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Acute respiratory illness in the community. Frequency of illness and the agents involved

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SUMMARY

Investigations of respiratory illnesses and infections in Tecumseh, Michigan, USA, were carried out in two phases, together covering 11 years. During the second phase, there were 5363 person-years of observation. Respiratory illness rates in both males and females peaked in the 1–2 year age group and fell thereafter. Adult females had more frequent illnesses than adult males; illnesses were less common in working women than in women not working outside the home. Isolation of viruses fell with increasing age; rhinoviruses were the most common isolate. Influenza infection rates, determined serologically, suggested relative sparing of young children from infection with type A (H1N1) and type B. Infection rates were highest in adult age groups for type A (H3N2). The isolation and serological infection rates were used to estimate the extent to which laboratory procedures underestimated the proportion of respiratory illnesses caused by each infectious agent; data from other studies were also used in this estimation. Severity of respiratory illnesses was assessed by the proportion of such illnesses that resulted in consultation of a physician. Rhinoviruses produced the greatest number of consultations. Overall, physician consultations were associated with 25·4% of respiratory illnesses.

INTRODUCTION

Although most infectious diseases formerly prevalent in the developed countries have been controlled, progress toward control of acute respiratory infections, the most frequent of these entities, has been slower. The most far-reaching change in mortality took place in the first half of this century, when deaths from acute respiratory illness gradually decreased until they nearly disappeared, except in recognized high-risk segments of the population, such as the elderly and very young; similar changes are now beginning to occur in the developing world [1, 2]. However, morbidity associated with respiratory illnesses continues to be a major

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societal burden [3, 4]. Vaccination would be an attractive control measure, but the large number of serologically distinct aetiologic agents involved suggests that this approach will not generally be applicable, given current technology [5, 6]. Recent developments with antiviral agents and interferon for prophylaxis and therapy against a broader range of agents have been somewhat more encouraging [7–9]. Because it is unlikely that any single preparation will be active against more than a portion of the respiratory pathogens, the relative importance of each aetiologic agent in illnesses of various characteristics should be determined. This will allow decisions on priority for control to be based on impact of specific pathogens within different age groups. Such estimates can be developed using, in large part, experience gained from 11 years of study of the community of Tecumseh, Michigan.

The current paper focuses on the second phase of this study and describes occurrence of respiratory illnesses by age and sex. It then reports on the isolation of the viruses involved; seasonality is also described. Data for some of these agents have been reported previously but not in the comprehensive form required for the current analysis. Serological infection rates of influenza are provided to allow comparison of differences in attack rates in 5 sequential years and as a means of estimating frequency of asymptomatic infection. Finally, estimates are made of the proportion of total respiratory illness caused by the specific agents.

METHODS AND MATERIALS

Study design

Tecumseh, a small city in southeast Michigan, USA and its surrounding rural area have been the site of a longitudinal study of acute respiratory infection. The observational portion of the study lasted 11 years. The first phase began in late 1965 and continued through 1971 [10]. The second phase lasted for nearly 5 years beginning in 1976 [11]. Methods used were similar in both phases of the study. Households or families were the unit of investigation throughout and they were recruited as a whole after being identified by a system of random stratified selection. At any one time approximately 1000 individuals or 10% of the community were under surveillance. Each household was recruited at a home visit when the study was explained and baseline information collected. At that point all members were asked to make appointments to visit the study clinic for the first blood collection. Thereafter a single family respondent was contacted weekly by telephone to obtain information on the onset of acute respiratory or enteric illnesses in any of the household members. The collection instrument has been described previously as have the case definitions [10]. For each acute illness reported details on symptoms, presence of fever, and other characteristics such as activity restriction and duration were collected. Illnesses were followed weekly to their conclusion, updating symptoms and other characteristics as they developed. An asymptomatic period of at least 2 days from the termination of a previous episode was required before a second illness was recognized as new.

During the first phase (1965–71), families were retained on report for periods of 1 year, and all members had blood specimens collected regularly at recruitment,

6 months later, and when surveillance terminated at 12 months. Recruitment was carried out continually to replace households whose period on report was ending, so that at any one time, some were entering while others were leaving surveillance. During the second phase (1976–81), blood was collected on the 6 month schedule, but households were retained on report for as long as possible. Replacement was carried out to maintain approximately 1000 individuals on surveillance. While the system of selection was also random, eligibility criteria changed over time. At the start of the first phase, only families with children whose parents were under age 45 were recruited, but this was later changed to make all families eligible. The latter strategy was continued into the second phase.

Laboratory studies

When an illness was reported within 2 days of onset, specimens for microbiological isolation were collected during both phases. The specimens were collected by study staff at home visits. Throat swab specimens were collected from all sampled individuals and, if nasal discharge was a component of the illness, a nasal swab was also collected. The one or two cotton swabs were placed in veal infusion broth enriched with 0·5% bovine serum albumin and 500 units of penicillin and 2 μg of amphotericin per ml. After the swabs were agitated in the medium they were discarded.

