

A comparison of influenza and respiratory syncytial virus infections among infants admitted to hospital with acute respiratory infections

BY E. O. CAUL, D. K. WALLER, S. K. R. CLARKE

Public Health Laboratory, Myrtle Road, Kingsdown, Bristol BS2 8EL

AND B. D. CORNER

Royal Hospital for Sick Children, St Michael's Hill, Bristol

(Received 1 June 1976)

SUMMARY

Among 741 children under 5 years admitted to hospital with respiratory infections during two winters, infection with influenza A virus was diagnosed in 70 (9%), with influenza B virus in 8 (1%), and with respiratory syncytial virus (RSV) in 259 (35%). Both influenza virus and RSV infections were diagnosed most frequently in children under the age of one year, and diagnosed more frequently in males than females. Influenza illnesses were more severe in boys than girls. Both infections occurred more often, but were not more severe, in children from a conurbation than in those from 'rural' areas. Convulsions were the cause of 36% of admissions with influenza A infections, but were rare in RSV infections. Bronchiolitis was the reason for 39% of admissions with RSV infections, but was rare in influenza infections. It is suggested that infants admitted to hospital are a good source of influenza virus strains for monitoring antigenic variation.

INTRODUCTION

Little is known about the incidence of infection and type of illness caused by influenza viruses in infants. Among those admitted to hospital, Grist (1973) described the findings of the joint Medical Research Council/Public Health Laboratory Service (MRC/PHLS) survey, and Brocklebank, Court, McQuillin & Gardner (1972) described the influenzal illnesses of infants admitted to hospital in Newcastle. Neither group of workers related these infections to the size of the population served.

In the present study, all the children under 5 years old with acute respiratory infections who were admitted to either Bristol Childrens' Hospital or Southmead Hospital during two winters from a circumscribed population were examined for respiratory virus infections as part of a collaborative study by the MRC Laboratory Working Party on RS Virus Infections. During both winters outbreaks of RSV and influenza virus infections occurred, and during the first winter there were also infections with influenza B virus. This paper describes the incidence of influenza infections severe enough to cause infants to be admitted to hospital and the type of illnesses found and compares the findings with those of RSV infections.

PATIENTS AND METHODS

Patients

It was intended to investigate all children under 5 years old admitted with acute respiratory infections. In fact, specimens were collected from about 90 % of those children admitted between 23 November 1973 and 4 April 1974 and between 19 November 1974 and 24 March 1975. The two hospitals served a semi-industrial conurbation of 480,000 people and the surrounding 'rural' area of suburban character of 270,000 people. Poor socio-economic conditions were found more often in the urban than in the 'rural' areas.

Specimens

Nasopharyngeal aspirates were obtained from most of the children, but throat swabs only were taken from a few. Influenza virus was isolated in monkey kidney or human embryo kidney cells, and RSV in bovine testis (Caul, Jacobs & Clarke, 1974), HEp-2, HeLa, or monkey kidney cells. Isolates were identified by the indirect immunofluorescent technique.

Immunofluorescence

Cells from nasopharyngeal secretions or from cell cultures were washed three times in phosphate-buffered saline, put into wells on slides coated with polytetrafluoroethylene, dried, and fixed with acetone at room temperature for 10 min. They were examined by the indirect immunofluorescent technique with (1) a rabbit anti-influenza serum made against A/Hong Kong/1/68 by Standards Laboratory, Central Public Health Laboratory, Colindale, London, and a fluorescein-conjugated sheep anti-rabbit globulin (Burroughs Wellcome); and (2) a bovine anti-RSV serum and fluorescein-conjugated rabbit anti-bovine globulin, both from Burroughs Wellcome.

RESULTS

In the winter of 1973/4, 297 children were tested; of these, 8 (3 %) were shown to be infected with influenza B virus (2 strains similar to the B/Hong Kong/5/72 variant and 6 intermediate serologically between the Hong Kong variant and earlier strains) and 9 (3 %) with influenza A virus, all of which resembled serologically A/Port Chalmers/1/73; and 135 (45 %) children were infected with RSV. Of the 444 children tested in 1974/5, 61 (14 %) had proved infections with influenza A virus (26 resembling A/Port Chalmers/1/73, 16 resembling A/Scotland/840/74, 19 untyped, of which 16 were diagnosed by immunofluorescence only) and 124 (28 %) with RSV.

