Appendix B

Prevalence of Respiratory Viral Diseases in the United States

Summary

Rhinoviruses are the most frequently identified causes of respiratory tract infections (RTI). Estimates of rhinovirus prevalence in upper respiratory tract infections range from 25% to over 80% depending upon the age of the population studied, the severity of infections, and the season of the study period. Other important viral respiratory pathogens include coronavirus, respiratory syncytial virus (RSV), adenovirus, influenza virus, and parainfluenza virus.

Rhinovirus, coronavirus and RSV are the agents most often associated with the mild, self-limiting upper RTI producing the symptoms of the "common cold" syndrome, accounting for 50% of all illnesses in the US. Coronavirus and RSV are also associated with the more serious upper and lower RTI prompting physician consultations and hospitalization. Adenovirus, influenza and parainfluenza RTI may produce symptoms characteristic of the "common cold", but these are almost always followed or accompanied by symptoms of lower RTI or systemic infections, and often require hospitalization and have a higher mortality rate.

Introduction

Several excellent reviews of the scientific literature concerning certain aspects of the epidemiology of respiratory tract infections have been published (Tyrrell 1988; Gwaltney, 1997; Turner, 1997). This is a summary and synthesis

of the key conclusions from these reviews and from pertinent literature published subsequently or beyond their specific scopes. While there is general consensus that respiratory tract infections are predominantly of viral origin, three factors make firm estimates for the prevalence of specific viral pathogens difficult. First, the causative agents were identified in fewer than 50% of the cases in the largest epidemiological studies, due to the limits of the methodology available at the time they were conducted. Second, data on the etiological agents of upper RTI (the common cold syndrome) are often conflated with that on lower RTI and systemic infections (*e.g.*, bronchiolitis, pneumonia, flu), confusing the ranking of frequency and severity. Third, multiple agents, viral and non-viral, are often identified in individual cases, making the primary cause unclear.

Several investigators have pointed out that specific viral prevalence measurements are likely to be influenced by the seasonal nature of RTI occurrence. RTI incidence begins to increase in August or September and then declines in April or May. This period is marked by sequential and relatively discreet outbreaks of different viral pathogens. Overall, viral RTI rates are higher for this entire period than in the summer, but rates for specific individual pathogens vary considerably within this period (Turner, 1997; Monto and Cavallaro 1971; Johnson *et al.*, 1996).

The following is a description of the viral types known to be important in respiratory tract infections and the data indicating their prevalence as causative agents in respiratory diseases.

Rhinovirus

Rhinovirus is a member of *Picornaviradae*, a family of non-enveloped and exceedingly small RNA-containing viruses. Other members of this family include the causative agents of foot-and-mouth disease, Hepatitis A and polio. Over 120 distinct rhinovirus serotypes have been identified, having considerable variation in certain chemical and physical characteristics resulting differences in detection sensitivity and ease of laboratory culture. (Rueckert, 1996)

Rhinoviruses are generally recognized as the single most important etiologic agents of the common cold (Turner 1997; Kellner *et al.*, 1988; Couch 1985; Rueckert, 1996; Gwaltney, 1997). This conclusion was first reached on the basis of a series of large prospective epidemiological studies undertaken in the sixties: the Tecumseh Study, the Seattle Virus Watch and the New York Virus Watch (Fox *et al.*, 1966, *Fox et. al.*, 1972; Monto *et al.*, 1971(a) and 1971(b)). Rhinovirus was detected in approximately 25% of upper respiratory disease episodes. Subsequent studies indicate that this underestimates the actual prevalence. Due to the limitations of the available techniques for isolation, culture and/or serological identification, the causative agents in more than half of the patients in these studies went unidentified. (Monto and Sullivan 1993) American Public Health Association guidance suggests that rhinovirus infection accounts for 20-40% of common cold cases in adults, but that "the etiology of about half of common colds has not been identified" (Benenson, 1995).