The specimens were transported to the laboratory on a daily basis. During the first phase of the study an additional throat swab was collected in Stuart's medium for isolation of haemolytic streptococci [12]. During that period veal infusion broth was also inoculated, sometimes after storage at −70 °C, into a tube of diphasic material for isolation of *Mycoplasma pneumoniae*. The veal infusion broth was inoculated into cell culture for viral isolation throughout all years of the study. For isolation of influenza and parainfluenza viruses, two tubes of primary monkey kidney were inoculated. The cultures were observed over 3 weeks and haemadsorption was performed twice weekly using guinea-pig erythrocytes; isolates were typed by haemagglutination-inhibition (HI) or haemadsorption-inhibition. For isolation of respiratory syncytial (RS) and adenoviruses, HL cells were inoculated and observed for 2 weeks. Isolates were typed by neutralization and RS isolates were subgrouped by a fluorescent antibody procedure using monoclonal antibodies [13]. WI-38 and similar cells were used for isolation of rhinoviruses and other, more uncommon viruses. The rhinoviruses were tested for acid lability and then typed by neutralization [14].

Serum specimens collected every 6 months were tested in parallel for rise in antibody titre. Tests were run throughout the entire study for influenza viruses, but for limited periods of surveillance for other agents including coronaviruses OC43 and 229E. The methods used have been described in detail previously [15]. For influenza, haemagglutination inhibition (HI) tests were run using as antigens the relevant viruses for that particular season. Such antigens were generally supplied by the Centers for Disease Control, Atlanta, GA, USA; all type B antigens were ether treated [16]. Infection rates for each influenza season were determined by examining sera from those individuals whose samples were obtained before and after that season. An infection was considered to have occurred in such individuals if there was a fourfold rise in titre and/or isolation of

the virus in question; those considered at risk were individuals with specimens available for the period in question.

RESULTS

Annual occurrence of respiratory illness

The annual frequency of all respiratory illnesses among persons on surveillance in Tecumseh during the second 5-year period is shown in Figure 1, along with the 95% confidence intervals. Also shown are the person-years of follow-up; for this purpose, both sexes have been combined. There was relative sparing of children until 1 year of age. This was a reflection of lower rates of respiratory illness in the first 6 months of life and a higher rate in the second 6 months. In the 1–2 year group, the rates were at the highest level and thereafter fell throughout childhood. During the childhood years, rates were generally somewhat higher in girls than boys, but as can be determined by the 95% confidence intervals, the differences were not statistically significant. In young adults the rates of illness increased, especially in women aged 20–34. Thereafter there was a general decline as age increased. Up to age 60 years the difference in rates between adult males and females was statistically significant.

The clear increase in frequency of illness in young adult women, not seen to the same extent in men, could well be related to the greater exposure of women of these ages to young children. If this is the case, women not working outside the home, who are usually exposed to their children during much of the day should have higher illness rates than those employed outside the home. An examination of the illness rates of these women was carried out in the age range with the sharpest differences between men and women: 20–24, 25–29, 30–34 years; rates were compared in those not working outside the home with those working full time. Non-employed women had consistently higher respiratory illness rates, with 2·9, 3·1, and 2·7 illnesses per year respectively as compared to the rate in employed women, with 2·5, 2·8 and 2·5 illnesses per year. The differences declined with increasing age and, above age 34 years, were no longer observed. However, even the rates in employed women noted above were higher than the rates in males 20–34 years of age. Thus, the effect of sex on overall illness rates in young adults is at least partially related to exposure to children or role in the family. These relationships in respiratory illness rates between the sexes may also be related to differential perception of infection as illness, in keeping with similar differences between the sexes in seeking care for many other acute and chronic conditions [3].

Isolation of viruses

Specimens for virus isolation were collected when an illness was reported within 2 days of onset, generally at the time of the weekly telephone call. One respiratory symptom was sufficient to trigger a request for specimen collection, which was carried out during a home visit. Table 1 shows basic data on the second phase of the study. A total of 2227 specimens were collected which produced 492 virus isolates, for an overall isolation rate of 22·1%. The isolation rates per specimen collected varied significantly by age: 31·3% in the 0–4 year olds, 21·2% in the 5–19 year olds, 18·6% in the 20–39 year group, and 15·8% in those 40 years of age