Age

More influenza virus infections were found in children less than 1 year old than in any of the other four annual groups (Table 1); followed by those between 12 and 23 months of age. Of the children admitted with influenza 42 % were less than

Table 1. Ages of children with proved influenza and respiratory syncytial virus (RSV) infections

Age	Total tested	Influenza infections				RSV infections	
		No. A	No. B	Total no.	% of specimens	No.	% of specimens
Months							
< 3	115	7	1	8	7	67	58
3-5	120	5	2	7	6	46	38
6-8	81	7	1	8	10	40	50
9-11	54	10	0	10	19	23	43
Years							
< 1*	370	29	4	33	9	176	48
1-< 2	148	19	0	19	13	39	26
2-< 3	97	8	1	9	9	23	24
3-< 4	78	8	1	9	12	16	20
≥ 4	48	6	2	8	17	5	10
Total	741	70	8	78	11	259	35

* Total of upper four rows.

1 year old, and eight (10 %) were less than 3 months old. The largest number of RSV infections occurred in infants less than 3 months old.

Diagnosis

The diagnosis was recorded in 725 of the children (Table 2). Those with convulsions were included only in the second winter; 36 % of children with proved influenza infections had convulsions, which occurred in children of all ages, but chiefly in those aged 1 and 2 years. A quarter of these children had no respiratory symptoms. RSV rarely caused convulsions (Fig. 1) – only 5 children had convulsions, one without respiratory symptoms. Influenza virus infections rarely caused bronchiolitis, whereas 39 % of children with RSV infections had bronchiolitis (Fig. 1). Upper respiratory infections occurred in 43 % of the children with influenza virus infections, many of whom had been admitted with convulsions.

Sex

Table 3 shows that, of the 738 children admitted with respiratory infections in whom the sex was recorded, more were boys than girls. However, the same proportion of specimens from each sex were positive for influenza viruses and this was also true for RSV infections. Of those children with influenza virus infection, more boys than girls had lower respiratory illnesses, but with RSV infections, the same proportion of each sex had infections of the lower respiratory tract.

Type of population

An estimate was made of the population under 5 years from which the two hospitals received their patients. In relation to this, a greater proportion of children were admitted with respiratory infections from the city (7.4 admissions per

Table 2. *Clinical diagnoses of children with influenza or respiratory syncytial virus (RSV) infections*

Diagnosis	Total tested	Influenza infections				RSV infections			
		No. A	No. B	Total no. specimens	% of specimens	% of influenza infections	No.	% of specimens	% of RSV infections
Upper respiratory	234	29	3	32	14	43	57	24	22
Croup	48	3	2	5	10	7	9	19	3
Bronchitis	158	12	2	14	9	19	50	32	19
Bronchiolitis	154	8		8	5	11	99	64	39
Pneumonia	110	10	1	11	10	15	41	37	16
Convulsions alone*	21	5		5			1		
Total	725	67	8	75	10	100	257	35	100
% with lower respiratory illness	58	—	—	44	—	—	74	—	—
Convulsions with respiratory illness*	62	17	—	17	—	—	4	—	—
Total convulsions*	83	22	—	22	—	36†	5	6	4

* 1974/5 only. † % of 61 1974/5 influenza A infections.

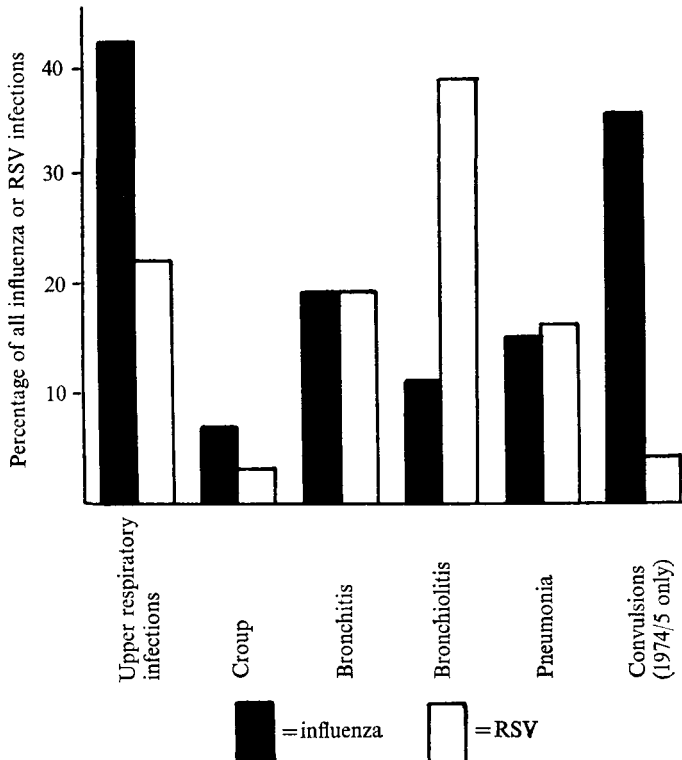


Fig. 1. Diagnosis of children with influenza or RSV infections.

