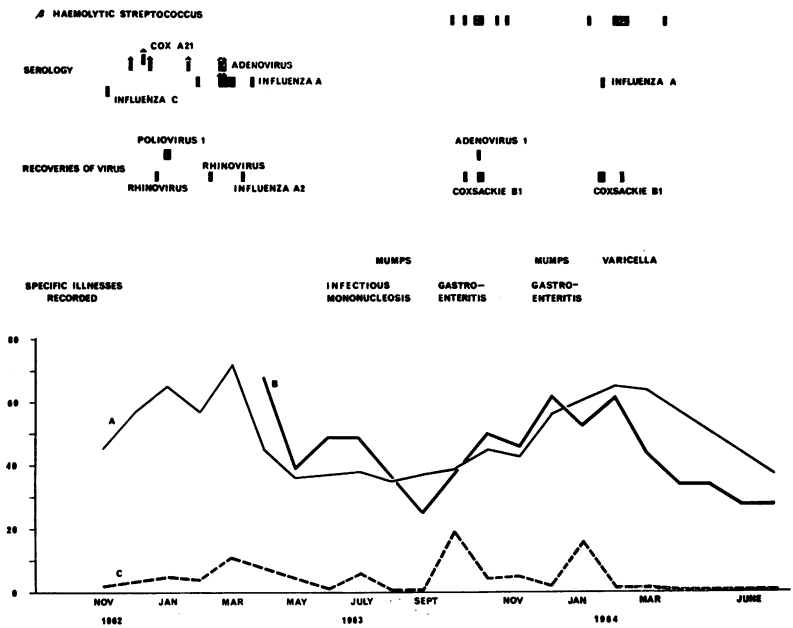

Figure 1
Respiratory illness in Sheffield 1962–1964

A=Incidence of first claims to sickness benefit in the insured population (expressed as percentage of total claims x 10)

B=Incidence of respiratory illness reported by survey families (expressed as percentage of persons at risk falling ill)

C=Incidence of cases of respiratory illness seen by R.N.P.S. (expressed as percentage of total cases seen)

Serology: ī =military cases showing fourfold or greater rise in antibodies when paired sera were tested against given antigens.
I =civilian cases showing fourfold or greater rise in antibodies when paired sera were tested against given antigens

is compared with that of all respiratory illnesses reported by the survey families (B). Both curves are quite comparable and suggest that the sample of population embraced by the survey families followed the same trend of illness experience as the insured population.

There were 45 survey families (189 individuals) who completed the record cards during the period 4 April 1963 to 19 June 1964, the total experience recorded being 60,458 person/days (165.64 person/years). The survey and investigated families resembled each other closely in size and constitution, almost all consisting of father, mother and one to three children.

The total number of respiratory illnesses recorded by the survey family population (expressed as illnesses/person/year) is given in table I. Those children who were five years of age and under, i.e. the pre-school age group, experienced the highest proportion of respiratory illnesses. With increasing age, the number of respiratory illnesses experienced by each person each year diminished. Girls experienced more respiratory episodes than boys but, in adults, the numbers were much the same. In the same table the febrile respiratory illnesses and the sore throats experienced by the survey families are analysed by age and sex. The numbers are less and there is little difference between the age groups. Adults, however, appeared to experience more sore throats each year than did their children.

Forty-eight episodes of respiratory illness were investigated from November 1962 to June 1964. Twenty-nine of the survey families notified illnesses to the laboratory. Two of these families notified four episodes, one notified three episodes, six families notified two episodes and 20 families notified a single episode. Thus 43 of the 48 investigated episodes occurred in the survey families. The remaining five episodes of respiratory illness were notified by general practitioners (three episodes) or were observed amongst the laboratory staff. These 48 episodes consisted of 107 ill persons and 78 well contacts, i.e. a ten per cent sample of the 976 respiratory illnesses recorded by the survey families. The periodicity of these investigated illnesses is given in figure 1, where it is seen to tally fairly well with that of the respiratory illnesses in the survey families and with the claims to sickness benefit.

