Session II: Chairman: Sir Charles Stuart-Harris

Viral and epidemiological findings in MRC/PHLS surveys of respiratory disease in hospital and general practice

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Summary

The results found and the laboratory methods used for the isolation of viruses and β haemolytic streptococci in two MRC/PHLS surveys of respiratory disease in patients in hospital and general practice are described. 717 viruses and 82 β haemolytic streptococci were isolated from 2418 children in hospital and 835 viruses and 435 strains of β haemolytic streptococci from patients seen in general practice. Virus isolation rates in the two surveys were 28.9% and 21.0% respectively. Rates by age, sex, time and by clinical categories are given and discussed in relation to isolations from control subjects, the cause of deaths in twenty-two of the children tested, and the incidence of convulsions and meningism found in those examined in these surveys.

In this paper are presented the results of attempted isolations of viruses and β haemolytic streptococci from swabs taken from sample patients. Isolation rates are given for both the general practice and hospital surveys by age groups and seasons of the year, and in relation to diagnosis. Over 85% of all specimens were examined by standard methods and all the expected agents were isolated from patients at some time during the survey in most laboratories. After allowing for the variation in respiratory syncytial (RS) virus isolation rate in the hospital survey and for the low rates in three areas in the general practitioner survey, where only a small number of specimens were examined, the total virus isolation rate was similar in most areas. These facts would suggest that whatever the limitations of the methods employed the deficiencies were likely to have operated equally in different groups.

Laboratory methods for the isolation of viruses and β haemolytic streptococci

Viruses

The standard culture systems used were secondary rhesus monkey kidney (MK) cells (Mair & Tobin, 1960), 'Bristol' HeLa (Peacock & Clarke, 1961; Report, 1964) or HEP 2 (Pal, McQuillin &

Gardner, 1963), human diploid lung fibroblasts [W138, (Hayflick & Moorhead, 1961); or HEL7, (Wellcome Reagents Ltd)] or primary human embryo kidney (HEK) (Tyrrell & Parsons, 1960). Where available, suckling mice less than 48 hr old were used to show the presence of Coxsackie viruses which failed to produce a cytopathic effect in cell cultures. Such a combination of systems permitted the isolation of myxoviruses, RS virus, adenoviruses, picornaviruses and *Herpesvirus hominis* (HVH). A few specimens were also tested in primary human amnion cells. Viruses were identified by standard methods.

All virus specimens were cultured in MK cells and almost all in either HeLa or HEP 2 cells. In general practice 51% were examined in W138 cells in the first year and 98% in the second year. In the hospital survey 56% were examined in HEP 2 in the first year and 73% in the second year. HEL7 was used less frequently in the second year in both surveys and HEK in the hospital one. A much higher percentage of specimens were inoculated into mice from the general practice survey than from hospitals.

Bacteria

Throat swabs taken into Stuart's medium were examined for β haemolytic streptococci of groups A, C or G. Standard methods used in the hospital survey were inoculation on to blood agar incubated aerobically and on to either blood or gentian violet blood agar incubated anaerobically. Incubation temperature was 36-37°C. In general practice laboratories used their usual routine methods.

Results

During the surveys 835 viruses and 435 strains of β haemolytic streptococci of groups A, C and G were isolated from 3966 sample patients in general practice and 717 viruses and 82 β haemolytic streptococci from 2418 patients in hospital. However, only those patients swabbed within 5 days of onset of symptoms have been analysed for isolation rates.

The total virus isolation rates were 28.9% in the hospital survey and 21% in the general practice

survey. In hospital, RS viruses (256 strains) were isolated most often followed by the parainfluenza viruses (147 strains), adenoviruses (88 strains), HVH (58 strains), influenza viruses (50 strains), enteroviruses (61 strains) and the rhinoviruses (44 strains). In general practice, however, the most frequently found viruses were the parainfluenza viruses (190 strains), rhinoviruses (175 strains), influenza viruses (159 strains), enteroviruses (127 strains), adenoviruses (93 strains), HVH (55 strains) and least of all RS viruses (36 strains).

In a small number of cases more than one agent was isolated from the swab from the same patient. Since it was impossible to decide with certainty which of either agent was responsible for symptoms, for simplicity of analysis and presentation, these cases have been included in the Tables for each agent separately, i.e. the same patient has been counted twice.