1000 children under 5 years in the population each winter) than from the 'rural' areas (4.5/1000) (Table 4). The same proportion of respiratory admissions from the two communities were the result of influenza virus infections, and of these, the same proportion had lower respiratory illnesses. The findings for RSV infections were similar.

DISCUSSION

The age distribution of influenza should vary from year to year depending on the immunity of the population to the current strain. With the appearance of a new type, to which none of the population is immune, infection rates would be about the same at all ages (Hope-Simpson, 1970). However, in years when a proportion of the population is immune to the current strain one would expect the infection rate to be highest in babies after they had lost their maternal antibody (Hall, Cooney & Fox, 1973), although this does not always occur (Monto & Kioumehr, 1975). Surveillance by the PHLS (1975) in 1973/4 and 1974/5 showed that influenza A virus infections severe enough to merit consultation with a doctor were most common in the 0 to 4-year age group, and commoner in the 5 to 14-year age group than in older groups, whereas influenza B virus infections were commonest in the 5 to 14-year age group (J. W. G. Smith, personal communication).

The age at which people are admitted to hospital with influenza virus infections will be related to the severity of the illness at different ages as well as the incidence of infection at different ages. Surveys which estimate the proportion of infants

Table 3. Sex of children with influenza and respiratory syncytial virus (RSV) infections

	Influenza infections				RSV infections					
	Total tested	No. A	No. B	Total no.	With lower respiratory illness		% of specimens	No.	With lower respiratory illness	
					% of specimens	No.			%	No.
Male	434	42	6	48	11	25	52	36	120	77
Female	304	28	2	30	10	9	30	33	78	77
% male	59	60	—	62	—	—	—	—	—	—

Table 4. Influenza or respiratory syncytial virus (RSV) infections in relation to type of population

	Influenza infections				RSV infections							
	Total tested	Population < 5 years	Admissions/1000 population/year*	No./1000 population/year*	With lower respiratory illness		% of admissions	No.	With lower respiratory illness			
					% of admissions	No.			%	No.	%	
Urban	524	35,230	7.4	54	0.8	23	43	185	2.6	35	144	78
Rural	217	24,081	4.5	21	0.4	10	43	74	1.5	34	55	74
% urban	71	59	—	72	—	—	—	71	—	—	—	—

* Average of two winters.

admitted to hospital who are infected with influenza virus give an impression of low incidence, for the influenza cases are diluted by the large numbers of RSV infections. A more significant figure is given if the influenza infections are related to the population at risk. In the present survey, the proportion of respiratory admissions who were infected with influenza viruses was lower under the age of 12 months than over this age, but the total number of influenza virus infections was greatest under the age of 12 months (Table 1).

In this routine diagnostic laboratory where no special influenza surveillance is done, the largest number of influenza isolations are made from babies admitted to hospital. That babies are a fruitful source of influenza isolates for serological analysis has been pointed out by Levine, Togo & Wald (1974).

The age distribution of children with RSV infections found in the present survey agrees with that previously observed (Parrott *et al.* 1973) with maximum numbers aged less than 3 months. This age distribution is probably explained by the lack of significant antigenic variation in RSV (Monto, Bryan & Rhodes, 1974), that severe infections meriting hospital admission occur only on primary infection, and because most children probably have their first RSV infection before the age of two years (Kim *et al.* 1973). Reinfections with RSV are probably frequent (Kim *et al.* 1973; Cooney, Fox & Hall, 1975), but the illnesses caused are probably milder than the primary infections.

The incidence of influenza A and B infections as detected serologically is the same in the two sexes (Hall, Cooney & Fox, 1973), but, as the present results show, males under the age of 5 years probably have more severe illnesses when they are infected with influenza virus for they are more often admitted to hospital with these infections than females. The proportion of admissions with influenza virus infections was the same for both sexes, but as the numbers of admissions of males with all acute respiratory infections was almost twice that of females, the number of males admitted with influenza infections was very much greater than the number of females. Of those with influenza virus infections, a larger proportion of males than females had lower respiratory infections.