Illnesses associated with virus infections

Two hundred and thirty-six throat swabs and/or nasal washings from 107 ill persons and 97 similar specimens from 55 well controls were inoculated into the five tissue culture systems which were used. Specimens were obtained from all the ill persons seen, but from only 55 of the 78 well contacts. Viruses were recovered from 15 of the ill persons and from two of the well controls; in one additional

TABLE I

ILLNESSES RECORDED BY SURVEY FAMILIES

Condition	*Respiratory illness*				*Respiratory illness with fever*				*Sore throat*			
Age (years)	*M*	*F*	*M:F*	*Total*	*M*	*F*	*M:F*	*Total*	*M*	*F*	*M:F*	*Total*
0–5	7.5*	7.7	1:1.0	7.6	1.7	2.6	1:1.5	2.1	1.5	2.4	1:1.6	1.9
6–15	3.7	6.1	1:1.6	4.8	1.0	2.1	1:2.1	1.5	1.4	2.4	1:1.7	1.8
Over 16	5.2	5.1	1:1.0	5.1	1.7	1.7	1:1.0	1.7	3.1	2.4	1:0.8	2.7
Total	5.7	6.0	1:1.1	5.8	1.6	2.0	1:1.3	1.8	2.2	2.4	1:1.1	2.3

*Illnesses/person/year.

TABLE IV

RESULTS OF SEROLOGICAL INVESTIGATIONS ON PAIRS OF SERA COLLECTED 1962–1964

Source of sera	*Influenza A*[ab]	*Influenza B*[a]	*Influenza C*[a]	*Adenovirus*[a]	*Coxsackie A21*[c]
Civilian	5/37	0/22	1/30	0/25	0/32
Military	3/40	0/30	0/31	5/31	1/40
Total	8/77	0/55	1/61	5/56	1/72

a=Complement fixation test
b=Haemagglutination inhibition test
c=Neutralization test

TABLE II

THE RELATIONSHIP OF CLINICAL FEATURES TO VIRUS AND BACTERIAL RECOVERIES

Diagnosis	*Number of cases*	*Virus recoveries*					*Number of viruses recovered*	*Bacterial recoveries*		*Total pathogenic viruses and bacteria recovered*
		Influenza A2	*Rhinovirus*	*Coxsackie B1*	*Poliovirus 11*	*Adenovirus 1*		*Number of cases tested*	*Number of β-haemolytic streptococci recovered*	
Common cold	43		2c	3d	1e		6	24	3	9
Feverish cold	15			1f			1	8	0	1
Sore throat	22					1bg	1	22	7	8
Bronchitis	6						0	5	3	3
Influenza	18	6ah		2i			8	14	1	9a
Other	3						0	2	0	0
Total	107	6	2	6	1	1	16a	75	14	30a
Well contact	55		1j		1k		2	33	6	8
Total: (Ill plus well contacts)	162	6	3	6	1	1	18	108	20	38

a=Including one serological conversion.
b=β-haemolytic streptococci also recovered.
c=Two females (29 years and 41 years).
d=Three males (1 year, 3 years, and 42 years).
e=One male (14 years).
f=One female (40 years).
g=One male (21 years).
h=Three males (14 years, 5 years, 39 years) and three females (43 years, 46 years and 75 years).
i=Two females (each 72 years).
j=One male (9 years).
k=One female (16 years).
l=Both recoveries from one family with no history of attenuated poliovirus vaccine administration.

ill person, there was a serological conversion (to influenza A2). Seventy-seven pairs of sera from cases of respiratory illness were tested against five respiratory viruses (table IV). There were few serological conversions to adenovirus and to Coxsackie A21 virus in the civilian (as opposed to the military) population; conversions to influenza A virus occurred in both groups.

Tables II and III show the relationship of clinical features to virus recoveries. Influenza virus infection was closely related to clinical influenza; rhinovirus infection to common colds; and Coxsackie B1 recoveries were related to minor respiratory illness of varying severity. It is of interest that, of the 13 persons who considered themselves ill enough to attend their general practitioners, evidence of virus infection was obtained in nine (virus recoveries from eight and serological conversion in one).

Illnesses associated with bacterial infection

Seventy-five throat swabs from ill persons and 33 throat swabs from well contacts were inoculated on to nutrient agar and blood agar plates. β-haemolytic streptococci were grown from 20 of these 108 specimens and were recovered in 13 out of the 48 family episodes of respiratory illness. On seven occasions, recoveries were made from ill members of the family and not from well contacts; on four occasions from both well and ill members; and on two occasions from well members only. Pathogenic viruses were recovered also on three occasions. It seems likely, therefore, that infection with β-haemolytic streptococci played a part in seven and possibly 11 of the 48 episodes of respiratory illness. It must be kept in mind, however, that a carrier rate of from 10–15 per cent may be found in normal health individuals (Brimblecombe *et al.* 1958, Holmes and Williams 1954, 1958).

