
Studies of the Community and Family: Acute Respiratory Illness and Infection

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Respiratory infections are the most common cause of acute morbidity, and have been the subject of numerous studies performed both before and after the identification of the major etiologic agents. A variety of different approaches have been used depending on the type of illness being studied and the questions being asked. Some approaches have been hospital-based if the intent was to study the small proportion of infections that result in severe disease, as opposed to the full range of illnesses and infections that occur in the family and the community. Other approaches, while examining illnesses of all severities, have focused on children or other specific segments of the population. Most studies have had a longitudinal design, so that seasonal variation in incidence could be determined.

This review will discuss investigations that examined the full range of respiratory illnesses. Morbidity alone was the focus of early studies, most of which were carried out during the era when knowledge of etiologic agents was limited. During that period, illness frequency and characteristics began to be established. Later investigations stressed etiology. Only a small number of studies have comprehensively examined illness incidence and agent-specific infection frequency in all household members. Such studies have also proved to be

valuable in allowing estimation of the transmission dynamics of etiologic agents in family members. These family studies of illnesses will constitute the current focus. Other contemporary investigations examining specific agents or limited age groups will also be discussed, but mainly in terms of their relation to the main focus. Particular attention will be paid to the methods used in the investigations, since methodological differences are clearly responsible for differences in results. Most of the etiologic agents, other than influenza, were identified during the late 1950s or thereafter, so the greatest attention will be given to studies conducted during that period. However, reference will be made to earlier investigations, especially the classic Cleveland (Ohio) Family Study. Studies of this type established much of our current knowledge of common respiratory illnesses; because of their size, duration, and costs, it is unlikely that they will ever be replicated.

MORBIDITY BY AGE AND SEX: BACKGROUND

Mortality related to acute respiratory illnesses, like that related to acute enteric illnesses, declined in the now developed countries during the first part of this century to the point that it became an unusual event, occurring only at the extremes of age and related to specific pathogens such as influenza. Morbidity remained the principal problem, and was repeatedly recognized as the most important cause of loss of productive time in the general population.

Studies describing the patterns in populations of respiratory illnesses of all types

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have been carried out since the first decades of the twentieth century. In the 1920s, longitudinal studies of families in Hagerstown, Maryland, demonstrated that acute respiratory illnesses, including influenza and "grippe," were over five times more frequent than the next leading cause of morbidity (1). Studies in several localities in the United States, reported by Wade Hampton Frost and Mary Grover (2), demonstrated that distinct seasonality was similar in widely differing geographic areas. This included the autumn peak in coryza, more recently associated with the rhinoviruses. Investigations in Baltimore, Maryland, families conducted at approximately the same time indicated the need to maintain a diary for accurately recording observations on illness made by a household member. Illness incidence generally decreased with increasing age, except for a modest increase in the age group 20–39 years. Attack rates in children aged 0–4 years were 4.5 per person-year, and in adults they were approximately 2.5 per person-year; above age 9 years, illness was more commonly reported in females than in males (3). These illness frequency estimates have stood the test of time and are similar to those found in many other investigations conducted in subsequent years.

The relevance and efficiency of studying respiratory illnesses in families was recognized in a series of investigations conducted under the sponsorship of the Milbank Memorial Fund in the 1940s. These investigations examined the effects of season, age, and sex on the frequency of respiratory illnesses in families in suburban New York. Again, there was a clear preponderance of illnesses in females older than 10 years of age. Many of the families studied were relatively large and included 900 school-age and 200 preschool children (4).

THE CLEVELAND FAMILY STUDY AND ITS CONTEMPORARIES

In the 1950s, there was increased interest in the subject of respiratory illnesses, again concentrating on the influence of familial

or household factors on incidence. In addition to the well-known Cleveland Family Study, investigations which took place at that time include those of Buck (5), conducted in 45 Canadian families, and the somewhat earlier English study of Lidwell and Sommerville (6). The latter investigation was conducted in the rural area of Wiltshire, United Kingdom, which became the location of the British Medical Research Council's Common Cold Unit, and identified the importance of school children in producing higher rates of illness in the adults in their households. Both studies also examined the questions of introduction of infection into the family and secondary transmission within the family, and in so doing, confirmed that school-age children were mostly responsible. Sequence of infection was used to determine which was an introduction case and which was a secondary case. There was recognition for the first time that apparently secondary cases might in fact be new introductions, given the continuing transmission in the community, and an attempt was made to correct for this likelihood mathematically. Overall incidence of illness appeared to follow a Poisson distribution (6). The Buck study also confirmed the role of children in the introduction of infection into families; however, these observations did not correct for new introductions that might appear, by timing alone, to be secondary cases (5).

The late 1940s and early 1950s were important not only because of the strengthening realization that the family was the most appropriate unit for the study of common respiratory infection, but also because of the emerging ability to identify the agents involved. The Cleveland Family Study bridged the period of the development of laboratory techniques. When this study started in 1948, only influenza and traditional bacterial infections could be identified; however, adenovirus infections could be identified by 1953 (7). In general, this seminal study is known mainly for its synthesis and confirmation of previous fragmentary observations on non-cause-specific morbidity. Its longitudinal nature,

covering nearly 10 years, was essential for the accumulation of sufficient observations to draw conclusions on subgroups and to take into account the year-to-year variation in frequency and intensity of outbreaks. The methods and observations provided a standard against which subsequent investigations were measured (8).

The population of the Cleveland Family Study was relatively small; at one time or another, 86 families were followed, for a total of 2,692 person-years of study. The median age of the parents at the time of entry was 33 years for fathers and 30 years for mothers. The families lived in a suburban area and were highly educated and relatively affluent. Physician examinations were carried out upon entry into the study, and the general health of the participants was found to be excellent. Frequent home visits were part of the design, especially at the start of the study, when each ill individual was visited by a staff physician who conducted an examination and collected specimens. The mother was responsible for recording the symptoms of illness, including the person's temperature, and notifying the study office whenever an illness of any type occurred. A field worker visited each household each week to check on the illnesses recorded. Blood specimens were collected in the spring and autumn of each year for an eventual performance of serologic tests.

Illness rates were calculated by age during the course of the study. Table 1 shows the age-specific annual frequency of common respiratory illnesses reported at the end of the full 2,692 person-years of observation. The annual numbers of illnesses observed are among the highest ever reported, either before or since, and are without a doubt a reflection of the frequent visits of a field worker and the willingness of the families in this self-selected group to detail all occurrences. This effect may be responsible for the fact that the overall illness incidence calculated at the start of the study was higher than that reported in the final summary; visits of a field worker occurred less often as the study progressed,

TABLE 1. Annual frequency of respiratory and enteric illness by age: Cleveland (Ohio) Family Study, 1948-1957*

Age (years)	Common respiratory disease	Infectious gastroenteritis
<1	6.72	1.00
1-4†	7.95	1.90
5-9†	6.21	2.01
10-14†	5.02	1.28
15-19†	4.71	1.20
20-24	4.09	1.02
25-29	4.82	1.12
30-34	4.45	1.08
35-39	3.83	1.21
40-44	3.68	1.14
45-49	3.97	0.75

* After Dingle et al. (8).

† Unweighted means of individual ages.

and it may be surmised that the enthusiasm of participants changed over time (9). Interestingly, the frequency of reported gastrointestinal illnesses, which had rarely been a focus of family studies, was similar to that reported elsewhere (10, 11).