The number of isolations and the rates of isolations for viruses and β haemolytic streptococci for children under 15 years of age in both surveys are given in Table 1 by size of town for hospital admission and for general practice as a whole. The total isolation rates in large and small towns were lower than in the conurbations and this was largely explained by the predominance of RS virus isolations in these large areas compared with the others. The isolation rates of influenza viruses, parainfluenza viruses, adenoviruses and enteroviruses showed little variation in relation to urban size. Similarly the isolation rate in those under 14 years of age sampled in general practice showed little difference from the rates found in the small town hospitals, the group which geographically and socially was probably most comparable with the population sampled

in the latter study, and when those under 14 years of age are considered. RS virus isolations tended to be high in hospitals where a high proportion of those admitted were children under 1 year of age suffering from lower respiratory tract infections. The RS virus infection in general practice and small town hospitals was considerably lower than in the conurbations or large towns although the isolations of the other viruses in the comparable age groups showed little variation from those obtained in the hospital in-patients. Even rhinoviruses, which might have been considered to cause more mild than severe disease, showed little difference in either survey except in the older population where the rate of isolation was twice that found in the hospital group.

More influenza B strains were isolated in the general practice survey than influenza A in contradistinction from the hospital experience, but this is explained by the earlier start of the former survey.

More parainfluenza type 1 strains were found in the general practice survey than type 3, which was isolated somewhat more commonly than parainfluenza 1 from the hospital patients. In both surveys parainfluenza 2 was found comparatively rarely and parainfluenza 4 on only one occasion.

Isolation rates by age and sex

The isolation rates by age are given in Table 2, those in the hospital survey being split into smaller groups than those in general practice. The overall isolation rates for children aged 0-4 years and 5-14 years can, however, be compared. In the general practitioner survey the virus isolation was higher in children (23.8%) than in adults, but the rates for different viruses showed various age patterns.

TABLE 1. Isolation rates (%) by size of town and in children <14 years of age in general practice

Virus	Conurbation	Large towns	Other towns	General practice
Influenza A	1.3	2.0	1.3	1.2
B	0.4	0.5	1.1	1.1
Parainfluenza	4.5	4.2	7.5	6.6
Adenovirus	3.9	2.8	3.6	3.3
Rhinovirus	1.5	3.5	1.4	3.2
RSV	16.9	8.7	2.4	1.6
HVH	2.8	1.2	2.4	1.1
Coxsackie A	0.1	0.2	1.3	2.1
B	1.3	2.0	1.4	1.4
Echovirus	0.7	—	0.6	0.9
Mumps	0.3	—	0.1	—
Total viruses	400	106	194	487
Total specimens	1190	401	827	2045
Rate (%)	33.6	26.4	23.5	23.9
No. β haemolytic streptococci	54	3	25	274
Total specimens	949	248	564	2045
Rate (%)	5.6	1.2	4.4	13.1

TABLE 2. Isolation rates (%) by age in general practice and hospital surveys

Virus	Hospital				GP	Hosp.	GP		
	0-5 months	6-11 months	1-4 years	0-4 Total years	0-4 years	5-14 years	5-14 years	15-44 years	45+ years
Influenza A	0.9	1.3	1.9	1.4	1.2	1.0	1.1	1.3	3.3
B	0.3	0.5	0.7	0.5	2.0	1.7	3.2	2.6	1.6
Parainfluenza 1	0.4	1.3	3.9	1.9	4.2	1.0	3.0	1.2	1.5
2	0.3	1.3	0.6	1.1	0.5	1.7	1.3	0.5	0.9
3	2.9	2.1	3.2	2.7	2.6	1.4	1.6	0.8	1.5
4	0.0	0.0	0.1	<0.1	0.0	0.0	0.0	0.0	0.0
Adenovirus	1.2	4.2	4.6	3.3	3.4	3.4	3.2	1.3	1.3
Rhinovirus	1.6	1.6	1.6	1.6	4.1	3.5	2.3	5.7	6.0
RSV	23.9	9.3	4.4	12.9	2.9	2.4	0.3	0.1	0.4
HVH	0.3	2.4	3.0	1.9	0.7	5.0	1.4	1.4	2.4
Coxsackie A	0.0	0.3	0.9	0.4	1.5	0.7	2.6	0.6	0.1
B	0.7	2.1	1.9	1.6	1.3	0.3	1.5	1.0	0.4
Echovirus	0.1	0.5	0.7	0.4	1.1	0.7	0.7	0.2	0.3
Mumps	0.0	0.3	0.4	0.2	0.0	0.0	0.0	0.0	0.0
Total virus	226	106	301	633	253	67	234	215	133
Total specimens	682	374	1075	2131	985	287	1060	1249	672
Rate (%)	33.1	28.3	28.0	29.8	25.7	22.3	22.1	17.2	19.8
No. β haemolytic streptococci	12	6	43	61	50	21	224	143	18
Total specimens	518	260	786	1564	985	197	1060	1249	672
Rate (%)	2.3	2.3	5.5	3.4	5.1	1.1	21.1	11.4	2.7