The relationship of these recoveries of bacteria to individual illnesses is given in tables II, III and IV. These show that most of the illnesses diagnosed as 'sore throat' or with 'sore throat' as a prominent symptom were associated with infection with β-haemolytic streptococci.

The aetiology of intra-familial outbreaks

In a study of illness in families, it is reasonable to group individual cases and to attribute a causative agent to each intra-familial outbreak. The outbreaks in which the probable or possible aetiology can be attributed in this way are given in table V. This shows that 15/46 (32.6 per cent) of such intra-familial outbreaks were probably or possibly associated with infection by micro-organisms. Seven out of these 46 episodes were associated, with greater or lesser certainty, with a virus infection.

The role of specific viruses and bacteria in the community

Influenza A. In the winter of 1962/1963, there were a number of recoveries of influenza virus and serological conversions to this virus. In figure 2, an attempt is made to correlate the influenza-like illnesses experienced by the survey families with the incidence of virologically proved influenza. It can be seen that there was a period of such illness in April 1963 and again in February 1964.

TABLE III

THE RELATIONSHIP OF CLINICAL FEATURES TO VIRUS AND BACTERIAL RECOVERIES

Clinical features	*Influenza A*	*Coxsackie B1*	*Rhinovirus*	β-*haemolytic streptococci*
History				
Nose blocked ..	1/6	1/6	—	2/14
Nose running ..	1/6	3/6	1/3	7/14
Sore throat	—	—	1/3	9/14
Cough	5/6	1/6	1/3	6/14
Sputum	2/6	—	—	3/14
Hoarseness	1/6	2/6	—	2/14
Chest pain	2/6	1/6	—	1/14
Wheezing	—	1/6	—	2/14
Shivering	—	—	—	2/14
Sweating	1/6	—	—	2/14
Headache	3/6	1/6	—	7/14
Muscle pains ..	2/6	1/6	—	4/14
Vomiting	1/6	—	—	—
Diarrhoea	1/6	—	—	—
Abdominal pain ..	—	—	—	—
Earache	—	—	—	1/14
Physical signs				
Nasal obstruction or discharge	6/6	Not	2/3	2/14
Throat injected ..	5/6	available	1/3	8/14
Ears	—	in all	—	—
Cervical		cases		
Lymphadenopathy ..	1/6		—	3/14
Chest signs	—		—	4/14
Temperature				
Over 98°C	5/6		—	6/14
Over 99°C	3/6		—	6/14
Over 100°C ..	1/6		—	4/14
Days in bed (average)	more than 1			1.5
Days off work (average)	more than 1			more than 2
Number of subjects examined ..	6	6	3[b]	14

b=one person—well control

TABLE V

INTRA-FAMILIAL EPISODES AND THEIR PRESUMED AETIOLOGY

Episode number	*Date of onset of index case*	*Types of illness seen in family episodes of respiratory illness*	*Agent probably[x] responsible*
7	10/2/63	Common cold (2 cases)	Rhinovirus
38	5/11/63	Sore throat and common cold	β-haemolytic strep.
58	18/3/64	Sore throat and bronchitis	β-haemolytic strep.
50	20/1/63	Bronchitis	β-haemolytic strep.
19	15/9/63	Sore throat (2 cases) and acute tonsillitis	β-haemolytic strep.
30	7/10/63	Sore throat with signs in chest	β-haemolytic strep. plus adenovirus
55	7/2/64	Common cold (cases and bronchitis)	β-haemolytic strep.
10	9/3/63	Influenza (6 cases)	Influenza A2
52	25/1/64	Influenza (5 cases)	Influenza plus Coxsackie B[1]
23	21/9/63	Feverish cold and sore throat	Coxsackie B[1]
28	3/10/63	Common cold (3 cases)	Coxsackie B[1]
			Agent possibly[y] responsible
51	23/1/64	Common cold	β-haemolytic strep.
56	5/2/64	Sore throat and common cold (2 cases)	β-haemolytic strep.
54	3/2/64	Sore throat, common cold and bronchitis	β-haemolytic strep.
1	17/11/62	Common cold and feverish cold	Rhinovirus