Definition of what constitutes an illness was also involved in these differences. The Cleveland Family Study made a conscious decision to be inclusionary, since mild or fleeting illnesses, when reported as symptoms which were thought to be deviations from health, often formed part of the chain of illnesses in the home. Also, a long period of absence of symptoms was not required before an illness with a change in characteristics was counted as a new event. By doing this, the investigators recognized that their criteria were different from the criteria used by previous investigators, such as Sydenstricker, who "carefully edited" illness reports to ensure that two illnesses were not counted when considering "successive or progressive conditions" (1).

Incidences of respiratory illnesses were also analyzed according to a number of other factors. More illnesses were reported for boys than for girls through the teenage years, but the differences were often small; in contrast, and in agreement with other studies, mothers consistently had higher illness rates than fathers. Overall, school attendance was associated with higher illness

rates in the family. At the time of the study, preschool children were infrequently in day care or in other group arrangements, and they typically acquired their illnesses from their parents or, more likely, from other siblings (8, 9). All calculations of secondary attack rates and other observations of transmission were based on linking observed illnesses with a prior illness (12, 13). The period of 9 days was chosen as the interval during which all subsequent illnesses would be considered secondary. Thus, although illnesses starting on the same day were termed coprimary, those illnesses starting on the next day were termed secondary, with no attempt being made to estimate reintroductions from the community during that period. Using this formula, the fathers were the least likely introducers of illness, with mothers, school-age children, preschool-age children at home, and preschool-age children in day care or preschool being the next most likely introducers, in that order.

Illness frequency was also evaluated by family composition, which reflected, as expected, the introduction probabilities. Secondary attack rates for each type of individual were remarkably consistent by family size; this was thought to be related to the lack of time (in the 9 days) for a second generation of cases to occur. However, more than 70 percent of the secondary cases had occurred within 5 days of the index case. Overall illnesses per family member increased with the size of the family, but this estimate was not controlled for age.

Seasonality was examined in terms of total respiratory illness and illnesses of specific symptomatic characteristics. The monthly occurrence of coryza closely followed the frequency of total illness. A sharp increase in illnesses occurred in September and continued through March. Fever and sore throat were less common in those illnesses seen earlier in the respiratory year than in those illnesses seen later (8).

In terms of the etiology of illness, streptococcal infections were examined in detail,

and higher rates of infection were observed from January through May. Among the viruses, only influenza could be identified from the start of the study. Type A (H1N1) viruses were isolated in 4 years, and type B viruses in 2 years (14). The study was actually continued beyond its planned closing in early 1957 to follow the appearance of the so-called Asian or A (H2N2) viruses that autumn (15).

Secondary attack rates were calculated during the nonpandemic years. In 1957, overall serologic infection rates were determined to be 55 percent, in contrast to highs of 27 percent in nonpandemic years, for both A (H1N1) and B strains of *Influenza-virus*. Further discussion of the influenza findings is given below. Finally, after the adenoviruses were first described in 1953–1954, serologic and then virus isolation studies were carried out to determine their contribution to common respiratory diseases (16). An outbreak of illness, consisting of fever, headache, and sore throat, was found to be associated with type 3. No civilian equivalent of the military acute respiratory disease was detected, even when looking for type 4 and type 7 antibodies. Antibodies in general were found to increase with age and to be associated with sporadic illness, but the autumn increase in illness incidence was demonstrated to be nonadenoviral in etiology.

In many ways, the Cleveland Family Study forms a bridge between those investigations in which only morbidity was examined and other studies which related the observations to laboratory results. An additional investigation, concerned mainly with morbidity, was carried out in England during 1952–1953 and was purposely designed, in contrast to the Cleveland Family Study, to include families of lower socioeconomic background (17). Each family was required to contain both a father and a mother and at least three children. Approximately 70 families were followed. An increase in introductions and secondary attacks contributed to the September peak of illness. Secondary attack rates year-round increased with the degree of crowding in

the home, but the pattern for introductions was less consistent, with overcrowded houses having the most but uncrowded houses having more than crowded houses, the intermediate category. Inadequacy of clothing also related positively to the frequency of coryza illness. No other indicators of lower socioeconomic class were found to be correlated with illness incidence.

IDENTIFICATION OF THE ETIOLOGIC AGENTS

During the late 1950s and early 1960s, nearly all of the viruses now known to be involved with respiratory illness were identified. Early studies, which first defined the syndromes of severe disease produced by some of the etiologic agents, were typically hospital-based. Thus, it was the hospital- or clinic-based studies of young children that determined that respiratory syncytial viruses were the principal etiologic agents of bronchiolitis and pneumonia in that population, and that the parainfluenza viruses were responsible for croup (types 1 and 2) and pneumonia (type 3) (18–23). Since rhinoviruses rarely cause illness severe enough to produce hospitalization, most of the studies that defined their role in the etiology of the common cold involved employee groups or similar populations (24, 25). Some of these studies began to detect the presence of the “pediatric” viruses in adults which, upon reinfection, were also defined as etiologic agents of the common cold (26). Inoculation of human volunteers with these viruses confirmed the ability of the virus to cause infection in a proportion of those individuals with prior antibody, and disease in a small number of those individuals infected (27). The challenge studies of human volunteers were important in determining disease pathogenesis during the 1960s and 1970s, and the effect of antiviral agents since that time (28).

The decade of the 1960s was an active time for the initiation and conduct of community-based studies. This was, to a large extent, related to the ability to identify the agents of disease. Three major investiga-

tions either were started or were being conducted during that time period, and there were, in addition, many other studies of shorter duration or more limited scope. The three studies which will be discussed in detail are the Cirencester, England, study by Hope-Simpson et al., the New York and Seattle Virus Watches of Fox et al., and the Tecumseh, Michigan, study by Monto et al. Each study consisted of a very different population and used different methods.

The Cirencester Study

As in many longitudinal investigations, the Cirencester Study had a pilot phase which detected respiratory infections at the frequency of seven per year, each infection having a mean duration of 10 days (29). The study itself took advantage of the practice structure of the British National Health Service, which allowed access to the illnesses of a regional population of more than 30,000. The population in the village of Cirencester itself was 13,000. There were two general practitioners involved, and all illnesses seen in these practices were eligible for study. Unlike the preliminary phase, which was designed to detect illnesses of all severities, the subsequent etiologic phase only identified illnesses of sufficient severity to cause an individual to consult a physician (30). The overall incidence of illness, which in the first phase closely resembled that seen in Cleveland, could not be estimated in the definitive phase. Thus, although community-wide in scope, this limitation decreased the ability of the investigators to describe the relation of the etiologic agents to the full spectrum of illnesses.

Given the limitations of case ascertainment, the study focused on etiology and attempted to be quite comprehensive from a laboratory standpoint. Group A hemolytic streptococci were the most common isolates at 6.6 per 100 specimens collected, followed at 6.2 percent by the rhinoviruses. This was a novel finding, since work with rhinoviruses was in its infancy; the laboratory methods used were highly appropriate

based on the standards then current, and involved the use of WI-26, WI-38, or human embryonic kidney cell cultures. The distinction between "M," or strains growing in monkey kidney cells, and "H," strains growing only in human cells, was still in use at that time. It is now known that this classification was not meaningful, but it does bear some relation to the serotypes described later. Once the laboratory methodology had stabilized, recovery of rhinoviruses was made essentially every month (31). Numbers of isolations by age roughly followed those of the practice population, indicating similarity in age-specific rates but with a slight excess in children under the age of 15 years. Most illnesses were afebrile, but, surprisingly, rhinoviruses were among the few viruses associated with deaths in elderly people. It is only possible to speculate whether this result is related to the comprehensive nature of the study, with even rhinoviruses producing death in the frail elderly, or whether it represents the chance association of a common infection with death.

