PAPERS AND ORIGINALS

Respiratory syncytial virus infection in north-east England

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Summary

During a period covering four winter epidemics 987 respiratory syncytial (RS) virus infections were identified in the children's wards that served a total population of about 875 000 in north-east England. The incidence of admission to hospital with RS virus infection tended to be twice as high among children in Tyneside as that among children from the rest of the catchment area. The risk of hospital admission with RS virus infection in the first year of life for city children was about 1 in 50. The risk tended to be increased when there was a high proportion of children in the population, overcrowded housing, and unemployment. There was no clear relation between climatic changes and the onset or progress of epidemics. Thirteen deaths associated with RS virus infection were identified, four of them sudden and unexpected at home, and nine of them in children with congenital or acquired abnormalities. Twelve children were admitted twice with distinct RS virus infections; the relative severity of their two illnesses depended on age. Hospital cross-infection accounted for 60 of the 987 illnesses.

Large families and overcrowding among poorer families seem to lead to a higher incidence of RS virus infection, and measures to reduce overcrowding and improve housing should help to reduce the spread of infection. Breast-feeding also protects infants from infection, but further information is needed to pinpoint the infants at greater risk and how they may best be protected.

Introduction

Infection with respiratory syncytial (RS) virus causes considerable morbidity and mortality in young children.¹⁻³ Winter outbreaks have been reported from many countries, including the United States,³⁻⁹ Finland,¹⁰ Japan,¹¹ and Australia.^{12,13} Kim *et al* calculated that the risk in infancy of admission to hospital with RS virus bronchiolitis was 4 per 1000 infants in Washington DC,³ but no one else has attempted to measure morbidity and mortality for a defined population.

Major yearly outbreaks of RS virus infection have occurred in north-east England for the past 12 years, and virus surveillance of children admitted to hospital with respiratory illness in this area has become increasingly complete. We therefore analysed in detail a period covering four RS virus epidemics in an attempt to assess more fully the incidence, clinical effects, and factors affecting spread of infection with this virus.

Methods

From 31 December 1971 to 31 May 1975 paediatric ward staff in Newcastle and Gateshead hospitals were encouraged to take nasopharyngeal secretions together with cough and nasal swabs for virus diagnosis from all children admitted with any form of respiratory tract illness. Specimens were examined for RS and other respiratory viruses by both the fluorescent antibody technique and tissue culture according to methods described elsewhere.¹⁴ Medical staff provided the age, sex, and clinical diagnosis in each case, the last according to agreed definitions.¹⁵ Surveillance was maintained over cases of hospital cross-infection as well as primary admissions. Cot deaths at home and respiratory deaths in hospital were investigated at necropsy for the presence of RS virus in respiratory secretions and lung.¹⁴

The catchment area extended from the Scottish border north of Berwick upon Tweed to a few miles south of the River Tyne, but excluded the towns to the north and south of the river mouth, which are served by other hospitals. The Pennines and Cheviot hills formed the western boundary of the area. In 1974 there were 874 990 people in this area (Northern Regional Health Authority figures). RS virus outbreaks in Cumberland were studied by means of posted specimens.¹⁶

Comparisons in the incidence of admission to hospital because of RS virus infection were made between part of the Tyneside conurbation (Newcastle upon Tyne and Gateshead) and less densely populated areas and between different parts of the city of Newcastle. Crude population figures derived from the 1971 census were used for overall comparisons between the conurbation and the rest of the

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catchment area. For comparing smaller populations more accurate methods were necessary. Population figures for nearby towns were derived from the *Registrar General's Annual Reports*. In the comparison city wards the home addresses of infants born live, excluding those who died soon after birth, were obtained from the community health services for two years of the study. Children aged over 12 months were excluded. Information on housing, social conditions, and population within city wards was obtained from census figures available in the social services department.¹⁷

Detailed information about climatic conditions before and during the early part of each epidemic was obtained from the Newcastle Weather Centre.

Results

From 31 December 1971 to 31 May 1975 987 RS virus infections were identified by the laboratory. Sixty of these were acquired in hospital by cross-infection.

Epidemic patterns—Outbreaks started during December in two of the four years studied and in the November and the January of the other two years (see figure). The peak of each outbreak occurred in February or March with a gradual rise and fall in the numbers of cases over at least two months before and two months after the peak. Once an outbreak began RS virus was isolated for at least six and sometimes eight consecutive calendar months. The peaks of the four outbreaks were 10, 12, and 10 months apart respectively.

Number of RS virus cases for each month of study.