Adjustments for these limitations can be made to better estimate the prevalence of specific causitive agents, so that an even higher percentage of

respiratory infection may be attributable to rhinovirus. Estimates taken from a long term, multi-year study indicate that rhinovirus was the causative agent for 34% of all respiratory illnesses during the 11-year study. (Table 1 after Monto and Sullivan, 1993). In more recent studies a higher prevalence of rhinovirus in RTI is observed. Herzog *et al.* (1986), in a study of interferon prophylaxis, detected rhinovirus in 55% of 122 patients with acute RTI. In a study of 200 young adults over a 10-month period, Makela *et al.* (1998) found rhinovirus to be the causative agent in half of the RTI cases, but rhinovirus was detected in 92% of the patients during a 2-month outbreak in the Fall.

By using reverse transcription polymerase chain reaction techniques to supplement viral culture and serology, Arruda *et al.* (1997) showed the highest frequency of viral detection in natural colds to date, and the highest incidence of rhinovirus. In a study of 346 cases of colds in adults in the Fall, viral etiology was confirmed in 83% of the cases and Rhinovirus was detected in 79% of the patients.

Table 1[a]

Estimated percentage of all respiratory illnesses caused by specific etiologic agents.

Etiologic agent	Percent of illnesses caused by each agent	Number of illnesses caused by each agent per 10,000 population[b]	Percent of illnesses with consultation	Number of illnesses with consultation per 10,000 population[b]
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

[a] Taken from Monto and Sullivan, 1993

[b] Annual average of all illnesses, Tecumseh, Michigan, 11-year study, 1965-1971 and 1976-1981.

While rhinovirus is clearly the most frequent cause of the relatively benign "common cold" syndrome, it is less prevalent in more serious cases. Studies on populations selected because of multiple visits to doctors or hospitalization generally cite other primary causative agents, or multiple infections, to be more frequent. The site of infection of rhinovirus is generally limited to the mucosa of the upper respiratory tract (Turner, 1997) and these infections are self-limiting. Experimental infections of volunteers have led to isolation of rhinovirus from the lower respiratory tract (bronchioles), but it is possible that this is a result of contamination from the upper respiratory tract (Halperin *et al.*, 1983; Calhoun *et al.*, 1994). In a study of respiratory infections in hospitalized children, rhinovirus was detected in only 11.5% of 519 patients; the highest incidence was among

those with upper RTI and lowest among those with lower RTI. These studies are consistent with ratings by Monto (1995) of the severity of RTI by pathogen for community-acquired viral respiratory infections. On a 4-point scale, rhinovirus infections ranked as 1 or 2, while other viral pathogens ranked 1, 2, 3, or 4. Nonetheless, this report ranked rhinovirus as "most important" among viral RTI because of the combination of severity and frequency.

Rhinovirus infection rates (mean infections per year) vary with age and have been estimated to be 0.59 for all ages, 1.21 for infants, 0.55 for young children (<age 9), and 0.2 for mothers (Cooney *et al.*, 1972). Other estimates are 0.74 for ages 19-32 (Gwaltney *et al.*, 1966) and 0.77 for ages 16-45 (Hamre, 1966). The rate of infection also varies with the time of year, and is highest in the fall at 1.28 per person-year. The true rates are undoubtedly higher than these given the limited detection methodology used in these epidemiological studies (Gwaltney, 1997).

Coronavirus

Coronavirus is the only genus of the family *Coronaviridae*, a classification based on chemical structure and replication strategy. Coronavirus virions are enveloped, round, medium-size (100-150 nm) particles containing single-stranded positive-sense RNA. Coronavirus is the causative agent of a variety of diseases in animals, but only acute RTI and perhaps acute gastroenteritis in man. Human coronaviruses are difficult to culture and most incidence studies depend upon serological techniques. The important human serotypes for RTI

are 229E, OC43, and B814. Each of these serotype groups contain enough antigenic variation so that infection with a 229E strain, for example, confers immunity only to the same strain of 229E, and multiple sequential infections with other 229E strains is possible (Reed, 1984).