While nearly all respiratory syncytial virus isolations were made from young children with sporadic recoveries from older individuals, the situation with the parainfluenza viruses was far different. Approximately 30 percent of parainfluenza isolations came from adults, with an increase in the number recovered from the elderly. This was one of the first pieces of evidence of the ability of these agents to produce disease upon reinfection. Observations on the cycling of influenza suggested to the authors that latency was a possibility, although no laboratory data were then (or are today) available to support this hypothesis. In fact, this speculation became the most remembered part of the Cirencester Study and deflected attention away from the well-documented observations.

The New York Virus Watch

Design. The studies of Fox et al., initially carried out in the New York City area, marked a return to the approach of going

directly to families and their members to identify illnesses and to collect specimens for isolation (32, 33). The study took place from 1961 to 1965 and evolved and changed during that time. Thus, it may be said that it was its own pilot study. There were initially two study sites, Stuyvesant Town, a middle income housing project in Manhattan, and an isolated rural community, Shelter Island, located off the eastern tip of Long Island. The Shelter Island site was dropped in 1963. Specimens were collected to identify enteric as well as respiratory pathogens, with initial efforts made to sample sewage, especially for polioviruses. Indeed, the original design derived a great deal of information from previous studies by the lead author that had been conducted in Louisiana, focusing on polio (34). Families eligible for recruitment were at first required to contain a child under the age of 10 years, but from December 1962 onward, new recruitments were limited to families with a newborn infant.

The design was based on the routine collection of respiratory and fecal specimens every other week from a preselected index individual. Mothers were asked to report by telephone all febrile illnesses, and from June 1963 onward, all respiratory illnesses whether febrile or not. Reports of these illnesses occasioned collection of additional specimens from both ill individuals and other family members. Blood was regularly collected from all family members every 6 months. In addition, there was an initial effort to collect acute and convalescent blood specimens. Illness definitions were derived from those used in the Cleveland Family Study. Any deviation from health, as reported by the family, was considered an illness and was so enumerated. Duration was likewise determined by the mother, except when a new illness developed before the end of an old one. Classification of illness was based on symptoms reported by the mother and the study nurse without reference to any medical intervention.

Results. The New York Virus Watch was structured to collect a large number of

specimens for virus isolation, and major findings related to viral recoveries with and without illness, including the occurrence of asymptomatic infection. However, in the course of identifying whether or not an isolate was associated with illness, the number of respiratory episodes per year and seasonality were determined. Overall frequency was lower than that reported in prior studies, perhaps because of the concentration on virus isolation rather than illness ascertainment. Seasonality was apparent, but it was difficult to show reproducible differences by month. Reporting of fever was felt to be a particular problem, since it was the caregiver of the household, typically the mother, who would report on the illness and who often did not take a child's temperature. This situation precipitated the change in reporting of illnesses, in which detection of fever was not required. The number of families under study in Shelter Island remained stable at approximately 20 during the 2 years of that segment of the overall investigation; in Stuyvesant Town, the number of families varied widely over the 4 years, from a high of close to 70 to a low of less than 30. The specimens for virus isolation taken routinely every 2 weeks were reliably collected, but additional specimens from persons with illnesses were often missed (34, 35).

Illnesses were twice as common in mothers than in fathers, and the median annual number of illnesses in children aged 5 years or older was 4.4, as compared with 5.4 in children younger than age 5 years. Differences in location (isolated Shelter Island vs. New York City) were far less important in terms of frequency of respiratory illness than differences among families. A great deal of effort was expended in virus isolation attempts, including efforts to recover difficult-to-cultivate enteric viruses such as *Coxsackievirus*. A total of 31,000 fecal and respiratory specimens were collected from family members. This number included nearly 2,400 specimens collected in relation to poliovirus vaccine inoculation (34). The term "Virus Watch" was actually coined to

reflect the attention given to infection regardless of whether it caused disease, and the results clearly indicate this approach. The most common isolates were the adenoviruses: 243 recoveries with 10 serotypes represented. Coxsackieviruses were the next most frequent isolates at 146, followed closely at 141 by the rhinoviruses. The number of rhinovirus isolates is even more noteworthy, since human diploid cell cultures were not used for the first 2 years of the study, and the results represent only the last years (36).

In light of current knowledge, the low number of or absence of isolates of some groups of viruses are surprising given the young age of the families being studied. This is particularly the case for the parainfluenza viruses—25 isolates during all the years of the study—and there were no isolates of respiratory syncytial virus or influenza. Even the authors suspected that poor laboratory techniques were responsible for this problem, which was undoubtedly the case. In spite of changes in the procedures employed, the authors were unable to improve isolation efficiency (34). With influenza viruses, for example, there were documented outbreaks of influenza in the area, and serologic specimens from participants did indicate that infections had taken place, as documented by a rise in antibody titer. For the other agents, the authors hypothesized that at least a partial explanation for the results was the fact that most specimens processed were not related to acute onset of illness but rather were those collected on a regular basis. As a result, those agents that are shed for a period of time after an illness, and those agents that produce asymptomatic infections, would be the most likely to be isolated.

The latter explanation would hold in terms of the frequency of identification of the adenoviruses (34, 37). Of the adenoviruses isolated for the first time in an episode, 56 percent were recovered from fecal specimens only and 24 percent were recovered simultaneously from both fecal and respiratory specimens. While 53 percent of

adenovirus isolates were detected only once in an episode, many were shed for very long periods of time. In fact, when the periods of excretion were distributed by percentile, it was found that duration for the 90th longest percentile was 305 days. Because of the emphasis on specimen collection, the New York Virus Watch provided more data on adenoviruses than any other population-based study (36). Although 10 serotypes were identified, the isolates were largely types 1 and 2, as would be expected in a study involving young children. Recovery of viruses from the respiratory tract was much more likely to be associated with disease (65 percent pathogenicity) than recovery of viruses with fecal excretion only (38 percent). While prolonged fecal excretion did not appear to have any relation to acute illness in the excreter, it did seem to be involved in viral transmission to other family members.

The Seattle Virus Watch

John P. Fox moved from New York to Seattle, Washington, in 1965, and resumed the Virus Watch Study in that city with a modified design (38). At approximately the same time, the community study in Tecumseh, Michigan, began (39). While these two studies were contemporaneous in their beginnings, they were quite different in many of their methods. The Seattle Virus Watch will be discussed first, since it was in its basic approach a continuation and refinement of the investigation begun in New York in 1961. As in the New York design, reliance was placed on a regular twice-monthly collection of specimens for virus isolation from two or three members of a family with a newborn infant. The specimens were collected from the infant, the mother, and the next oldest sibling, if present, and included both nasopharyngeal and fecal swabs. Special additional specimens were collected from all family members when any member experienced an illness thought to be viral. Blood specimens were collected every 6 months from all participants but

the infant, who was not bled. The goal was to have as many families as possible under surveillance by this method, designated "continuing observation."