Climate—Daily maximum and minimum temperatures; daily temperature range; daily rainfall quantity and duration; hours of sunshine; presence of fog, frost, snow or hail; 9.00 am readings of barometric pressure; relative humidity; dew point; and wind direction were analysed and weekly trends compared over the two months ending a week before the first isolation of RS virus in Newcastle. The week immediately before each first isolation was excluded to allow for incubation and prodrome. Statistical analysis showed no relations that were consistent for all four epidemics.

Incidence—The incidence of admission with RS virus infection in the conurbation was 1 per 3400 total population and 1 per 7300 for the rest of the catchment area during the 1973-4 outbreak. During the 1974-5 outbreak the incidence for the conurbation was 1 per 3000 and for the rest of the catchment area 1 per 6900. For comparison the incidence in the Whitehaven area of rural Cumbria was 1 per 7000 in

1973-4 and 1 per 39 000 in 1974-5. For Newcastle the incidence of RS virus infection in infancy that needed hospital admission ranged from 1 per 38 to 1 per 62 and for nearby industrial towns from 1 per 60 to 1 per 76 children. In two small country towns the incidence was 1 per 102 and 1 per 135. There was a clear trend to a higher incidence in industrial areas than in rural ones.

The incidences in certain city wards, chosen because of differences in socioeconomic conditions and housing density were also compared (table I). Although the numbers of admissions from individual wards were too small for statistical validation, there seemed to be a direct relation between incidence and percentage of children in the population, percentage of households with more than six people or more than one person per room, and the percentage of unemployed unskilled workers. There was little or no relation to density of total population, housing density, or average number of people in the house. One small area on the city map yielded RS virus admissions in each of the four epidemics with a consistency that was unique in comparison with other areas. We investigated the social conditions in this area and found that it consisted of a few streets with unusually poor and overcrowded housing.

Categories of illness—Table II shows the frequency with which RS virus was identified among total respiratory infections in all children during the study. Overall RS virus was associated with 20.5% of these illnesses. Mild and doubtful cases of respiratory infection were included in our surveillance, which accounts for the many children classified as having upper respiratory tract infections. In 22.1% of children the illness was confirmed to be in the upper respiratory tract, and 2.4% had croup. Most suffered from lower respiratory tract disorders—bronchitis (14.5%), pneumonia (6.9%), and especially bronchiolitis (54.1%).

TABLE II—Contribution of RS virus to total respiratory infections in hospital

	Total No of respiratory infections	RS virus	All other viruses	No of Virus-negative cases
Upper respiratory tract infection	2537	218 (8.6%)	886	1433
Croup	307	24 (7.8%)	152	131
Bronchitis	898	143 (15.9%)	196	559
Bronchiolitis	721	534 (74.1%)	82	105
Pneumonia	354	68 (19.2%)	74	212
Total	4817	987 (20.5%)	1390	2440

Age—Table III shows the age distribution for the different categories of illness. The peak age for RS virus bronchiolitis was 2 to 3 months.

Sex—In each epidemic there was a predominance of male patients, with an overall male to female ratio of 1.4:1.

Cross-infection—Sixty children acquired RS virus by hospital cross-infection, and their illnesses are shown in table IV. Twenty-nine were aged under 12 months and 16 of these (55%) developed lower respiratory tract illness. For primary admissions the proportion of children under the age of 12 months with lower respiratory tract illnesses was 88%.

Reinfection—We identified 12 children who were admitted twice with distinct RS virus infections. The interval between the onset of the two illnesses ranged from 16 days to 14 months, with a mean of 66 days. The relative severity of the two illnesses seemed to depend on the age at the time of the second illness. The second illness tended to be more severe when it occurred before the age of 14 weeks (five children) but less severe after this age (seven children), though still severe enough to necessitate readmission to hospital. The only exception was a boy with a ventricular septal defect who had RS virus bronchiolitis at the age of 10 weeks and a more severe attack aged 22 weeks.

TABLE I—Comparisons in incidence of RS virus admissions in infancy from contrasting city wards

City ward	Incidence of RS virus admissions in:		% of population ≤4 years old	% of population 5-11 years old	% of households with ≥6 people	% of households with ≥1 person per room	% of unemployed unskilled, manual workers
	1974-5	1974-5					
A		1/70	3.5	8.7	3.6	3.3	1.2
B		1/110	5.0	7.0	3.5	2.6	1.7
C	1/26	1/47	8.1	9.4	4.8	10.8	5.1
D	1/36	1/41	8.1	13.0	9.0	16.6	10.2
E	1/52	1/26	7.1	12.9	9.0	16.4	5.4