Parainfluenza viruses types 1 and 3 were isolated more often in children than in adults, especially in those under 5 years of age (see Clarke, this symposium). The rate for parainfluenza virus type 2 though, was highest in children aged 5-14 years, as it was in the hospital survey. With types 1 and 3 the rates were highest in children aged 1-4 years admitted to hospital, though that for type 3 was almost as high in infants under 1 year old and in the first 5 months of life.

Isolation rates for the influenza viruses tended to increase with age in the hospital survey but were very similar in the general practitioner survey at all ages except in those aged 45 years or more, where the rate was more than twice that in any other age group. A similar pattern, but less marked, was found with influenza B, but here in the GP survey the maximum isolation rates were in school-children and young adults (see Grist, this symposium).

Isolation rates for adenovirus were low in babies less than 6 months of age as compared with those found in older children, who in turn yielded these agents more commonly than in adults (see Pereira, this symposium). In the general practitioner survey this was true for all types, mainly 1 and 2, but type 3 seemed to be as common in adults as in the younger age groups. In both surveys the most commonly isolated adenoviruses were types 1, 2 and 5.

Rhinovirus isolation rates were higher in adults in the general practice survey than in children, but these viruses were isolated twice as often in pre-

school children—a finding not paralleled in the hospital survey (see Higgins, this symposium).

The rate of isolation of RS virus decreased with age and was ten times higher in babies admitted to hospital at less than 6 months of age than in older children or in adults (see Gardner, this symposium).

The rate for *Herpesvirus hominis* (HVH) increased with age, possibly reflecting increased carrier rates rather than increase in the frequency of primary infection which should have been most frequent in the younger age groups. However, it is interesting to note that herpesvirus was isolated more commonly from those over 45 years of age than those under, perhaps suggesting an increased recurrence rate with advancing age, or a reflection of a higher infection in infancy than has been prevalent since the war.

Infections with echoviruses and Coxsackie A viruses were more common in children than in adults but Coxsackie B isolation rates showed less variation with age. In general practice Coxsackie viruses were found most frequently in the 5-14 years age group as opposed to the hospital survey where enteroviruses tended to be more frequent in children aged 1-4 years. In the general practitioner survey Coxsackie A viruses were found almost as frequently as Coxsackie B, whereas these latter viruses were the commonest of the enteroviruses isolated from those admitted to hospital. Type B5 was the most common type isolated because of the countrywide epidemic of this agent in 1965.

Table 3 illustrates the isolation rate in the different culture systems in relation to individual viruses. Nearly all the influenza and parainfluenza viruses were isolated in monkey kidney. Adenoviruses were isolated almost equally successfully in HeLa, HEP 2 and amnion, but considerably less well in other systems. Rhinoviruses were found most frequently in HEK and human embryo fibroblasts. Although M strains of rhinovirus will grow in monkey kidney cultures only a few were isolated in this system. RS virus was found most often in HeLa cells although in the hospital survey HEP 2 was also useful in detecting this virus. Less than a quarter of RS viruses were isolated in monkey kidney cultures. HVH grew in all systems including mice, although in them and in monkey kidney cultures the isolation rate was low. Fifty-six of sixty-six Coxsackie A viruses were isolated in suckling mice.

Isolation rates in relation to swabbing after the onset of the disease during the first five days are given in Table 4. The overall isolation rate was similar on each of the five days. RS virus rate apparently increased from 4% on the first day to 15% on the fifth day, whereas the parainfluenza 1 viruses were isolated more successfully on the first day than on subsequent days.