Logistics was a limiting factor, since so many specimens needed to be processed. To increase the number of families under observation, a second group, designated "telephone families," were recruited and followed. These families, which also contained a newborn infant, did not wish to be followed as intensively as the main study group. The design for this group included blood collection every 6 months, a weekly telephone call to identify illnesses, and specimen collection from all family members when an illness was reported, not to occur more than twice per year. The main study group was followed from November 1965 to August 1969; the telephone surveillance ended in September 1968 because of incomplete data ascertainment.

All families studied were drawn from the Group Health Cooperative of Puget Sound, Inc., a comprehensive prepaid health maintenance organization which served approximately 10 percent of the population of the Seattle metropolitan area. Recruitment was restricted to certain geographic areas and was far more easily accomplished than it had been in New York. For the continuing observation families, illnesses were reported by telephone or on a form collected every 2 weeks when a study nurse visited to collect specimens. As in New York, reliance was basically placed on the mother's judgment concerning whether symptoms represented an illness, which, for inclusion, was required to persist for more than 1 day. Respiratory illnesses were classified as upper unless there was a croupy cough or physician diagnosis of bronchiolitis or pneumonia.

The number of individuals in the continuing observation group varied between 214 and 349. Two years of observation was expected, but if a new child was born into the family, further participation was possible. The number of individuals in the telephone surveillance program was approximately the same, but it was probably a less

stable group, the authors felt, because of a lower original commitment to the program. In light of what was viewed as an excessive dropout rate, the telephone surveillance was discontinued early. This resulted in the telephone group having slightly under half the person-months of observation as the continuing observation group.

In table 2, the total annual rates of respiratory illness are shown; these rates were derived from the comprehensive data presented by the authors (38). The lower frequency of illness reported by the telephone group is immediately apparent. The pattern of age-specific rates is also somewhat different, given the relatively large number of observations in the two groups. In both groups, illness frequencies in the mothers were higher than those reported for all but children under the age of 6 years. The relation of the rates between adult males and adult females was even more dramatic than that described in earlier studies; it may in part be related to the fact that the mother was responsible for reporting illness for the entire family. The authors felt that the difference between the two surveillance groups might be related to self-selection for the less rigorous type of study (telephone group), but they could not make this statement with certainty, since there had not been random assignment.

Most, but not all, of the problems in virus isolation associated with the New York Vi-

rus Watch were not encountered in Seattle, where a highly proficient group of microbiologists and virologists worked on the project using techniques which had by then become well defined (40). Viruses, such as influenza, which evaded detection in New York, were frequently recovered in Seattle, and the studies were supplemented by use of the collected sera to identify infections not detected through nasopharyngeal specimen collection. However, there was still considerable attention given to enteroviruses, which were even then recognized as showing only a marginal association with respiratory illness.

Again, use of human embryo kidney allowed recognition of adenoviral infection at greater frequency than in other contemporaneous or later studies. Adenoviruses were by far the most frequent isolates in fecal specimens, and the second most common in respiratory specimens (40). Rhinoviruses were the most frequent single group of isolates recovered from respiratory specimens collected from all age groups. Rhinoviruses were identified using WI-38 cells, not one of the cell lines routinely employed from the start of the study. The authors saw these results as verifying those from the first investigations in Tecumseh, in which rhinoviruses were by far the most frequently isolated type of virus (41).

A major change from the New York Virus Watch to the Seattle Virus Watch was expansion of observations using serology (42). The sensitivity of antibody response in identifying infection in persons with virus isolation was determined. The parainfluenza viruses were carefully examined by rise in titer to a single type or to any of the first three types as detected by complement fixation or hemagglutination inhibition (43). Infections, as defined by fourfold or in some cases twofold responses to one or more viral type(s), were observed, by means of person-years, in 46 percent of subjects under 2 years of age, 59 percent in subjects 2-5 years of age, and 40 percent in subjects aged 6-19 years and those aged 20 years or more. These very high infection rates were similar to the rates reported 2

TABLE 2. Annual total respiratory illness rates in the Seattle (Washington) Virus Watch, 1965-1969*

Age group (years)	Continuing observation		Telephone group	
	Person-years	Illness per person-year	Person-years	Illness per person-year
<1	127	4.5	52	3.3
1	97	5.0	43	2.2
2-5	167	4.8	63	2.7
6-9	90	3.0	37	1.2
10-19	67	1.9	32	1.3
Mothers	209	3.2	102	1.9
Fathers	209	2.2	102	1.1
Total	966	3.5	431	1.9

* After Fox et al. (38).

years earlier in the Tecumseh Study (44). Secondary attack rates were calculated on the basis of observed infections and illnesses. They were felt to be most reliable for the youngest families, in which members were likely to be the least immune. Rates were 76 percent for 1-year-old infants and 25 percent for adults; the calculation was made after subtracting the apparent "introducer" from the data. In terms of pathogenicity (the proportion of infection resulting in disease), calculated in terms of virus shedding, illness association declined sharply with age, from 78 percent for infants aged 0–1 year to 11 percent for subjects above the age of 10 years.

In contrast to the parainfluenza viruses, respiratory syncytial virus was only rarely isolated, probably because of the laboratory techniques used, and the data basically came from serologic determinations. Infections were detected in 16 percent of infants aged 0–1 year, 35 percent of subjects aged 2–5 years, 25 percent of subjects aged 6–19 years, and 17 percent of adults; because of use of the complement fixation technique, in which antibody is known not to be detectable for long periods, only 10 percent of the infections in subjects aged 10–19 years were termed reinfections. However, through use of the most sensitive techniques, it is actually known that antibody is universally present in subjects by the age of 2 years, so nearly all of these episodes were in fact reinfections (45). For *Mycoplasma pneumoniae*, also rarely isolated, the serologic infection rates were rather flat across all ages at approximately 12 percent per year. For both agents, pathogenicities were not calculated because of the lack of agent isolation; again, in some cases, twofold rises in titer were counted as infections (43). Twofold changes in titer have generally not been regarded as diagnostic of infection, because they may represent either true infection or experimental variation in the test.

Influenza became a major focus of the Seattle Virus Watch, since, unlike the situation in New York, there were regular viral isolations and the importance of the disease

could be clearly recognized. However, the serologic studies relied on the complement fixation techniques, which are known to be less sensitive and specific than hemagglutination inhibition (42). Infections for both were highest in subjects aged 2–5 years, based again on use of a twofold as well as a fourfold rise in titer. Secondary attack rates were calculated by observation from these data, with the type B strain showing higher rates than the type A strain. Rises in antibody titer were detected in the off season for both type A and type B viruses, which were interpreted as representing continuing circulation in the summer. Such an observation was also concurrently made for type A in Tecumseh (46). Finally community prevalence of antibody, at least by complement fixation, did not seem to influence which agent appeared in subsequent years, such that two type A (H3N2) outbreaks followed each other in spite of high levels of antibodies. Therefore, it was concluded that prediction of the next year's outbreak was hazardous.