The preponderance of boys among children admitted to hospital with all respiratory infections was also observed by Mufson, Krause, Mocega & Dawson (1970) and found in the MRC/PHLS hospital survey (Miller, 1973). When expressed as an infection rate, i.e. as the proportion of children admitted who are infected with a particular virus, this preponderance is lost (Poole & Tobin, 1973). A similar male preponderance has been shown with acute respiratory illness in the community (Monto & Ullman, 1974).

The same is found with RSV infections. Such infections are equally common in the two sexes when judged serologically (Monto *et al.* 1974), but the infected males are probably more severely ill, for they are more often admitted to hospital (Parrott *et al.* 1973). This was confirmed in the present survey, for twice as many boys as girls were admitted with RSV infections; however, an unexpected finding was that, of those admitted, the same proportion of boys as girls had lower respiratory infections.

Since there were more males than females among the children yielding neither

RSV nor influenza viruses, it is probable that other respiratory viruses also cause more severe illness in males than females.

Little has been written about the incidence of influenza in different population groups. In the present study, although the difference in social conditions between the urban and rural areas was not great, admissions to hospital of children with acute respiratory infections were estimated to be greater per 1000 population from the urban than from rural areas, but of those admitted, the same proportion were infected with influenza viruses. The same was found with RSV infections. This may be because these and other respiratory viruses spread more easily in crowded conditions, causing a higher infection rate, or because children from lower social classes were admitted from the city for social reasons, or were more severely affected. The last two explanations are unlikely, since the same proportion of urban and rural children with RSV or influenza virus infections had infections of the lower respiratory tract. 'Rural' children may be admitted less often merely because it is less convenient.

The admission rate reported here, which is probably a slight underestimate, per 1000 population under 5 years of age of 0.135 for influenza B in 1973/4, 0.15 for influenza A for 1973/4, and 0.61 for influenza A in 1974/5 compares with the finding of the PHLS influenza surveillance (1975) in England during the same two winters of a 'virologically estimated' consultation rate in general practice per 1000 population under 5 years of 13.7 for influenza B in 1973/4, 17.5 for influenza A in 1973/4 and 59.0 for influenza A in 1974/5 (J. W. G. Smith, personal communication). The comparison indicates that about 1 in 100 children under 5 years with influenza who were seen by their doctors were admitted to hospital.

RSV is very labile and it is probable that in any RSV survey depending on virus isolation alone a significant proportion of infections will be missed. Neither is the serological diagnosis of infection infallible, as maternal antibody in the acute serum can disguise antibody rises, and very large amounts of antigen are needed in the complement fixation test to detect a primary antibody response (Jacobs & Peacock, 1970). A more accurate measure of the total number of RSV infections is obtained by immunofluorescence, as in the present study. However, because suitable specimens were not obtained from all children, the incidence found here was probably underestimated by 15%. This incidence of RSV infections per 1000 population under 5 years of 1.7 for 'rural' areas and 2.6 for the city for children admitted to hospital each winter compares with an incidence of RSV infections detected by immunofluorescence in rural Cumberland of 2.37 and in the Tyneside conurbation of 8.35 (Downham *et al.* 1974).

The present survey showed that convulsions were a common cause for admission with influenza A virus infections under 5 years of age, and that bronchiolitis was rare – the converse of what was found with RSV infections. Similar results were found in influenza virus infections by Brocklebank, Court, McQuillin & Gardner (1972). In the present survey children with convulsions were not included in the first year when influenza B virus infections occurred, but Kerr, Downham, McQuillin & Gardner (1975) found that convulsions were less frequent in influenza B virus infections than in those due to influenza A virus.

We are grateful to Professor N. R. Butler, and Drs D. Burnam, D. C. L. Savage and F. Carswell for permission to study patients under their care; to Drs P. G. Swift, D. Stevens and C. Haines for supplying clinical details; to Messrs N. J. Bishop, V. Annette and G. W. Smyth and Misses M. Bateman and J. Burrows for technical help; to Dr M. S. Pereira for serotyping of influenza strains; and Dr P. G. Higgins and Dr H. R. Cayton for helpful advice. The investigation was part of a larger collaborative study organized by the Medical Research Council Working Party on Respiratory Syncytial Virus.