Adult populations around the world are largely positive for the presence of antibodies to both 229E and OC43 serotypes (Hasony and Macnaughton, 1982). Antibody to both types appear in early childhood and the percentage increases rapidly with age (McIntosh *et al.*, 1970).

There is a high variation in the incidence of coronavirus infection rates among patients with RTI from year to year. An average incidence of 15% observed over a six-year study represents a range from 1% in 1964-65 to 35% in 1966-67 (Hamre and Beem, 1972). An infection rate of 34% was found in the Tecumseh, Michigan study in 1966-67 as well (Monto, 1974). Monto and Sullivan (1993), based on this study corrected for several factors, estimate 14% of all respiratory illnesses are caused by coronavirus (Table 1). Outbreaks of both OC43 and 229E serotype groups occur in winter or spring. However, while nationwide 229E outbreaks seem to peak in two-year intervals, OC43 outbreaks are annual and more local in nature (Monto, 1974).

Among children, one study determined an overall infection rate of 5%, although a peak infection rate of 19% was seen in one winter outbreak (Kaye, 1971). Of the 200 patients in the most recent common cold etiology study by Makela *et al.*, (1998), 17 were positive for coronavirus.

In otherwise healthy individuals, lower RTI infections are rare. Viruses with 229E antigen were recovered from two infants with pneumonia (McIntosh *et al.*, 1974). Although several epidemiological studies have failed to detect coronavirus in lower RTI (McIntosh *et al.*, 1970, 1978), in adults with chronic pulmonary disease (Buscho *et al.*, 1978; Gump *et al.*, 1976; Smith *et al.,* 1980) and in young asthmatic children (McIntosh *et al.*, 1973) coronavirus lower RTI have caused severe complications.

Respiratory Syncytial Virus

Respiratory syncytial virus (RSV) is currently classified as a member of the *Paramyxoviridae* family, *Pneomovirinae* subfamily, genus *Pneumovirus*. These virions are enveloped, 150 to 300 nm in size, and enclose a single strand of negative-sense RNA. Differences with other members of the *Paramyxoviridae* family resulted at one time in its removal from that family and then subsequently reinstated as part of the subfamily.

RSV is a far more important pathogen in children than in adults. In adults it is responsible for less than 5% of total RTI, about half of which become serious enough for physician consultation and or hospitalization (Monto, 1994). However, in infants under the age of two, RSV is the primary viral etiological agent of acute febrile respiratory disease, bronchiolitis, bronchitis, pneumonia, and croup (Benenson, 1995). Infants between the ages of six weeks and six months are most likely to develop RSV bronchiolitis or pneumonia with peak incidence at two months (Gardner, 1973; Parrott *et al.*, 1973). It is highly

contagious, and surveys throughout the world have shown that half of infants who live through a single epidemic are infected. In day care centers, the attack rate approaches 100% during epidemics (Henderson *et al.*, 1979; Sims *et al.*, 1976).

In a 13-year Washington, DC hospital surveillance study, RSV was detected in 43% of children with bronchiolitis and 25% with pneumonia (Kim *et al.*, 1973). In a similar study in Newcastle-Upon-Tyne, RSV infection was detected in 75% of infants under 1 year of age diagnosed with bronchiolitis and in 22% of those with pneumonia (Gardner, 1973).

Immunity is only partially effective as reinfection is common at all ages (Glezen *et al.*, 1978). Hospital staff on pediatric wards have an infection rate of 25% to 50% during epidemics (Hall *et al.*, 1975, 1978, 1979; Hall and Douglas, 1981; Murphy *et al.*, 1981). In infants, reinfection sometimes occurs within several weeks of recovery from the primary infection (Beem, 1967). Mortality due to RSV is not common in developed countries. In the US, approximately 200-500 hospitalized children die each year with RSV infections. (Shay *et al.*, 2001) Of these, nearly 80% occur among infants less than 1 year old.