The Tecumseh Study

Frequency of acute illness. The studies of acute infectious diseases in Tecumseh, Michigan, began in late 1965, at almost the same time as data collection started in the Seattle Virus Watch. Tecumseh had been identified in the late 1950s as a site for a comprehensive, longitudinal evaluation of health and disease in an American community (47). The design was in large part a creation of Thomas Francis, Jr., and was intended to be a study of a true community and its residents (48). Tecumseh was selected as a site because its borders could be easily defined and because it was conveniently located near the University of Michigan campus in Ann Arbor, Michigan. Its population, somewhat more than 10,000, was also considered ideal. The intent was to define the characteristics of the residents of the study area and carry out investigations on either the entire community or defined subsets. The original study began in 1959, and all community residents of any age

were eligible for examination and collection of blood specimens. The major focus at that time, and in the second series of examinations starting in 1962, was a variety of chronic diseases, especially those of the cardiovascular system, as well as diabetes mellitus and rheumatoid arthritis.

The studies of acute infection began in late 1965, continued to 1971 (phase 1), began again in 1976, and concluded in 1981 (phase 2). Ten percent samples of the overall community were used in these studies, and were selected so as to represent all socioeconomic strata. Case definitions were similar to those used in the Cleveland Family Study (39). The laboratory methods were derived from those used in a study conducted among families living in the former Panama Canal Zone (49). Using virus isolation and seroepidemiologic approaches, the Panama Canal Study had demonstrated the importance of rhinoviruses as the most frequent cause of respiratory infections, with infections increasing in frequency with crowding of sleeping conditions. It also identified rates of infection with other common respiratory viruses not known to be regularly present in the tropics (50, 51).

In Tecumseh, data were collected using three different methods: weekly questionnaires to identify illness onset, specimen collection for agent isolation from participants with illness, and regular blood collection for serologic identification of infection. Households (sometimes termed families) were always recruited as a whole and were contacted weekly by telephone. Thus, having a telephone was a requirement for inclusion; in fact, the rare household without a telephone was visited weekly during the first year, but this proved to be too costly. The weekly telephone call was intended to collect information on the occurrence of acute respiratory and enteric illnesses. The form used has been reproduced elsewhere (39).

When an illness had not been reported during the previous week, a series of questions were asked to identify the onset of an acute episode in any family member. Only

if an illness was recognized were further questions on symptoms asked. Thus, it was the respondent's perception of whether an illness had occurred that triggered collection of symptomatic data. This method was unlike the method used in other studies, where symptom occurrence was recorded and certain rules were then applied to decide whether these symptoms represented an acute respiratory illness (52). In Tecumseh, simple reporting of an illness without additional, specific required symptoms was insufficient for an episode to be recognized as an acute respiratory or enteric illness. For example, if the respondent said that a family member had influenza or a cold but did not report any required respiratory symptoms, the event was not counted as a respiratory illness.

Illnesses were followed on a weekly basis to their conclusion, with changing symptoms being recorded; a termination date was finally entered when the respondent said that symptoms were no longer present. Illnesses were categorized into syndromes according to the types of symptoms present during the entire illness. A new illness was recognized if there were 2 symptom-free days before the onset of new symptoms, a definition similar to that used in the Cleveland Family Study.

The frequency of respiratory illness for the first phase is shown in table 3 by age and sex (53). Illness rates fell with increasing age among subjects in the youngest age group through the age of 2 years. Thereafter, increases in illness frequency were seen in subjects in the 15- to 19-year age period for females and in the 25- to 29-year age period for males. Rates then fell again with increasing age. Illnesses were more common in males under the age of 2 years, but in all other age groups, especially adults, illnesses were more frequent in females. Results for the second phase (1976-1981) were similar (54). The most interesting difference between the two phases was illness frequency in subjects under the age of 2 years. Illness frequency in infants under 1 year of age was lower than that in subjects aged 1-2 years, the peak year; this was

TABLE 3. Mean annual incidence of total respiratory illness per person-year, Tecumseh, Michigan, 1965–1971*

Age group (years)	Mean annual illness incidence			
	Person-years (n = 4,905)	Males	Females	Both sexes
<1	121	6.3	6.0	6.1
1–2	302	6.0	5.4	5.7
3–4	284	4.4	5.1	4.7
5–9	844	3.4	3.7	3.5
10–14	720	2.4	3.1	2.7
15–19	318	2.1	2.8	2.4
20–24	234	2.2	3.3	2.8
25–29	397	2.4	3.1	2.7
30–39	897	1.9	2.7	2.3
40–49	502	1.4	1.9	1.7
50–59	125	1.3	1.8	1.6
≥60	161	0.9	1.4	1.3

* After Monto and Ullman (53).

mainly a result of lower illness rates being recorded during the first 6 months of life.

This difference between the two study phases was probably related to the ability to update ages more accurately during the second phase. In the first study phase, individuals were replaced after a year of study, and their age at enrollment was used throughout the study year. For example, if they were enrolled at 6 months of age, they remained in the age group "less than 1" throughout the year. In contrast, in the second study phase, individuals continued to be reported on as long as they were willing, and their ages were updated quarterly. Thus, the effect of maternal antibody in reducing illness frequency, probably present during the first study phase, could only be identified during the second study phase.

Higher frequency of illness in adult females, as compared with adult males, was observed in both study phases. A question was raised concerning how much of this difference was related to exposure to children and how much was related to differential perception of infection as illness. Exposure to children would be partially reduced in women working outside the home; therefore, in the 1976–1981 period, women were asked about their employment history. Rates of respiratory illness in the

25- to 40-year age group for women working outside the home were intermediate between those women not working and the rates for males, indicating that exposure to children was at least a contributor to this observation (55).

Other family characteristics and their contribution to illness experience could be examined in this community-based study. Previous family studies had shown dramatic associations between family size and illness rates of children and parents; however, these analyses typically did not control for the ages of the children. When this was done in Tecumseh, the effect was less dramatic. Age and number of children did relate to the illness frequency of parents; for children, position in the family was also related to the illness rates of other children. Of interest, in terms of their divergent results, was the relation between illness and infection frequency and family income and education (53, 55). Since the same individuals were represented in the analyses, it was unnecessary to control for age. As family income increased, illness rates decreased, as did infection rates determined serologically. However, as the educational level of the head of the household increased, infection rates went down but illness rates went up. This indicates that household income is related to both infection and illness, probably through crowding as an intermediary factor. Infection rates actually go down with higher education levels; this is because education and income are highly correlated. Individuals who have attained a higher educational level are also likely to live in less crowded situations. However, the results suggest that families with a higher level of education are more likely to perceive those infections that do occur as illnesses; in other words, given the same infection rate, illness rates would be higher in this group.

Identification of infectious agents. If an illness was reported in the course of a telephone contact, and the onset occurred 2 days or less prior to the contact, attempts were made to collect a specimen for isolation. Eligibility for collection of specimens was based on reporting of qualifying respi-

ratory symptoms after the respondent reported recognizing an illness. Any duration (1 day or more) or number of qualifying symptoms (one or more) triggered specimen collection, unlike the situation in other studies, which required more symptoms or a certain duration of symptoms but often did not require the respondent's perception that an illness had occurred.

In the first study phase, an infectious agent was detected in 24.9 percent of specimens; in the second study phase, when hemolytic streptococci and *M. pneumoniae* were not sought, the frequency was 22.1 percent (53, 54). An analysis was carried out on specimens collected during the second study phase to determine factors influencing isolation rates. They were principally affected by age; recovery of viruses was highest in specimens collected from those under the age of 5 years, with frequency dropping with increasing age. This was a reflection of the recognized phenomenon of more virus being shed by young persons. Specimens with a higher titer of virus would survive better during transport from Tecumseh to the laboratory. All illnesses reported within 2 days of onset were eligible to be sampled for virus isolation, which meant that specimens should have been collected from two of seven (28.6 percent) subjects with reported illnesses. In fact, the proportion of reported illnesses for

which specimens were collected was fairly stable in subjects aged less than 40 years (17–19 percent) but was only 12 percent in subjects aged 40 years or more (54).