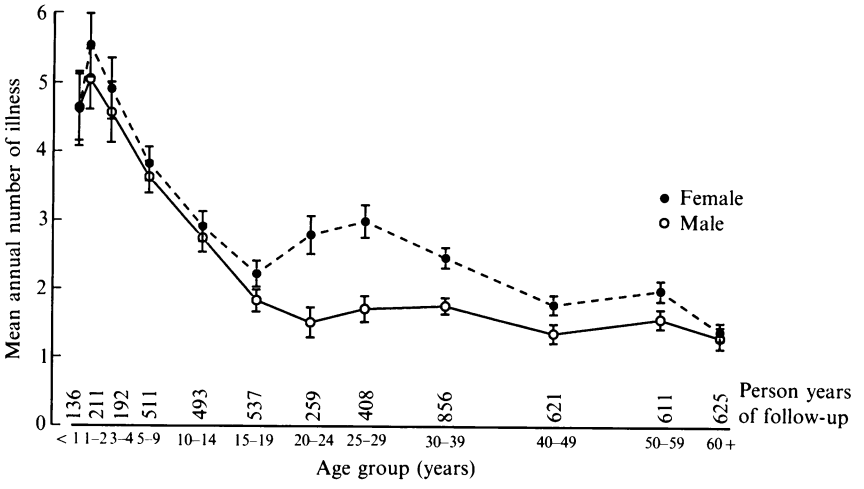

Fig. 1. Mean number of respiratory illnesses (and 95% confidence intervals) experienced per year by age and sex. Tecumseh Michigan, USA 1976–81.

Table 1. *Person-years of follow-up, number of respiratory illnesses, sampling and isolation rates. Tecumseh, Michigan, USA 1976–81*

	Age group (years)				
	0–4	5–19	20–39	40+	Total
a. Person-years of follow-up	539	1541	1523	1757	5360
b. Number of respiratory illnesses	2657	4373	3326	2784	13140
c. Mean annual number of respiratory illnesses (b/a)	4·9	2·8	2·2	1·6	2·5
d. Number of respiratory illnesses sampled for virus isolation	504	844	581	298	2227
e. Proportion of illnesses sampled for isolation (d/a)	19·0%	19·3%	17·5%	10·7%	16·9%
f. Number of virus isolates	158	179	108	47	492
g. Proportion of sampled illnesses with isolates (f/d)	31·3%	21·2%	18·6%	15·8%	22·1%

and above ($\chi^2 = 36{\cdot}4$, $P < 0{\cdot}001$). It would be expected that 2/7 or 28·6% of illnesses would be eligible to be sampled. In fact, since arrangement of a home visit was needed for specimens to be collected, the proportion so evaluated was lower. The actual percentage of illnesses sampled by specimen collection was 17·5–19%, except in the over 40 year olds of whom nearly 11% were sampled. The identities of the viruses recovered by age are shown in Table 2. Two rates are calculated; one is the actual isolation rate per 1000 person-years; for this calculation age-specific denominators were based on the number of individuals on report during each year. The other rate is adjusted to compensate for the fact that only a portion of illnesses had specimens collected (11–19%, depending on age); this rate, in parentheses, is an approximation of a cause-specific illness rate. Rhinoviruses were the agents most commonly isolated in all age groups, except, by a small amount, in the 5–19 year olds. Among the 0–4 year olds, rhinoviruses represented 39% of

Table 2. *Annual isolation rates of respiratory viruses, Tecumseh Michigan, USA, 1976–81. Actual rates per 1000 person years, and rates per 100 person years adjusted by proportion of illnesses sampled (in parentheses)*

Agent	Age group (years) 0–4 (539)*	5–19 (1541)*	20–39 (1523)*	40+ (1757)*
Rhinoviruses	113·2 (59·6)†	25·3 (13·2)	38·7 (21·5)	9·7 (8·8)
Influenza A (H3N2)	16·7 (8·8)	10·4 (5·5)	5·9 (3·3)	6·8 (6·2)
Influenza A (H1N1)	7·4 (3·9)	26·6 (14·0)	2·0 (1·1)	0·0 (0)
Influenza Type B	3·7 (1·9)	20·8 (10·9)	7·2 (4·0)	3·4 (3·1)
Parainfluenza viruses	53·8 (28·3)	14·3 (7·5)	3·9 (2·2)	2·3 (2·1)
Respiratory syncytial viruses	55·7 (29·3)	7·1 (3·7)	6·6 (3·7)	2·3 (2·1)
Adenoviruses	33·4 (17·6)	6·4 (3·4)	4·6 (2·6)	1·1 (1·0)
Other	9·2 (4·8)	5·2 (2·7)	2·0 (1·1)	1·1 (1·0)
Total	293·1 (154·3)	116·1 (61·1)	70·9 (39·4)	26·7 (24·3)

* Number of person – years of observation.
† Actual isolation rates per 1000 (adjusted isolation rates per 100).

all isolates followed by RS (19%) virus and parainfluenza viruses (types 1–3 combined, 18%). Adenoviruses followed in frequency and there were relatively small numbers of influenza isolates. In contrast, in the 5–19 year olds, influenza viruses, especially type A (H1N1), were the agents commonly recovered, together representing 58% of isolates. Interestingly, parainfluenza viruses still accounted for 12% of isolates even at these ages. Among the young adults (20–39 years), rhinoviruses represented one half of the isolates and combined influenza types and subtypes accounted for an additional 21%. The 40 and over age group had by far the lowest isolation frequencies and the smallest proportion of specimens collected, reflected in the rates shown. Rhinoviruses were 36% of isolates, followed by influenza A (H3N2) at 25·5% and type B influenza at 12·8%.