X=Virus or bacterium recovered from ill persons and not from well contacts
Y=Virus or bacterium recovered from ill persons and also from well contacts
Number of family episodes of respiratory illness investigated=16
Number of family episodes of respiratory illness in which a microbiological agent could be incriminated=11 (probable)—23.9 per cent; 4 (possible)—8.7 per cent; 15 (probable and possible)—32.6 per cent
Number of outbreaks in which no significant microbiological agent was recovered=31

TABLE VI

THE RELATIONSHIP OF RECOVERIES OF β-HAEMOLYTIC STREPTOCOCCI TO SORE THROATS

	Individuals with		
	Sore throats	*Other illness*	*No illness*
β-haemolytic streptococci recovered	7	7	6
Cases studied	23	60	39
Percentage yielding β-haemolytic streptococci	*30.4*	*11.7*	*15.4*

This corresponds to the incidence of cases of clinical influenza seen and diagnosed in the investigated families and also to two peaks of illness in the community.

β-haemolytic streptococcus. During the winter of 1963/1964, a considerable number of β-haemolytic streptococci were recovered from ill persons and from their well contacts. In figure 3, the incidence of sore throats reported by the survey families is related to the incidence of illness in the community and also to recoveries of streptococci. Although clinical sore throats were seen sporadically throughout the course of the survey, a distinct peak in the incidence of reported sore throats occurred in February 1964. This was associated with a peak in recovery of β-haemolytic streptococci and also formed part of the winter wave of respiratory illness.

Coxsackie B1. This virus was prevalent during the winter of 1963/1964 and those individuals who yielded this virus suffered from a variety of minor respiratory illnesses (tables II and III). It is difficult, therefore, to form any typical picture of illness in which the investigated and survey families might be compared. Nevertheless,

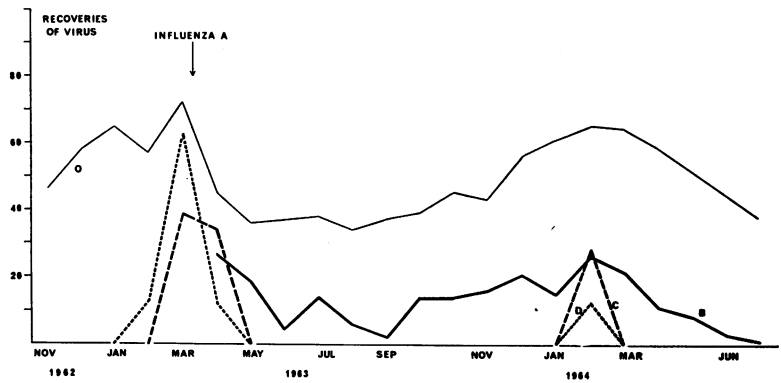

Figure 2
Influenza in Sheffield 1962–1964

A=Incidence of first claims to sickness benefit in the insured population (as in figure 1)

B=Incidence of respiratory illness in survey families which included feverishness, ache in back or limbs and/or headache (expressed as percentage of persons at risk falling ill)

C=Incidence of cases of illness seen by R.N.P.S. and diagnosed as clinical influenza (expressed as percentage of total cases seen)

D=Incidence of pairs of sera showing fourfold or greater rises in HAI or CF antibodies to influenza A (expressed as percentage of total pairs of sera tested)

figure 1 shows clearly that the illnesses associated with infection by this virus formed part of the 1963/1964 peak of winter illness.

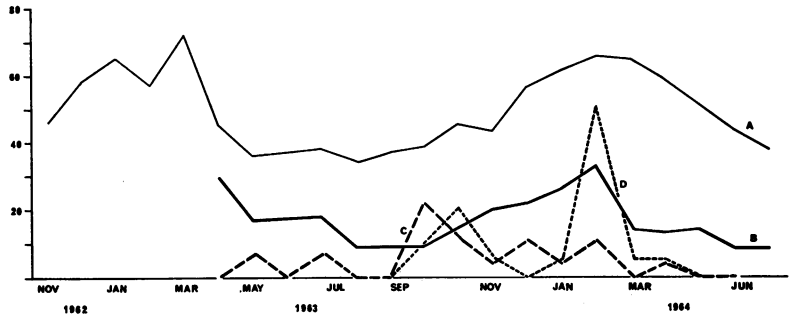

Figure 3
Sore throats in Sheffield 1962–1964
A=Incidence of first claims to sickness benefit in the insured population (as in figure 1)
B=Incidence of respiratory illness in survey families which included sore throat (expressed as percentage of persons at risk falling ill)
C=Incidence of cases of illness seen by R.N.P.S. and diagnosed as sore throat (expressed as percentage of total cases seen)
D=Incidence of recoveries of β-haemolytic streptococci (expressed as percentage of total specimens tested)