Specimen collection can be used along with other factors to adjust the results of virus isolation to represent the confirmed etiology of all recorded respiratory illnesses. Indeed, the Tecumseh Study, in contrast to the Virus Watch, had been designed to focus on illness as the major entry point to specimen collection. Tecumseh could thus be much larger and study a more heterogeneous population, which allows its data to be more safely generalized to the overall American population. These projections were useful to policy-makers in determining priorities for agent control through vaccine or antiviral agent development.

Results of such an estimation are shown in table 4. The estimates are the percentage of illnesses caused by each pathogen; also shown are the numbers of these illnesses that would result in physician visits. The latter estimates were made possible because of the community basis of the study; all illnesses were recorded and the respondents were asked if the illness resulted in a physician consultation. The importance of agents such as rhinoviruses and influenza viruses was documented; the role of agents that cannot be reliably isolated, such as coronaviruses, was based on results from

TABLE 4. Estimated impact of respiratory agents in producing all respiratory illnesses; percent of such illnesses caused by each agent and percent with physician consultation: annual number per 10,000 population of all such illness and those with consultation*

Etiologic agent	Percent of illnesses caused by each agent	Number of illnesses caused by each agent per 10,000 population	Percent of illnesses with consultation	Number of illnesses with consultation per 10,000 population
Rhinoviruses	34	8,325	17.6	1,465
Coronaviruses	14	3,428	17.6	603
Influenza	9	2,204	37.9	835
Bacterial	8	1,959	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 agents or noninfectious	23	5,630	21.5	1,211
Total	100	24,484	25.4	6,215

* After Monto and Sullivan (54).

studies which used special techniques. Data such as these have also been determined by age strata (54).

Virus isolation was also valuable in determining the seasonality of the agents. These results were similar for both study phases (54, 56). Rhinoviruses were isolated in essentially all months; however, the peak period each year was September-October, shortly after the opening of schools. All rhinoviruses isolated in Tecumseh were serotyped. The September peaks were shown to be the sum of mini-outbreaks produced synchronously by many different serotypes. The hypothesized role of the schools in this yearly phenomenon was confirmed in later years by the demonstration that it also occurred at the same time among university students living away from home. Another increase in rhinovirus isolation frequency occurred in the spring. The period after rhinovirus isolations each year was a time of parainfluenza predominance; in some years, types 1 and 2 alternated; type 3 was also present during this time period and returned in the spring.

Respiratory syncytial viruses were isolated for a limited time each year; in the first study phase, a "long-short cycle" in sequential outbreaks could be demonstrated. The long-short cycle was characterized as follows: A major outbreak would occur one year in midwinter. During the following year, isolations of respiratory syncytial viruses were limited in number and took place in the spring. The year after that, the outbreak would again take place in midwinter. Thus, there seemed to be a role of population-wide immunity in delaying activity to the spring as well as in minimizing activity (57, 58). Similar patterns were shown in clinic-based studies (59). Isolates have recently been grouped with newly available monoclonal antibodies. Subgroup A and subgroup B virus were present in varying proportions, with subgroup A predominating in all but 2 years; these subgroups have recently been redefined as "group A" and "group B" (60). There was no evidence of major antigenic change in the isolated viruses from 1966 to 1981,

suggesting that if a vaccine were developed, it would not need to be updated over time (61). Autumn illnesses were almost purely rhinoviral in etiology, allowing rhinovirus-specific anti-infective agents to be studied. Rhinoviruses were plentiful at later times, but other viruses were also present (62).

Influenza viruses were isolated in each respiratory disease season. Generally, type A (H2N2) was isolated until 1967, after which type A (H3N2) virus outbreaks occurred in midwinter (46, 63). Outbreaks of type A (H1N1), after its reappearance in 1978, as well as type B outbreaks, took place in late winter and early spring. As described below, influenza activity was followed extensively by serologic analysis, allowing various evaluations of transmission dynamics.

Serologic studies. The Tecumseh Study was designed to make extensive use of serologic analysis to detect infections. This approach was based on the realization that virus isolation is affected by uncontrollable variables, including transit time in transporting specimens to the laboratory, variation in the sensitivity of cell cultures from week to week, and the practical problem of arranging to meet participants at home for specimen collection. In contrast, sera collected over time can be tested together to achieve uniformity in detection of significant changes in antibody titer. Throughout both phases of the study, blood specimens were collected every 6 months. However, the specimens were not collected from all participants at the same time; rather, they were collected on a staggered basis, so that in any single month, approximately one sixth of the individuals being reported on were having blood specimens collected. The data generated by testing these specimens could be analyzed in one of two ways. The three specimens collected in the course of a full year from an individual could be used to give information on the infection experience of that individual per person-year, a method termed "horizontal analysis." Alternatively, changes in antibody titer over particular time periods could be

examined in all paired specimens spanning the period to determine when particular agents entered or left the population, a method termed "vertical analysis."

Serologic analysis extended and complemented information on agents that could be isolated, but it was the only source of data on pathogens, such as the coronaviruses, that could not be reliably recovered. Much of the work on these agents was conducted during the first phase of study. It was possible, using the vertical analysis, to show that coronaviruses 229E and OC43 were mainly transmitted during the spring. There was clear cycling of these agents over time, with one strain being prevalent in some years and the other strain being active in other years. The extent to which a coronavirus could produce a community-wide outbreak of infection was shown with the 229E virus in sera collected in 1967. During the peak months, more than 15 percent of all tested individuals were infected. Horizontal analysis indicated that all age groups were involved, with some sparing of the youngest individuals (64, 65).

Serologic studies with respiratory syncytial viruses and parainfluenza viruses confirmed the seasonality of each of the agents demonstrated by virus isolation (44, 57, 66). A striking observation concerning these viruses was the dramatic demonstration of the extent to which reinfection occurs in both older children and adults. Reinfection frequency of at least once every 5 years was more clearly shown for the parainfluenza viruses than for respiratory syncytial viruses, largely because of the greater sensitivity of the serologic test used, hemagglutination inhibition (44). By comparing illness-associated isolation rates with serologic or total infection rates, the pathogenicity, or proportion of symptomatic infections to total infections for the parainfluenza viruses, could be estimated. This proportion decreased markedly with increasing age, from 73 percent to 13 percent. The situation with respiratory syncytial viruses is likely to be similar. Recognizing the reinfection potential of these viruses is of help in understanding their transmissibil-

ity and the fact that a potential vaccine can only reduce the potential for severe disease in young children, not eliminate it. It also suggests that maternal immunization, to affect severe disease in children in the first months of life, might be required in each pregnancy.