Seasonality of the viral agents

Certain viruses, such as influenza, are well known to be highly seasonal in occurrence. Such has been the case in Tecumseh; all transmission of type A (H1N1) and type B viruses took place from January through early April and A (H3N2) from December through February. The seasonality of other agents is less well known. The monthly occurrence of these viruses is shown in Figure 2. The figure is based on a respiratory year beginning in July. Rhinoviruses were isolated in every month. In the past the increase in rhinovirus isolation associated with the opening of schools in the autumn has been emphasized [12]. The pattern is less apparent in this distribution, in which slightly more rhinoviruses were isolated in May–June than in September–October. Much greater seasonality is found with the combined parainfluenza viruses. In fact, types 1 and 2 were mainly recovered in the autumn–early winter period, and were not isolated in the months from April through August. Parainfluenza type 3 also was active in the autumn, but was isolated as frequently in the remaining months. RS virus exhibited the most clear-cut seasonality, resembling closely distribution of influenza viruses. Adenoviruses

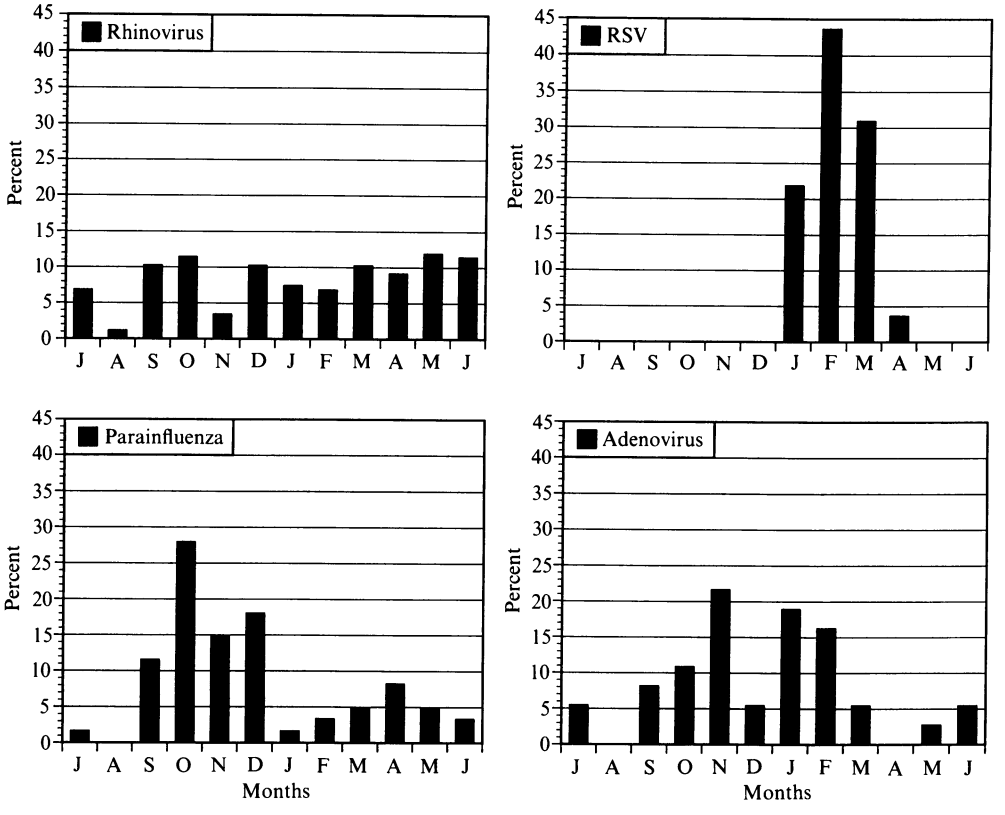

Fig. 2. Proportion of indicated respiratory viruses isolated in each calendar month during 5 years of study.

were recovered mainly in the colder months, with the exception of December during which frequency of isolation fell.

Influenza infection rates

Sera collected from participants on a 6-monthly basis were tested by haemagglutination inhibition to identify significant increases in antibody titre. Antigens used were those viruses documented as circulating in a particular season. In each case, infection rates were determined for those having paired sera available before and after the documented period of virus circulation resulting in different number of pairs tested for each season. The data, including 95% confidence intervals (CI), are shown in Tables 3–5. The two A subtypes and type B can be compared in terms of the age specific infection rates. In both type A (H3N2) outbreaks, (Table 3) the highest rates were among children under age 10 years, with lower rates experienced by adults; with one exception the age specific rates among those 20 years of age and over remained in the 10–20% range. In each of the years in which A (H3N2) occurred, A (H1N1) also caused outbreaks; the A (H1N1) period followed the A (H3N2) but with overlap especially in 1980–1. Thus the question of interference between the two subtypes needs to be considered.