REFERENCES

- BROCKLEBANK, J. T., COURT, S. D. M., MCQUILLIN, J. & GARDNER, P. S. (1972). Influenza-A infection in children. *Lancet* *ii*, 497.
- CAUL, E. O., JACOBS, J. W. & CLARKE, S. K. R. (1974). Bovine-testis cells for routine isolation of respiratory syncytial virus from infants. *Journal of Medical Microbiology* *7*, 301.
- COONEY, M. K., FOX, J. P. & HALL, C. E. (1975). The Seattle Virus Watch. VI. Observations of infections with and illness due to parainfluenza, mumps, respiratory syncytial virus and *Mycoplasma pneumoniae*. *American Journal of Epidemiology* *101*, 532.
- DOWNHAM, M. A. P. S., ELDERKIN, F. M., PLATT, J. W., MCQUILLIN, J. & GARDNER, P. S. (1974). Rapid virus diagnosis in paediatric units by postal service. Respiratory syncytial virus infection in Cumberland. *Archives of Disease in Childhood* *49*, 467.
- GRIST, N. R. (1973). Influenza virus infections. *Postgraduate Medical Journal* *49*, 807.
- HALL, C. E., COONEY, M. K. & FOX, J. P. (1973). The Seattle Virus Watch. IV. Comparative epidemiologic observations of infections with influenza A and B viruses, 1965-1969, in families with young children. *American Journal of Epidemiology* *98*, 365.
- HOPE-SIMPSON, R. E. (1970). First outbreak of Hong Kong influenza in a general practice population in Great Britain. A field and laboratory study. *British Medical Journal* *iii*, 74.
- JACOBS, J. W. & PEACOCK, D. B. (1970). Differentiation of actively and passively acquired complement-fixing antibodies in infants with respiratory syncytial virus infection. *Journal of Medical Microbiology* *3*, 313.
- KERR, A. A., DOWNHAM, M. A. P. S., MCQUILLIN, J. & GARDNER, P. S. (1975). Gastric 'flu, Influenza B causing abdominal symptoms in children. *Lancet* *i*, 291.
- KIM, H. W., ARROBIO, J. O., BRANDT, C. D., JEFFRIES, B. C., PYLES, G., REID, J. L. & CHANOCK, R. M. (1973). Epidemiology of respiratory syncytial virus infection in Washington D.C. I. Importance of the virus in different respiratory tract disease syndromes and temporal distribution of infection. *American Journal of Epidemiology* *98*, 216.
- LEVINE, M. M., TOGO, Y. & WALD, E. R. (1974). Practicability of influenza surveillance by virus culture of children. *American Journal of Epidemiology* *100*, 272.
- MILLER, D. L. (1973). Collaborative studies of acute respiratory disease in patients seen in general practice and in children admitted to hospital. Aims, field methods and morbidity rates. *Postgraduate Medical Journal* *49*, 749.
- MONTO, A. S., BRYAN, E. R. & RHODES, L. M. (1974). The Tecumseh study of respiratory illness. VII. Further observations on the occurrence of respiratory syncytial virus and *Mycoplasma pneumoniae* infections. *American Journal of Epidemiology* *100*, 458.
- MONTO, A. S. & ULLMAN, B. M. (1974). Acute respiratory illness in an American community. The Tecumseh study. *Journal of the American Medical Association* *227*, 164.
- MONTO, A. S. & KIOUMEHR, F. (1975). The Tecumseh study of respiratory illness. IX. Occurrence of influenza in the community, 1966-1971. *American Journal of Epidemiology* *102*, 553.
- MUFSON, M. A., KRAUSE, H. E., MOCEGA, H. E. & DAWSON, F. W. (1970). Viruses, *Mycoplasma pneumoniae* and bacteria associated with lower respiratory tract disease among infants. *American Journal of Epidemiology* *91*, 192.
- PARROTT, R. H., KIM, H. W., ARROBIO, J. O., HODES, D. S., MURPHY, B. R., BRANDT, C. D., CAMARGO, E. & CHANOCK, R. M. (1973). Epidemiology of respiratory syncytial virus infection in Washington, D.C. II. Infection and disease in respect to age, immunologic status, race and sex. *American Journal of Epidemiology* *98*, 289.

- P.H.L.S. WORKING GROUP (1975). A programme for collaborative influenza surveillance. *Journal of Hygiene* **75**, 1.
- POOLE, P. M. & TOBIN, J. O'H. (1973). Viral and epidemiological findings in MRC/PHLS surveys of respiratory disease in hospital and general practice. *Postgraduate Medical Journal* **49**, 778.