An interesting application of the vertical analytic technique was the demonstration of the long cycle of near-absence and return of *M. pneumoniae* (66). This pathogen, originally called the Eaton agent, was recognized as the cause of primary atypical pneumonia as long ago as World War II. That entity appeared to be absent for long periods of time, and questions were raised concerning the correctness of the etiologic association. The agent was identified as a species of *Mycoplasma* in the early 1960s (67). Isolation and serologic methods were quickly developed which then were used to learn more about the spectrum of illnesses associated with the agent in addition to pneumonia. In the first phase in Tecumseh, *M. pneumoniae* could not be isolated during the first years, which raised questions about the sensitivity of the techniques used, especially when the agent began to be recognized in later years. Serologic techniques confirmed that the start of the study had just missed a period of active transmission, since fourfold drops in complement fixation titer were common in the population. In the later years, the return of *M. pneumoniae* could also be documented by rises in antibody titer. These infections in all age groups were associated with mild respiratory illnesses and, rarely, pneumonia. The multiyear cycle of *M. pneumoniae* has since been confirmed (57).

Comparison of the studies

A summary of the key elements of the various studies is shown in table 5. The Cleveland Family Study was small and followed a fairly homogenous group of families closely, with frequent visits by medical personnel. It set the standard for morbidity, but the infectious agents, aside from influenza and adenoviruses, had not yet been

TABLE 5. Characteristics of family and community-based studies

Study	Size (maximum)	Starting date and duration	Collection of morbidity data	Collection of specimens for pathogen identification	Collection of blood for serology
Cleveland, OH, family	86 families	1948, 10 years	Visit	With illness	Spring and fall, limited use
Cirencester, England	30,000 persons	1954, 8 years	Practice contact	With illness	Some acute and convalescent
New York Virus Watch	70 families	1961, 4 years	Visit and telephone	Regular, every 2 weeks	Every 6 months, limited use
Seattle (WA) Virus Watch	349 persons	1965, 4 + years	Visit or telephone	Regular, every 2 weeks	Every 6 months, increased use
Tecumseh, MI	1,000 persons	1965, 11 years	Telephone call	With illness	Every 6 months, extensive use

identified, and little infection data resulted. In contrast, the Cirencester Study was well supported by the laboratory and produced, for the first time, data on the ubiquitous rhinoviruses. It also identified the potential of agents such as parainfluenza for reinfection. It assumed that most significant illnesses would result in contact with the medical practice, but morbidity ascertainment was clearly a problem.

The New York Virus Watch emphasized the agent and collected specimens on a regular basis as a means of identifying asymptomatic infection. In spite of the relatively small number of families followed, an extremely large number of specimens was collected. There were technical problems in identifying some of the viruses, and the best data were obtained on adenoviruses and rhinoviruses, as well as on overall morbidity. The Seattle Virus Watch used generally similar overall methods, and, as a result of many improvements in laboratory techniques, data became available on agents such as influenza and respiratory syncytial viruses. Because regular collection of specimens during asymptomatic periods continued, isolation rates were still low; however, these results were supplemented by identifying infections serologically. The Tecumseh Study was intended to work with a larger group of families and to identify the effects of familial and individual factors on morbidity. Ascertainment of illness occur-

rence was exclusively by telephone, a method thought to be less sensitive than home visits. However, a recent study using this system to identify the lower respiratory illness syndrome indicated good sensitivity (68). The major technique used to identify infection comprehensively was serologic analysis, with agent identification employed to help in the timing and characterization of circulating viruses. Calculation of asymptomatic infection rates, unlike those in the Virus Watch Study, was indirect, which resulted in different estimates. Thus, the studies all provided different kinds of information; this was mainly a consequence of study design, but was sometimes based on study deficiencies.

PATHOGENS OF SPECIAL INTEREST

Rhinoviruses

The existence of the rhinoviruses had been suspected in early challenge studies involving human volunteers. They were first identified in cell and organ culture in the late 1950s, with techniques for reliable isolation being developed in the early 1960s. Use of human diploid lung cells WI-26 and then WI-38 in cultures incubated on roller drums was the key to their isolation (37, 69). Clinical studies could only give an inkling of the role of the rhinoviruses in respiratory illness, since these episodes did not frequently produce

physician consultation. Only family- or community-based studies could fully identify their frequency and impact. Some early studies that comprehensively examined the illnesses of adults did document the frequency of infection with these agents, as well as their antigenic diversity. One of the most important of these investigations involved employees of State Farm Insurance, an industrial group in Charlottesville, Virginia (25, 52, 70). These investigations were the first to identify many of the features of rhinoviruses known today, since the subjects, mainly working women, were expected to experience more frequent illnesses than adult males (4, 8). The longitudinal nature of these investigations was a factor in the large quantity of important information generated; also of great value was the periodic extension of the study to families.

One of the most controversial elements was speculation about mechanisms of transmission. On the basis of data that rhinoviruses could survive on surfaces, it was shown experimentally that rhinoviruses could be transmitted by finger-to-nose inoculation. It was concluded that this type of indirect transmission was most important in the spread of the common cold (71). Recent experimental studies conducted at the University of Wisconsin indicate that this mechanism is not required for rhinovirus transmission, which may be more frequently spread by droplets (72). Rhinovirus transmission has been the subject of a recent review (73).

The New York Virus Watch, with its emphasis on virus isolation, produced new information not only on adenoviruses, as described above, but also on rhinoviruses, the agent most frequently identified. The fact that the New York Virus Watch was carried out when techniques for identifying these agents were in their infancy limited the ability of the authors to examine familial transmission (36). The Tecumseh Study, on the other hand, used these laboratory methods from the start, and because of the large and relatively diverse population studied, it was able to use rhinovirus data to

substantiate age and sex patterns reported in Cleveland, Ohio, for respiratory illnesses in general. This confirmed that a majority of these illnesses are of rhinoviral etiology (8, 52). The Tecumseh Study followed a small short-term investigation of respiratory infection in the American tropics in which, on the basis of serologic investigation, it was hypothesized that certain types of rhinovirus transmit better than others (49). These types might then have a higher priority in vaccine development or other efforts at control. The term "common" for the virus types producing higher infection rates was developed, and the hypothesis was tested in Tecumseh. All rhinovirus isolates from Tecumseh were serotyped, a laborious activity (44, 74). As a result, it was clear that, while there were common types, they varied sufficiently from year to year to be of little help in prioritization. However, it was also clear that when sufficient antisera were used, essentially all rhinoviruses could be typed, thus putting an end to speculation regarding an endless array of types (75). However, it should be remembered that approximately 100 different antisera were required in order to draw this conclusion.

The Seattle Virus Watch and its late extension, the Seattle Family Study, also examined rhinovirus serotypes extensively and confirmed that these agents caused more respiratory illnesses in all age groups than any other. Common types were also sought in the Seattle data, and again were identified, but also without a small enough number or enough consistency to be useful (76). Serologic studies of rhinovirus infections have been difficult to carry out because of the possibility of cross-reactions and the necessity of using so many individual types (77, 78). The Seattle studies, in common with those conducted in Tecumseh and Charlottesville, demonstrated the protective value of homotypic antibody in preventing infection. The rhinovirus infection rates in the Seattle family studies were lower than those in the original Virus Watch, probably because there were fewer young children in the former investigation.

Influenza viruses

In contrast to the rhinoviruses, techniques for identification of influenza infection, either through virus isolation or serologic analysis, have been available for decades. The Cleveland Family Study spanned the 1957 pandemic of type A (H2N2) influenza and examined the potential for transmission of influenza by identifying secondary illnesses occurring within families (14, 15). This was carried out by simple observation, the classic method. The first illness in a family was identified and any subsequent illnesses which started during the incubation period were assumed to be the result of intrafamilial transmission. Currently these are referred to as "apparent" secondary infections, since they could also be community-acquired reintroductions.