The A (H1N1) viruses reappeared in 1977–8 after a global absence of approximately 20 years. As shown in Table 4, infection rates were 50% in the

Table 3. *Rates of infection with influenza type A (H3N2) during two outbreak periods, Tecumseh Michigan, USA*

	1977–8				1980–1			
		Infected				Infected		
Age (years)	Total tested	No	%	(95% CI)*	Total tested	No	%	(95% CI)*
0–4	28	12	42·9	(25·7, 61·4)	122	29	23·8	(16·9, 31·9)
5–9	52	20	38·5	(26·0, 52·1)	73	18	24·7	(15·8, 35·5)
10–14	64	20	31·3	(20·8, 43·3)	78	8	10·3	(4·9, 18·5)
15–19	58	17	29·3	(18·7, 41·9)	51	4	7·8	(2·5, 17·8)
20–29	61	8	13·1	(6·3, 23·4)	92	10	10·9	(5·7, 18·5)
30–39	94	18	19·2	(12·1, 28·0)	152	23	15·1	(10·1, 21·5)
40–49	103	16	15·5	(9·5, 23·5)	77	15	19·5	(11·8, 29·5)
50–59	133	9	6·8	(3·4, 12·1)	93	11	11·8	(6·4, 19·6)
60+	103	13	12·6	(7·2, 20·1)	76	12	15·8	(8·8, 25·3)
Total	696	133	19·1	(16·3, 22·2)	814	130	16·0	(13·6, 18·6)

* Mid-p exact confidence intervals.

15–19 year olds, 29% in the 10–14 year olds, and 11% in the 5–9 year olds. In this year major outbreaks were experienced on many university campuses in the United States but with less activity in the community [17]. It was in the next year (1978–9) that community outbreaks were recognized, involving considerable school absenteeism. In that year, Tecumseh infection rates were over 50% in the 5–14 year olds and approximately 28% in the under 5 and 15–19 age groups. In the third A (H1N1) season (1980–1), the infection rates were considerably lower than in either previous outbreak, except in younger children. Infections with these viruses rarely produced symptoms in individuals who lived through the previous A (H1N1) period which terminated in 1957 [17]. Small numbers of infections were detected in those individuals, especially in the first two outbreaks. Of considerable interest is the increase in infection frequency seen consistently in older individuals, suggesting increased susceptibility [18].

Infection frequencies for type B influenza viruses are shown in Table 5. They were similar in overall age-specific pattern to those seen with A (H1N1), with highest rates in the school age children. In fact, the type B infection frequencies in the two outbreaks were roughly similar to one another in the 5–19 age groups. However, infection rates seen in both younger and older individuals in 1979–80 were higher than in the 1976–7.

Estimation of proportion of total respiratory illness caused by specific infectious agents

To attribute the total number of illnesses experienced by the population fully to specific causes, it is necessary to estimate the factors by which laboratory procedures understate the occurrence of the aetiologic agents when in fact an infectious agent was involved. This factor will be different for different groups of agents. While agent identification, usually by isolation, might be expected to give the most accurate estimate of the aetiology of symptomatic infections, practical considerations, such as transportation and timing of collection in relation to

Table 4. *Rates of infection with influenza type A (HN1) during three outbreak periods, Tecumseh Michigan, USA*

	1977–8				1978–9				1980–1			
		Infected				Infected				Infected		
Age	Total tested	No	%	(95% CI)	Total tested	No	%	(95% CI)	Total tested	No	%	(95% CI)
0–4	29	2	6·9	(1·2, 21·0)	28	8	28·6	(14·2, 47·1)	130	14	10·8	(6·3, 17·0)
5–9	46	5	10·9	(4·1, 22·5)	78	43	55·1	(44·0, 65·9)	77	14	18·2	(10·7, 28·0)
10–14	51	15	29·4	(18·2, 42·9)	83	42	50·6	(39·9, 61·2)	80	11	13·8	(7·4, 22·6)
15–19	57	29	50·9	(38·0, 63·7)	77	21	27·3	(18·2, 38·0)	52	7	13·5	(6·1, 24·8)
20–29	47	2	4·3	(0·7, 13·4)	45	5	11·1	(4·2, 22·9)	100	4	4·0	(1·3, 9·4)
30–39	78	5	6·4	(2·4, 13·6)	125	0	0·0	(0·0, 2·4)	158	0	0·0	(0·0, 1·9)
40–49	78	3	3·9	(1·0, 10·1)	108	1	0·9	(0·1, 4·5)	84	0	0·0	(0·0, 3·5)
50–59	103	2	1·9	(0·3, 6·3)	98	6	6·1	(2·5, 12·3)	102	1	1·0	(0·1, 4·7)
60+	64	5	7·8	(2·9, 16·5)	82	7	8·5	(3·8, 16·2)	79	2	2·5	(0·4, 8·1)
Total	553	68	12·3	(9·8, 15·2)	724	133	18·4	(15·7, 21·3)	862	53	6·1	(4·7, 7·9)

* Mid-p exact confidence intervals.