Four hundred and thirty-five strains of β haemolytic streptococci comprising 382 Group A and 53 Group C or G were isolated in the general practice survey, giving an isolation rate of 11.0% as compared with only 4.7% in the hospital survey. In the former the rate was conspicuously high in children aged 5–14 years (21%) but much less (5%) in younger children, and low in adults over 45 (2.7%). The differences were less pronounced for streptococci belonging to Groups C and G as the rate for these groups was highest in young adults. There was a marked difference in the isolation of β haemolytic streptococci from children admitted to hospital; only in the 0–4 year age group did the isolation rate approach the comparable one for the general practice survey. This would suggest that most cases of β haemolytic streptococcal infection are either treated successfully in general practice,

or that the organism is difficult to isolate in hospital because of pre-admittance antibiotic therapy.

Analysis of isolation rates by sex showed no really significant differences in rates: in general practice female children under 5 years of age had a slightly higher rate of parainfluenza virus type 1 than rhinoviruses, while males had a higher rate of parainfluenza type 3. In pre-school children males had a predominance of adenovirus type 2 and echoviruses.

Looking at the relative importance of different agents in the same age group it should be noted that in very young babies the isolation rate of RS virus was 8 times the rate of the virus found next most commonly in this age group, namely parainfluenza type 3. Other viruses seemed of relatively little importance before 6 months of age. In the second 6 months of life RS virus still predominated, but parainfluenza viruses, adenoviruses, enteroviruses and HVH were beginning to be isolated twice as often as RS virus; and adenoviruses, enteroviruses and herpesviruses were isolated at about the same rate as in older infants. The isolation rate of rhinoviruses tended to increase with age, although in general practice they seemed more common in children under 4 years of age than they did among such children admitted to hospital.

Isolation rates by time

Isolation rates are summarized for the hospital survey by months in Fig. 1 and for the general practitioner survey by 4-week periods in Fig. 2, the common time of duration between the two surveys being marked by the horizontal lines in the figures; the general practitioner survey commenced 6 months before that in hospitals. Both surveys coincided with the influenza A outbreaks of 1964–65 and 1965–66, while the general practitioner survey was also concerned in the influenza B outbreak which occurred from December 1964 to April 1965. Influenza A isolations were mainly made in the winter of 1965–66, the virus being found over a period of 4–5 months, most isolations being early in 1966. RS virus was found in the three winters covered by the surveys, the main difference between the two being the number

TABLE 4. Virus isolation rates (%) by day of swabbing

Day of swab	Survey				Virus							
	GP		Hospital		RSV rate	Parainfluenza type rate			Influenza rate	Adeno- virus rate	Entero- virus rate	Rhinovirus rate
	No. specimens	Rate	No. specimens	Rate		1	2	3				
1	229	16.6	98	30.6	5.1	1.5	1.2	3.1	1.5	1.5	1.0	3.4
2	1303	21.9	594	27.3	4.4	2.3	1.0	2.0	1.4	0.8	1.1	3.5
3	1353	21.1	673	26.0	8.9	2.7	0.9	2.1	0.6	0.9	0.3	3.4
4	787	21.7	612	30.6	15.9	2.0	0.4	1.8	1.2	1.0	0.4	2.7
5	470	19.4	441	33.1	15.4	2.2	0.2	1.8	1.0	1.0	0.9	3.5

FIG. 1. Isolation rates (%) by time. Hospital survey.

of isolations made and the more sporadic nature of its detection in the GP survey than in the hospital one. In the latter survey RS virus was picked up every month except one in at least one of the hospitals involved.

Parainfluenza virus type 1 tended to be isolated during the winter months, while type 3 was found at most times of the year with a predominance, more marked in the hospital survey, for maximum isolation rates to be obtained during the summer. In 1966 isolations of parainfluenza type 1 began in the early summer in Scotland and north-east England, shortly afterwards in the north-west and midlands, but not until the autumn in the south. It finally disappeared from all areas early in 1967. In both surveys parainfluenza type 2 tended to be found less frequently and to occur in clumps in different areas without any special relationship to the time of year.

FIG. 2. Isolation rates (%) by time. General practice survey.