There was a further problem with influenza in the Cleveland Family Study. The incubation period in experimental influenza infections is known to be 1–2 days. It was not possible to show in Cleveland families that an increased number of cases occurred 1–2 days after a primary case; the mean interval to the apparent secondary cases was 7.4 days. It was concluded that secondary transmission had not been documented, even though it must have taken place (8). It is now known that this view of secondary infection assumes that transmission occurs on the first day of illness, when in fact it can and does take place over several days from onset, making assessment of secondary transmission by simple observation even more difficult.

In Tecumseh, influenza infections were shown to cluster in families, another example of the probability of intrafamilial transmission (46). Later, the Houston (Texas) Family Study also was able to demonstrate such clustering of infections. This study was about one third the size of the Tecumseh Study, and it viewed illnesses in families against the background of large-scale independent community surveillance. In common with the Tecumseh Study, the Houston Family Study demonstrated relative sparing of young children with type A

(H1N1) influenza, as compared with type A (H3N2) (79). The high frequency of reinfection with type A (H3N2) viruses in the first years of life was also documented for the first time in the Houston study (80). Data from the Houston Family Study have recently been compared with data from the Tecumseh Study in estimating the population impact of influenza outbreaks (81).

The New York Virus Watch did not isolate influenza viruses, but important data were gathered in the Seattle Virus Watch and the subsequent Seattle Family Study, where, as in Tecumseh, extensive serologic analysis was used to complement isolation data. Both studies were able to estimate the pathogenicity of influenza infections—that is, the frequency with which such infection resulted in disease. The estimates in Tecumseh (15–34 percent) were based on comparison of serologic infection rates with actual illness rates during outbreaks, and this resulted in lower estimated pathogenicity than in Seattle, where viral isolation with and without illness was compared (82).

USE OF FAMILY AND COMMUNITY DATA TO ESTIMATE TRANSMISSION PARAMETERS

It has been recognized for years that the calculation of secondary infection frequencies in families based simply on the observed sequence of illness was an act of faith in the linkage of these events. This was first clearly stated by Buck in 1956, who said that to do so "one must believe that infections in successive family members within a short period of time are more likely to be related to each other than to have been separately acquired from outside sources" (6, p. 1). It is now possible to estimate mathematically the probability that observed infections in a family are more likely to be acquired from within the family than from outside, but only if infection rates for the community as a whole are available. Thus, the "community probability of infection" can be used to modify the apparent secondary attack rate to be more representative of true secondary spread.

Data from the Tecumseh and Seattle studies have been used for this purpose. They were suitable for such analyses because both studies used virus isolation and serologic analysis to determine frequency of infection and agent-specific disease. The Tecumseh population was a defined, representative portion of its community. The overall Seattle population studied was less representative, but its size was sufficient that aggregate results may safely be viewed as representing the community frequency of infection.

The methods were first applied to influenza, since the most extensive serologic studies had been carried out at both sites for these viruses. In addition, the epidemic nature of influenza, with transmission limited to relatively short periods of time, made it possible to use serologic data on the assumption that infections which took place in a family might have been linked. This would not have been possible for agents that are more perennial in their periods of prevalence. The initial analyses examined type A (H3N2), type A (H1N1), and type B influenza outbreaks from the 1975–1979 seasons; all have different age-specific infection frequencies in observational data. A community probability of infection was calculated. Also determined was the calculated secondary attack rate, using serologic data for all infections rather than basing it on observed illnesses. Type A (H1N1), type A (H3N2), and type B influenza were found to be in decreasing order in terms of both ease of spread in the household (secondary attack rate) and intensity of the epidemic in the community. Children were found to be the main introducers of infection into families, with some variation among subtypes (83).

The procedure was further extended for influenza in terms of both years of data (through 1980) and the models employed. Procedures were used to estimate the effect of changes in contact parameters, which in some cases produced marked increases in overall infection rates. This demonstrated that household spread is important in maintaining a link among mixing groups such as

schools and neighborhood clusters (84). Finally, the method was applied to probable rhinovirus illness data in Tecumseh, and results were compared with those found for influenza. This analysis involving illnesses was carried out because it is impossible to comprehensively detect rhinovirus infections serologically, and because the early autumn illness peak is nearly all rhinoviral in etiology. One of the conclusions was that families with only preschool children were more likely to acquire infections with rhinovirus and influenza type B virus from the community than were families with only school-age children (85).

OTHER STUDY DESIGNS

Studies involving designs other than those described above have made many contributions to our understanding of the characteristics of respiratory infections. While community and family studies are necessary to understand the full spectrum of respiratory illness, severe manifestations are relatively uncommon, and hospital studies are needed to define the potential of agents to produce certain clinical syndromes. As indicated previously, it was hospital-based studies that initially described the ability of certain agents to cause croup and bronchiolitis in young children (18–23). Hospital-based studies continue to play a role in developing knowledge concerning respiratory infections (86, 87). For example, much of the information about the distinct strains of respiratory syncytial virus infection comes from hospital-based studies (88). However, a general problem in these studies is the inability to determine a denominator for calculation of rates, unless the institution in question serves a clearly defined population.

With practice-based studies, it is also often difficult to establish a denominator. However, unlike hospital-based studies, it is possible to examine illnesses more comprehensively, since any episode causing physician consultation can be identified (89). This will be more comprehensive for agents, such as influenza, which are more

likely to produce severe illness. In fact, the studies of influenza in Houston relied to a large extent on collection of specimens from practice sites to give a comprehensive evaluation of agents moving through the city (90, 91). These studies were supplemented by other more family-based investigations examining issues such as reinfection and social factors involving infection and disease (92, 93). The latter phase of the Cirencester study was, in fact, practice-based, but because of the system of medical care in the United Kingdom, it could calculate population-based rates. Practice-based surveillance of infectious diseases should be emphasized as health care delivery evolves in the United States. It is an efficient way of collecting information on agents severe enough to bring individuals into the care of physicians, and results will become more generalizable as issues of access to care are resolved.

Community studies have identified the importance of school-age children in introducing infection into the family (94). When the Cleveland study was carried out, day care was rarely used by the middle-class families followed. Over time, having children in day care has become more the rule than the exception, and following children in day care has become a valuable method of determining incidence of illness and infection in young children. The method was effectively used in Chapel Hill, North Carolina, some years ago, and these studies defined the frequency of severe illnesses associated with parainfluenza and respiratory syncytial viruses, among others (95, 96). It has continued to be an efficient method of studying pediatric respiratory infection, and day care has affected the transmission dynamics of certain pathogens, as demonstrated by the later phases of the Tecumseh Study.

SUMMARY AND CONCLUSIONS

Studies of acute respiratory illnesses in families and their communities have been carried out for most of this century. The initial studies established the importance of

these illnesses in terms of their frequency and severity. Age-specific illness rates and principles concerning disease transmission were documented in the period before identification of the etiologic agents. Since that time, the knowledge base has been expanded dramatically. Of all the viruses, rhinoviruses cause more illness of any severity than any other in all age groups. As a result, rates of rhinovirus-specific illnesses resemble those of all-cause respiratory illnesses. The greatest advantage of community-based studies is their ability to study transmission. Since control of infection for most of the agents has been difficult to achieve by conventional means, interruption of transmission should be examined as a possible alternative (97).

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