Table 5. *Rates of infection with influenza type B during two outbreak periods, Tecumseh Michigan, USA*

	1976–7				1979–80			
		Infected				Infected		
Age	Total tested	No	%	(95% CI)*	Total tested	No	%	(95% CI)*
0–4	53	2	3·8	(0·6, 11·9)	70	6	8·6	(3·5, 17·0)
5–9	82	23	28·0	(19·1, 38·5)	71	25	35·2	(24·8, 46·8)
10–14	82	29	35·4	(25·6, 46·1)	83	23	27·7	(18·9, 38·1)
15–19	61	9	14·8	(7·4, 25·3)	64	11	17·2	(9·4, 27·9)
20–29	117	4	3·4	(1·1, 8·0)	81	5	6·2	(2·3, 13·1)
30–39	115	6	5·2	(2·1, 10·5)	146	18	12·3	(7·7, 18·4)
40–49	113	4	3·5	(1·1, 8·3)	92	6	6·5	(2·7, 13·1)
50–59	122	3	2·5	(0·6, 6·5)	100	9	9·0	(4·5, 15·9)
60+	96	3	3·1	(0·8, 8·3)	79	10	12·7	(6·6, 21·4)
Total	841	83	9·9	(8·0, 12·0)	786	113	14·4	(12·1, 17·0)

* Mid-p exact confidence intervals.

Table 6. *Annual serological infection rates, per 100 and their relation to adjusted isolation rates, influenza and parainfluenza viruses. Tecumseh, Michigan, USA, 1976–81*

Age group (years)	Influenza Type A (H3N2)		Influenza Type A (H1N1)		Influenza Type B		Parainfluenza viruses	
0–4	14·0*	63%†	9·7*	40%†	2·6*	73%†	28·3*	73%†
5–19	10·0	55%	19·3	73%	11·4	96%	7·5	22%
20–39	6·4	55%	2·3	48%	3·0	133%	2·2	11%
40+	5·6	111%	2·1	0%	2·6	119%	2·1	13%
All ages	7·4	73%	7·7	61%	5·1	108%	6·3	25%

* Rise in antibody titer per 100 per year (for parainfluenza viruses – types 1, 2 and 3 combined, 1965–71).

† Adjusted isolation rates/rise in antibody titer × 100.

illness, can create limitations. In addition, isolation rates will be affected by titres of the agent shed which will vary based on a number of factors, particularly prior antibody status. The lower isolation rates which occurred with increasing age may well be a reflection of this phenomenon.

Identifying significant rise in antibody titre is generally a much more comprehensive method of determining infection. However, the infections which are identified may be either symptomatic or asymptomatic, and issues of sensitivity and specificity of the test are still of concern. Combining the methods gives a better idea of the overall rates of illness and infection. Such a comparison is shown in Table 6. Here, the isolation rate for a particular agent is divided by the serological infection rate. The resulting value is an estimate of pathogenicity, assuming equal sensitivity of both procedures. The calculations for influenza are made using data contained in previous tables. The isolation data used in this calculation are the adjusted values from Table 2. The serological results from

Tables 3–5 have been recalculated on an annual basis to make them comparable to the isolation results and are shown as such in Table 6. This compensates for the fact that type A (H3N2) and type B occurred twice in the period and type A (H1N1) three times. For parainfluenza viruses, the adjusted isolation rates from Table 1 are also used. Since no comprehensive serology on parainfluenza was carried out in the second phase of the Tecumseh study, these rates come from the first phase [19].

As shown in Table 6, the overall isolation rate of type A (H1N1) and type A (H3N2) was 61 and 73% of the serological infection rate. It has been estimated in studies using similar methods that approximately 25% of influenza infections are asymptomatic [20]. Thus, these results would suggest that the isolation rates underestimate the actual proportion of illnesses caused by the agent by a factor of 1·2. However, with type B, the serological rates were less than those observed by isolation. This points out the problems associated with calculations of this sort; the sensitivity of the laboratory procedure is a limiting factor. It is known that the haemagglutination-inhibition test for type B is not as sensitive as for type A, but the degree of insensitivity is not well established [16, 21]. The table suggests the extent by which serologic infection rates for type B underestimated actual infection.