Rhinoviruses and adenoviruses were found throughout the period of both surveys with perhaps a tendency to be isolated more often in the winter and spring than in the summer. Rhinoviruses were isolated throughout the surveys with no real evidence of significant seasonal variation in their frequency. Similarly HVH was isolated throughout in most practices and hospitals with no evidence of seasonal variation or particular local epidemicity.

Enteroviruses were generally more prevalent in the summer than in the winter, with Coxsackie virus type B being unusually prevalent throughout the country in the summer of 1965. It was isolated in nearly every practice and hospital. No other enterovirus was isolated with exceptional frequency in any particular area although there was some clustering on occasion in some of the practices suggestive of small local outbreaks.

Similarly the isolation rate of β haemolytic streptococci showed little definite seasonal variation although the rate was rather higher in the winter of 1964–65 than subsequently. In some practices, however, fluctuations in prevalence were evident; these

were sometimes short-lived and sometimes more prolonged.

Isolations and clinical categories

Isolation rates for viruses and streptococci in relation to clinical diagnoses are given in Fig. 3 for the hospital survey and in Fig. 4 for that in general practice.

For all age groups combined, virus isolation rates in both surveys were highest in cases of clinical influenza and bronchiolitis/pneumonia, and lowest in those diagnosed as primary otitis media. Isolation rates of over 40% were found in cases of bronchiolitis admitted to hospital and in bronchiolitis and pneumonia of children encountered in general practice (Tables 5 and 6).

Common cold

In the GP survey the most frequently isolated viruses in all age groups from this syndrome were rhinoviruses except in children aged 5–14 years. The next commonest were the parainfluenzas, which

FIG. 3. Isolation rates (%) by age and clinical category. Hospital survey. A = 0–5 months; B = 6–11 months; C = 1–4 years; D = 5–14 years.

FIG. 4. Isolation rate (%) by age and clinical category. General practice survey. A = 0–4 years; B = 5–14 years; C = 15–44 years; D = ≥ 45 years.

were the most common in the hospital survey after RS virus. Adenoviruses were found more frequently in children than in adults.

Primary otitis media

Adenoviruses and RS virus were the main viruses isolated from otitis media but β haemolytic streptococci seemed to play a more important part in this syndrome than viral agents. Virus isolation rates in this syndrome were appreciably lower than in other syndromes in both surveys.

Pharyngitis and tonsillitis

In general practice the predominant agents isolated in patients of all ages with pharyngitis were β haemolytic streptococci Group A. The viruses found showed a wide range of different agents. Adenoviruses were frequent and in both surveys picornaviruses were isolated as often as myxoviruses. When the diagnosis was tonsillitis, adenoviruses were found more commonly than in pharyngitis.

Croup/laryngitis

The parainfluenza viruses of all three types predominated in children in both surveys, with the

TABLE 5. Isolation rates (%) of virus by age and clinical category (hospital survey)

Clinical categories	0-5 months		6-11 months		1-4 years		5-14 years		All ages	
	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.
Common cold	18.8	80	33.3	30	29.2	103	21.1	19	25.4	232
Primary otitis media	13.0	23	23.3	30	15.3	78	9.1	11	16.0	142
Pharyngitis	25.8	31	42.1	38	36.7	148	18.5	27	34.0	244
Tonsillitis	14.3	7	20.8	24	30.8	172	27.8	54	32.7	257
Croup	25.0	12	29.7	37	32.6	144	29.7	37	31.3	230
Bronchitis	32.7	150	28.0	82	20.3	177	18.2	44	25.6	453
Bronchiolitis	43.2	222	26.1	46	25.6	31	50.0	4	38.9	303
Pneumonia	31.8	154	25.6	86	21.8	216	21.8	87	24.8	543
Influenza	66.6	3	0.0	1	66.6	6	50.0	4	57.0	14

TABLE 6. Isolation rates (%) of viruses by age and diagnosis (general practice survey)

Diagnosis	0-4 years		5-14 years		15-44 years		45 and over	
	Rate	No.	Rate	No.	Rate	No.	Rate	No.
Common cold and sinusitis	23.0	343	21.6	171	17.0	305	19.3	166
Primary otitis media	7.7	52	8.3	48	0.0	12	0.0	3
Pharyngitis	21.0	190	19.4	520	12.8	556	15.3	111
Laryngitis and croup	31.0	58	38.9	36	15.5	58	7.7	39
Tracheitis	20.7	82	29.0	93	17.6	85	22.1	95
Bronchitis	25.0	104	19.0	58	13.3	45	15.8	95
Pneumonia and bronchiolitis	43.0	86	15.4	26	0.0	11	30.0	40
Influenza	45.7	70	33.3	108	35.0	177	26.8	123

rhinoviruses becoming more important with age and predominating in adults.