TABLE III—Percentage distribution against age in illnesses due to RS virus

		Months												Years				
		Age:	<1	1	2	3	4	5	6	7	8	9	10	11	1	2	3	≥4
Upper respiratory tract infection..	..	..	1.4	4.3	6.7	5.8	4.8	4.8	3.4	2.9	3.8	2.9	1.4	1.4	28.4	15.1	7.2	5.8
Croup	..	..	..	..	..	4.2	4.2	4.2	4.2	4.2	4.2	4.2	4.2	4.2	25.0	20.8	16.7	12.5
Bronchitis	..	..	0.7	4.2	5.7	7.8	3.5	7.8	5.0	5.7	3.5	3.5	4.2	3.5	17.7	9.2	9.9	7.8
Bronchiolitis	..	..	2.7	15.8	17.9	17.9	10.6	10.3	7.6	4.4	4.4	2.1	2.5	1.3	2.5	0.2	..	..
Pneumonia	..	..	2.9	10.3	14.7	10.3	7.4	2.9	5.9	1.5	5.9	..	..	7.4	13.2	8.8	2.9	5.9

TABLE IV—Illnesses associated with hospital cross-infection by RS virus

	Upper respiratory tract infection	Croup	Bronchitis	Bronchiolitis	Pneumonia	Total
Children <12 months	13	..	4	9	3	29
Children ≥12 months	25	..	6	..	..	31

Deaths—Thirteen children died in association with RS virus infection, 11 of them under 1 year of age. Virological investigations at necropsy on nine of these children showed RS virus in respiratory secretions and lung tissue in eight. In one microcephalic child virological findings were negative at necropsy but RS virus had been identified 24 days earlier at the onset of a bronchitis that persisted until death. In the four children who did not undergo necropsy RS virus had been identified during their terminal illnesses one to 14 days before death. Four of the 13 children died suddenly and unexpectedly at home with the clinical features of "cot death," three of them with no demonstrable cause of death apart from their RS virus infection, and one, a 6-month-old baby, with cystic fibrosis, whose death had not been expected. Eight of the nine children who died in hospital had underlying medical problems: two had congenital heart disease (one was a mongol), one cystic fibrosis, one microcephaly, one recurrent febrile convulsions, and one medulloblastoma; one died aged 10 weeks after delivery at 32 weeks' gestation; and one who had been in hospital for two months with severe whooping cough developed RS virus bronchiolitis and pneumonia a few days after discharge.

Discussion

This study has attempted to measure the more severe effects of RS virus infections on a defined population. The shape of each RS virus epidemic resembles those reported by others, usually with alternating short and long periods between epidemic peaks.³⁻⁸

Nearly all reported epidemics, including those in the southern hemisphere, occur in winter and early spring. In Finland, at more extreme latitudes, one epidemic began in April and lasted only until June, ending abruptly when warmer weather arrived.¹⁰ Mufson was able to show statistically significant effects of temperature and humidity on the timing of outbreaks.⁸ Epidemic spread partly depends on rising numbers of susceptible infants born after the previous epidemic, as well as climatic changes.

The higher incidence of RS virus in industrial areas than in rural ones may be a result of greater opportunities for spread of virus. The wide variation of incidence between different city wards, which lie within an area of about 32 square kilometres, argues against air pollution as a major influence. The incidence of severe infection also seems to be related to the proportion of children in the population who introduce the virus into families,^{5-9,10,18} overcrowding within households being an important factor. Adults carry the virus,¹⁹ but over 5 years of age infection is usually trivial and medical advice is not sought.²⁰ Glezen and Denny found that babies from low-income families were admitted with RS virus infection more often and at a younger age than babies from middle-income families.²¹ The results of our analysis are in keeping with this. Large families and overcrowding in poorer families are probably responsible for these trends.

Our findings of a preponderance of males among RS virus

admissions and of a peak age of 2 to 3 months for RS virus bronchiolitis agree with those of others.^{6,21} We have reported that RS virus infection is often acquired by children in hospital, often resulting in severe illnesses.²² The ratio of RS virus lower respiratory infection to upper respiratory infection in infancy in general practice is unknown but our cross-infection studies suggest that it is approximately 1:1.

Twelve children were reinfected with RS virus, sometimes after a surprisingly short interval. Infants show a poor serum antibody response when infected with RS virus.²³ Systemic cell-mediated immunity to RS virus can be induced by inactivated vaccine or by natural infection, but neither it nor serum antibody appears to protect against RS virus infection.²⁴ The observation that some vaccinated children developed severe illnesses on subsequent natural infection led to the suggestion that second infection with the virus might be more severe due to hypersensitivity.²⁵ Closely spaced second infections in hospital may be severe, though in a general practice study widely spaced second infections were mild.²⁰ It seems likely from our data that age, apart from hypersensitivity, may determine the relative severity of two natural infections.