For parainfluenza, the annual infection rate was originally designed to be a conservative estimate of infections, since if there was a rise in titre to more than one parainfluenza virus type in the same time period, it was assumed to be a cross-reaction and not two independent infections. Comparison of these rates with the adjusted isolation rates in Table 2 again provides an estimate of the asymptomatic infection rate, assuming equal sensitivity of both procedures. According to these data, approximately 27% of the infections in the first 5 years of life were asymptomatic rising to 89% in the 20–39 year olds. This indicates the importance of subclinical infections in older children and adults. Both infection and illnesses caused by parainfluenza viruses must be underestimated by these data. The serological results obviously underestimate actual infections since, should infection with more than one type of parainfluenza virus occur in a year, they would have been counted only once. Additionally, other than with type 3, the relative insensitivity of the HI test was clear in the original data [19]. By age 5 infection with each of the three parainfluenza types is essentially universal but the annual rate of rises in titre for types 1 and 2 during the first 5 years of life only averaged 6·4 and 8·7% respectively. For similar reasons, isolation of viruses must be relatively insensitive for identifying cause-specific illness rates. To compensate, the parainfluenza infection and illness rates need to be increased in all age groups by a factor of 1·8. Such a factor raises the under 5 infection rates to 3·5 episodes for all three types over a period of 5 years, still a minimum estimate, since there must not only be one infection for each of the three parainfluenza viruses but also some reinfection during that time. This factor will be used to estimate the proportion of respiratory illnesses actually caused by parainfluenza viruses.

No similar data are available for other respiratory pathogens. It is likely that agents known to be labile and difficult to isolate, such as respiratory syncytial virus, should probably be increased by a greater factor and more stable agents, such as adenoviruses, by a lesser amount [22]. However, a factor of 1·5 was used

as a mid-measure for these pathogens as well as miscellaneous other agents to account for their lability.

Group A haemolytic streptococci and mycoplasma were identified in the earlier surveillance period (1965–71) but not in the later period. Culture of haemolytic streptococci had been attempted uniformly using a semiquantitative method; *Mycoplasma pneumoniae* isolations were carried out using diphasic media. Of all specimens received, 3·3% contained significant numbers of Group A haemolytic streptococci; isolation of *M. pneumoniae* was much more infrequent at 0·5% of specimens [23]. These results were age adjusted and were applied to the 1976–81 period. Since *Chlamydia pneumoniae* was unrecognized at the time of the original surveillance, isolations are assumed to be at the same frequency as *M. pneumoniae* (24); both of these agents, as well as haemolytic streptococci are, are now grouped together, termed 'bacterial infections' and again adjusted upward by the factor of 1·5.

Rhinoviruses and coronaviruses present particular problems since coronavirus cannot be isolated with generally used cell systems and there is evidence that a group of rhinoviruses exist which can be isolated only in organ culture. Estimates of the proportion of illnesses caused by such fastidious rhinoviruses can be derived from a study by Larson, Reed and Tyrrell [25]. They conducted an exhaustive study of 38 respiratory infections in adults using not only all cell culture and human tracheal organ culture, but also inoculation of human volunteers. A total of 45% of these illnesses were identified to be rhinovirus or probable rhinovirus in etiology. Of these 17 rhinoviruses, 6 or 35% were not isolated in cell culture but instead in organ culture or human volunteers. In contrast all parainfluenza and influenza viruses were recovered in cell culture while no coronaviruses were so identified; coronaviruses were actually related to 18% of illnesses, but only by isolation in organ culture and volunteers. Based on these data, the results for the 20–39 year old are adjusted such that the proportion of illnesses attributed to rhinoviruses became 45%. The proportion attributed to rhinovirus in other age groups was adjusted upward by the same factor. A similar process was followed for coronaviruses, setting the proportion of coronavirus-associated illnesses in young adults at 18%, that reported by Larson and colleagues [25]. It was assumed that coronavirus distribution in other age groups would follow that of rhinoviruses. Thus, the overall coronavirus frequency was 40% of that of the rhinoviruses (18/45).

In Table 7 are shown the resulting estimated percentage distributions of causes of all reported respiratory illness; this distribution summarizes data for all age groups, based on the age-specific occurrence of respiratory illness in the Tecumseh population. Rhinoviruses are the most common aetiologic agent, causing more than one third of illness and are followed by coronaviruses. Influenza viruses are next most common, in spite of their highly seasonal behaviour. Bacterial infections as a group are slightly less frequent, followed by parainfluenza and respiratory syncytial virus. It is estimated that 23% of respiratory illnesses cannot be attributed to an infectious aetiology based on these data. This figure includes illnesses which are truly of non-infectious nature, others caused by agents not yet identified and still others caused by various other agents currently known but which for technical reasons could not be identified. To give the numerical impact

Table 7. *Estimated percentage of all respiratory illnesses caused by specific etiologic agents. Percentage of such illnesses with physician consultation and annual numbers of each in the population (10000) of Tecumseh Michigan, USA*

Etiologic agent	Percent of all illnesses caused by each agent	Number of illnesses caused by each agent per 10000 population	Percent illnesses with consultation	Number illnesses with consultation per 10000 population
Rhinoviruses	34	8325	17·6	1465
Coronaviruses	14	3428	17·6	603
Influenza	9	2204	37·9	835
Bacterial	8	1959	48·6	952
Parainfluenza viruses	4	979	26·2	257
Respiratory syncytial viruses	4	979	55·6	544
Adenoviruses	2	490	43·2	212
Other viruses	2	490	27·8	136
Unknown and/or non-infectious	23	5630	21·5	1211
Total	100	24484	25·4	6215

of this distribution, results are also expressed in terms of numbers of illnesses of each type experienced by a population of the size and age distribution of Tecumseh, based on the actual illness rates shown in Figure 1.