Lower respiratory tract infection

In the hospital survey a high isolation rate of RS virus was found in all three categories of lower respiratory tract infection, i.e. bronchitis, bronchiolitis and pneumonia, the rates in those under 6 months of age being particularly high (23-38%). This virus also was the most frequently found in young children in general practice with bronchiolitis or pneumonia. Rhinoviruses and adenoviruses were also found in some cases in this age group.

Influenza

As would be expected, influenza viruses A and B were the most commonly isolated agents in cases diagnosed as influenza. Isolation rates for them were a little less in adults than in children in the general practice survey, but not greatly so. In children, and to a lesser extent in adults, strains of parainfluenza virus type 1, rhinovirus, RS virus and Coxsackie A virus were isolated, indicating that this syndrome can be produced at all ages by agents other than the influenza viruses themselves.

β haemolytic streptococcal infections

These bacteria were isolated more often in general practice than in hospital patients. The highest rates in both surveys were found in cases of pharyngitis

or tonsillitis at all ages (Tables 7 and 8) and in otitis media in children and young adults.

Convulsions and meningism

In infants less than 1 year of age admitted to hospital convulsions occurred in a quarter of those infected with influenza, parainfluenza 1, Coxsackie and adenoviruses, but not with parainfluenza type 3, RS virus or rhinovirus. In children 1-4 years of age all viruses were associated with convulsions but the frequency in rhinovirus and RS virus infections was less (10-21%) than with influenza, adenovirus and β haemolytic streptococci infections (41-42%). In older children only adenoviruses produced convulsions with any frequency (33%). Meningism was only reported with streptococcal infections and not in any of the children admitted to hospital with virus infections.

Deaths

Twenty-two (0.9%) of the children admitted to hospital died. Three babies, two aged 4 months and one girl aged 5 weeks, died of staphylococcal pneumonia and another aged 3 months from *E. coli* septicaemia and pneumonia. Five infants aged 1-3 months and one child aged 3 years died from viral infections. Four, including the child, yielded RS virus and the other two a parainfluenza virus type 3 and an adenovirus type 1 respectively. Another infant with parainfluenza virus type 3 infection also

TABLE 7. Isolation rates (%) of β haemolytic streptococci by age and clinical category (hospital survey)

Clinical categories	0-5 months		6-11 months		1-4 years		5-14 years		All ages	
	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.
Common cold	0.0	59	0.0	18	0.0	68	5.0	20	0.6	165
Primary otitis media	5.0	20	0.0	21	12.0	65	10.0	10	8.6	116
Pharyngitis	9.5	21	4.8	21	5.5	109	21.4	14	7.3	165
Tonsillitis	0.0	5	15.4	13	9.6	125	17.6	34	11.3	177
Croup	0.0	10	0.0	29	3.2	93	11.1	18	3.3	150
Bronchitis	2.5	119	0.0	70	4.9	141	6.7	30	3.3	360
Bronchiolitis	1.8	166	3.8	26	0.0	18	0.0	2	1.9	212
Pneumonia	2.6	116	3.2	62	4.2	166	7.6	66	4.1	410
Influenza	0.0	2	—	0	0.0	1	33.3	3	16.7	6

TABLE 8. Isolation rates (%) of β haemolytic streptococci by age and diagnosis (general practice survey)

Diagnosis	0-4 years		5-14 years		15-44 years		45 and over	
	Rate	No.	Rate	No.	Rate	No.	Rate	No.
Common cold and sinusitis	2.3	343	7.6	171	1.6	305	1.2	166
Primary otitis media	11.5	52	18.8	48	8.3	12	0.0	3
Pharyngitis	12.6	190	34.6	520	22.8	556	11.7	111
Laryngitis and croup	1.7	58	8.3	36	0.0	58	0.0	39
Tracheitis	1.2	82	3.2	93	2.3	85	0.0	95
Bronchitis	3.8	104	5.2	58	2.2	45	2.1	95
Pneumonia and bronchiolitis	3.5	86	7.7	26	0.0	11	0.0	30
Influenza	4.3	70	10.2	108	3.9	177	0.8	123

had an infection with *Pseudomonas pyocanea* and a *Proteus* species. Fifteen of the children had malformations or diseases known to be associated with recurrent or continuing respiratory disease. Heart failure contributed to the deaths in half the cases and hyperpyrexia or prolonged convulsions or anaemia in another five.