In 70% of the children who died there was a pre-existing medical problem, but there were four cot deaths at home. The possible mechanisms which may link respiratory virus infection with cot death have been discussed.²⁶ Surveillance of home deaths was incomplete during the study, and probably underestimated childhood mortality associated with RS virus. A total study of all deaths of Newcastle children is in progress.

A recent investigation in 10 centres in Britain confirms that our experience with RS virus on Tyneside is not unique.²⁷ Epidemics of RS virus infection may be overlooked unless virus surveillance of all admissions for a large population is maintained by one laboratory. The extensive morbidity and mortality associated with the virus, when viewed across the whole country, emphasise the need for prevention. Breast-feeding offers protection; this fact should be added to the growing arguments in its favour.²⁸ Killed vaccines against RS virus have been unsuccessful,²⁵ and a live attenuated vaccine is still distant. Evidence will shortly be presented from a controlled study of risk factors for severe RS virus infection in an attempt to define groups of babies who should be protected as far as possible from infection. Mapping the addresses of the admitted children drew attention to areas in which housing conditions were bad, and analysis of this kind may be helpful in establishing social and health priorities. Clearance of crowded poor quality homes may reduce the incidence of RS virus infection if replacements provide more family space. In children's wards measures can be taken to reduce the incidence of cross-infection.^{19,22}

The incidence of RS virus infection and the risk to the individual infant is considerable, and more complete information throughout community studies are still needed.

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Reversal of narcotic depression in the neonate by naloxone

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Summary

Naloxone 40 µg was administered intravenously one minute after birth to 20 out of 44 neonates whose mothers had been given pethidine in labour. These neonates were compared with 20 others whose mothers had had only lumbar epidural block. Alveolar P_{CO_2} , alveolar ventilation, and ventilatory rate were measured 10 and 30 minutes after birth. The untreated neonates of mothers who had had pethidine showed significant ventilatory depression compared with infants in the epidural and naloxone-treated groups. The naloxone-treated neonates were comparable with the epidural group, although the effects of naloxone were diminishing at 30 minutes. Naloxone is an effective narcotic antagonist which should be considered to be the drug of choice for treating narcotic depression in the neonate.

Introduction

Narcotic analgesics, which are widely used during labour, may depress neonatal ventilatory function.¹ Nalorphine and levallorphan are unsatisfactory antagonists because they have substantial agonist activity and may therefore cause ventilatory depression. Naloxone, an effective antagonist free of agonist activity,^{2,3} should be more appropriate in treating the neonate suffering

from narcotic depression, but no evidence exists of the effectiveness of naloxone in the newborn.

Method

Maternal consent for the investigation was obtained. Mature healthy neonates (38-42 weeks) delivered spontaneously or by easy forceps delivery whose mothers received pethidine during labour were randomly allocated to receive either naloxone (pethidine-naloxone group) or no treatment (pethidine group). Naloxone, 40 µg in 1.3 ml of water, was injected into the umbilical vein one minute after birth; this dose was based on adult doses. These neonates were compared with those whose mothers had had analgesia only by continuous lumbar epidural block using bupivacaine hydrochloride 0.5% without adrenaline (epidural group).

The time to first breath, the time of onset of sustained ventilation, and the Apgar score at one and five minutes were recorded. Ten and 30 minutes after birth the alveolar P_{CO_2} was measured by rapid infrared analysis of the expired gas, continuously sampled through a nasal catheter. Carbon dioxide excretion was measured by entraining expired gas in a steady air flow drawn through a gently applied facemask. The carbon dioxide concentration of the gas flow was continuously measured by an infrared carbon dioxide analyser; the output signal of the analyser was electronically integrated to provide a measure of carbon dioxide excretion. Alveolar ventilation was calculated, after appropriate corrections, from the alveolar P_{CO_2} and the rate of carbon dioxide excretion.⁴ Alveolar P_{CO_2} and carbon dioxide excretion were measured sequentially in 30-second periods. Ventilatory rate was recorded.

The plasma pethidine concentration of umbilical venous blood was measured by gas chromatography.

Statistical analysis was performed using Student's *t* test or, when appropriate, the Mann-Whitney U test.⁵

Results

Sixty-four neonates were studied. Forty-four were delivered to mothers who had received pethidine, and 20 of these received naloxone. The mean (SD) dose of pethidine administered to the mothers was

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