The effect of different agents should not only be measured by the number of illnesses produced, but also by their severity. For example, while rhinoviruses are the most common isolate they generally produce among the most mild illnesses; other viruses, such as influenza viruses, produce more severe illnesses. In Tecumseh the frequency of physician consultation has been used as a useful indicator of perceived severity. On the right side of Table 6 are shown the reported frequency of consultation of physicians for illnesses associated with each of the agents or groups of agents; these are shown both as a percentage of illnesses with consultations and as a number. Since no data are available from the Tecumseh study on the proportion of consultation associated with coronavirus illness, the frequency reported for rhinoviruses is used. Even with only 17·6% physician consultations, rhinoviruses are estimated to have produced 1465 contacts annually in Tecumseh, more than caused any other group of agents. Bacteria and influenza consultations were next in frequency. Among the remaining agents, RS virus, because of the high frequency of consultations stands out from the others. The group of unidentified agents and non-infectious illness remains an important element among the 6215 consultations resulting annually from respiratory illness in Tecumseh.

DISCUSSION

The occurrence of respiratory illnesses was determined in both phases of the Tecumseh study. They represent one of the few sources of data on the incidence of these common illnesses in a general population group. Results for the second phase, as shown, resemble those previously reported with two exceptions. In the first phase, the highest rates of total respiratory illness were found in individuals under age 1 year, and rates decreased throughout childhood [23]. In contrast, in

the second phase, the youngest children were found to have lower rates than those in the next older age group, children ages 1–2 years. These differences may be related to the techniques employed in data analysis. Participants were followed for 1 year in the first phase and, for technical reasons, their ages at entry were used throughout their year on report. In the second phase ages were updated on a quarterly basis. Thus, the methods used could have at least partially been responsible for the differences observed. Sparing of the under 1 year age group, because of lower rates in the first 6 months of life, is in keeping with the known role of maternal antibody in preventing infection in very young children; this has been clearly documented with RS and certain parainfluenza viruses [12, 26]. It is also in keeping with the findings of the Cleveland Family Study, one of the few investigations with enough observations for this phenomenon to be recognized [4]. The overall differences in illness frequency between adult men and women have been reported before. Prior speculation that exposure to children in the home was at least partially responsible has now been better substantiated [23].

Isolation rates overall varied significantly with age. Reinfections with many respiratory agents occur throughout life, so it is likely that the titre of virus shed is reduced in older individuals. Since home collection of specimens and transportation from Tecumseh to the laboratory were required, with the potential for loss of viable virus, such differences in titre could have produced the effect. Another, less likely explanation is that currently unrecognized agents or non-cultivable agents are more prevalent in older age groups. This might partially be the case, since non-cultivable rhinoviruses and all coronaviruses could not have been recovered with techniques used [27, 28]. These agents are proportionally more likely to be involved in illnesses of older than younger individuals.

To determine priorities for control it is necessary to attribute the aetiology of all respiratory illnesses to specific agents. Such projections must be based on estimates of the proportion of pathogens not detected by cell culture derived by comparison with other methods of agent detection and serology. The estimates used were based on data from the Tecumseh study itself or from other studies when available and were sometimes rather arbitrary in nature. However, these adjustments did not often change the ranking; in all studies rhinoviruses remain the most common cause of all respiratory infections. The coronavirus estimates are based on data external to the Tecumseh study, but are in keeping with other estimates which focused on illnesses [29]. The importance of coronavirus infections has also documented previously in Tecumseh [15]. The large residual percentage of illnesses not attributable to an agent at present is in part a reflection of the decreasing isolation rate with increasing age and presents a challenge for the future.

Overall, these data again demonstrate the overwhelming impact of respiratory infections in producing illnesses which are at least annoying and which often lead to economic and health consequences. The role of age, sex and family composition in determining frequency of these infections is in general agreement with that demonstrated previously [30–32]. In planning for control measures, particularly antiviral drugs or new vaccines, it will be important to bear in mind these patterns of disease occurrence as well as the proportion of illnesses due to specific pathogens. Young adults, especially women, as well as all children, should be the

prime target populations, and various viruses, including rhinoviruses, coronaviruses, and influenza should be the agents given the highest priority. At the same time, bacterial infections, in particular those caused by haemolytic streptococci, should not be forgotten especially in view of currently available treatment.

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