Controls

In the hospital survey an attempt was made to swab a control group of children who had no respiratory systems at the time of sampling and who remained symptom free for at least 48 hr afterwards. Although age to age matching of case and control was not carried out, the age distribution was similar for all sampled patients, and the comparison between the isolation rates in the control subjects and patients with respiratory illness was confined to children admitted to the same hospital and to the same month. The controls were included in order to increase the likelihood of both groups being exposed to a similar risk of infection with currently prevalent viruses. The total virus isolation rate in patients with respiratory illness was about four times that in control subjects - a highly significant difference statistically (Table 9). The isolation rates of individual virus types was low in both groups: in every case the isolation rate was greater in patients than in controls. However, the difference in rates

TABLE 9. Isolation rates from control subjects and patients admitted to hospital at same time

	Controls	Patients	
Parainfluenza 1	1.4	4.6	(s)
Parainfluenza 3	1.4	2.8	(n.s.)
Adenovirus	1.4	4.2	(s)
Rhinovirus	0.7	1.7	(n.s.)
RS	0.7	11.7	(s)
HVH	1.1	1.9	(n.s.)
Enteroviruses	0.7	2.0	(n.s.)
Total viruses	21	187	
Total specimens	280	648	
Rate per cent	7.5	28.9	(s)
β haemolytic streptococci	7	24	
Total specimens	121	472	
Rate per cent	5.8	5.1	(n.s.)

s statistically significant difference ($P < 0.05$);
n.s. not significantly different.

was significant at the 5% level only for parainfluenza virus type 1, all types of adenoviruses combined, and RS virus. The frequency of isolation of β haemolytic streptococci was similar in patients and controls. This was unexpected but may be related to prior antibiotic treatment of patients with respiratory illness. However, control studies of this kind are of limited value in establishing the aetiological roles of agents isolated in cases of acute respiratory disease. This is mainly because it is difficult to be sure that patients and controls are

similar in all relevant respects including the risk of exposure to infection and consequent immunity. However, these results would confirm the other studies using controls in which virus isolations from children with respiratory disease have been consistently higher than in those without.

Discussion

This survey has in general followed the pattern that had been suggested by the earlier MRC survey and by workers in different areas of the United Kingdom (Report, 1965; Holzel *et al.*, 1965; Gardner, 1968; Tyrrell, 1968; Jacobs *et al.*, 1971).

However, when comparing different sized towns, it is apparent that RS virus is a more important pathogen in the early months of life in the large conurbations than in the other areas of the country, or in general practice. The remaining viruses showed little dramatic variation between areas and the distribution of viruses found in general practice and in small town hospitals environmentally similar to them showed little difference. It would seem that there is little selection by hospitals of cases infected with specific viruses but rather that at all times viruses can cause graduations of severity of illness which sometimes are severe enough for the case to be admitted to hospital.

Viruses were more easily isolated from the younger age groups, but this is not surprising as they are more likely to be undergoing primary infections than adults. Viruses are more likely to cause severe infections involving the lower respiratory tract at the extremes of life, being isolated from over 40% of cases of bronchiolitis and pneumonia in the young, and accounting for 30% of such infections in the elderly. These latter figures are very similar to the findings of Foy *et al.* (1973). In their study 35% of adults had chest infections caused by viral or mycoplasma infections. β haemolytic streptococcal infections, on the other hand, are diseases of general practice and cases due to them are rarely admitted to and treated in hospital. They were a substantial causative agent in pharyngitis amongst school-children and young adults and a cause of otitis media in children.

Control studies of a limited nature indicated a causal relationship of virus infections to respiratory disease especially in the cases of parainfluenza type 1, adenovirus, RS and influenza viruses.

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