Discussion

Much of the investigation of acute respiratory disease has been either epidemiological study of communities, with relatively little search for aetiological agents (e.g. Dingle *et al.* 1953) or comprehensive microbiological studies of small, circumscribed groups of individuals, the results of which may not necessarily hold for the community at large. The present study was an attempt to combine favourable features of both types of approach and to give a balanced account of respiratory illness, as seen in one city over two years. In it, many illnesses which did not reach the care of the general practitioner were studied, as well as some which did. Relatively few pathogenic viruses were recovered from specimens taken during the course of these illnesses. The reasons for this paucity deserve discussion.

Recent surveys of respiratory illness have shown that high rates of virus recovery are possible. Thus, Parrott *et al.* (1963) found that 83 per cent of children admitted to hospital with bronchiolitis and 22 per cent of children seen in outpatients yielded pathogenic viruses. Tobin (1964) found that up to 38 per cent of children admitted to hospital with acute respiratory illness yielded pathogenic viruses. Hamre and Procknow (1963) found that 30.6 per cent of university students with respiratory disease yielded pathogenic viruses and Higgins *et al.* (1964) found that 25 per cent of patients

with acute respiratory disease seen by a local general practitioner yielded such viruses. These surveys suggest that the rate of recovery of viruses is higher in patients admitted to hospital than in those seen in outpatients or in their homes.

In the study which we have described, there was evidence of virus infection in 9/13 (69 per cent) of patients ill enough to be seen by a general practitioner. The overall figure for all patients ill enough to call an investigator (but not necessarily ill enough to call their own doctor) was 16/107 (15 per cent). It appears, therefore, from other workers' data and from our own study, that the proportion of viruses recovered from cases of respiratory illness may vary, possibly directly, with the clinical severity of such illness.

The relationship between individual virus recoveries and clinical syndromes was noteworthy. The incidence of clinical cases of influenza, virologically proved, was paralleled by an increased incidence in the survey population of individuals experiencing influenza-like symptoms and of individuals falling ill in the community. This picture was followed, to a lesser extent, by that presented by β-haemolytic streptococcal infection and its relation to clinical sore throats. Serological investigations showed that infections with Coxsackie A21 and with adenovirus were confined to military personnel, stressing the role of these viruses as causes of respiratory illness in closed communities. Serological conversions to influenza A virus, however, were seen in both groups, suggesting a wider spread.

The overall picture shows that there was a sizeable epidemic of influenza A2 in 1963, which had a noticeable effect upon absenteeism, as reflected by the incidence of first claims to sickness benefit. Few illnesses and fewer viruses or bacteria were recorded in the summer of 1963. With the onset of winter in 1963/1964, a renewed burst of microbiological activity was seen and peaks of illness incidence in the survey families and in first claims to sickness benefit were matched by recoveries of β-haemolytic streptococci and pathogenic viruses. These ceased as the spring of 1964 merged into summer. These findings agree with those of the Collaborative Study of Acute Respiratory Virus Infections (Medical Research Council, 1965).

About one-third of the intra-familial episodes of respiratory illnesses were attributable to virus or bacterial infection. The precise identity of the micro-organisms which were recovered, of course, is only relevant to one particular community studied at one particular time. We put in our thumbs and identified some of the plums prevalent in the plum-pudding of respiratory illness in Sheffield from 1962–1964. Much remained uninvestigated; we did not identify the causative agents of many illnesses reported by the survey families, e.g. infectious mononucleosis, gastro-enteritis,

Nevertheless, it seems clear that much of the minor illness experienced by the volunteer families (and, possibly, much of the minor illness seen by their general practitioners) was due, in the first place, to well-defined viruses or bacteria.

Summary

A longitudinal study of respiratory illness was carried out in a group of families in Sheffield from November 1962 to June 1964. The trend of illness in these families correlated well with the estimated total incidence in the community. A ten per cent sample of respiratory illnesses was investigated for pathogenic viruses or bacteria: these were recovered from about one-third of cases and of intra-familial episodes. In those cases ill enough to seek attention from their general practitioner, the recovery rate was much higher and it is suggested that the rate of recovery of viruses is related to the severity of illness.

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