Adenovirus

Human adenoviruses belong to the family *Adenoviridae* and the genus *Mastadenovirus* (mammalian adenovirus). Virions are non-enveloped icosahedral particles 80-100 nm in diameter containing double stranded DNA. There are 51 known serotypes of human adenovirus. All are capable of

oncogenic transformation of cultured rodent cells. In addition to RTI they cause a variety of diseases in humans including conjunctivitis, hemorrhagic cystitis, and gastroenteritis (Elnifro, 2000; Allard *et al.*, 2001).

Adenovirus is the etiologic agent in 5% of acute RTI in children under the age of five (Brandt *et al.*, 1969). In some cases these patients develop tonsillitis that is clinically indistinguishable from that caused by Group A *Streptococcus* (Ginsberg *et al.*, 1955; Harris *et al.*, 1971). Mallet *et al.* (1966) estimate that 10% of childhood pneumonias are caused by adenovirus. Adenovirus pertussis-like syndrome is difficult to distinguish from whooping cough usually caused by *Bordetella* (Nelson *et al.*, 1975).

In two epidemiologic surveys, adenovirus was identified in 17 of 254 cases of community-acquired pneumonia in hospitalized children (Juven *et al.*, 2000) and in 13 of 519 children hospitalized with acute RTI (Kellner *et al.*, 1988).

Adenovirus RTI is much less common in adults, with the exception that serotypes 3, 4, and 7 are associated with acute respiratory disease in military recruits, tending to occur under conditions of fatigue and crowding (Huebner *et al.*, 1958; Mogabgab, 1968; Barraza, 1999). Adenovirus was the cause of 1% of common colds in a ten-month epidemiologic study of young adults (Makela *et al.*, 1998).

Influenza & Parainfluenza

Influenza viruses are members of the *Orthomyxoviridae* family. These are medium sized (150-200 nm) enveloped viruses with single stranded negative sense DNA. A closely related family, the *Paramyxoviridae* which includes the

genus *Parainfluenza* is also made up of large, enveloped, single-stranded, negative sense RNA viruses.

Influenza is a contagious acute respiratory disease known to have caused epidemics since ancient times. Prevalence in RTI varies drastically over time due to the frequent occurrence of epidemics with highly variable attack rates. Influenza virus are of three types, designated A, B, and C. Type A are associated with widespread epidemics and pandemics (Murphy and Webster, 1985). Type B epidemics are less frequent and more regional, and type C is associated with sporadic cases and minor localized outbreaks.

Influenza viruses are unique among the etiological agents of RTI in undergoing significant minor and major changes in antigenic response over time. Completely new subtypes (antigenic shift) of Type A appear at irregular intervals, apparently a result of recombinations among human, avian, and swine influenza varieties. These are responsible for pandemics that attack 20% to 30% of the general community and up to 50% of closed populations (schools, nursing home, etc.). Such pandemics occurred in 1889, 1917, 1957, and 1968. Less drastic changes (antigenic drift) occurs in both Type A and Type B resulting in epidemics of influenza across the U.S. at least yearly. (CDC, 2002b) In some cases, infection rates are highest in children due to persisting immunity among adults to related strains from previous epidemics.

Exclusively upper RTI is rarely associated with influenza Type A. Tracheobronchitis is typical, most often accompanied by fever. In children,

gastroenteritis symptoms are usual. Common complications include conjunctivitis, otitis media, and pneumonia (Lamb, 1996).

Epidemiologic survey data invariably associate some cases of RTI with influenza virus, but the episodic epidemic nature of this disease makes it difficult to measure its frequency relative to other RTI agents. Monto and Sullivan (1993) estimate, from data collected in large, multi-year studies, that 9% of RTI is caused by influenza (see Table 1). Influenza A or B was detected in twelve of 200 RTI patients in a ten-month study (Makela *et al.*, 1998). Of 254 cases of community-acquired pneumonia, 4% were caused by influenza A and influenza B (Juven *et al.*, 2000).

Parainfluenza types 1, 2 and 3 are second only to RSV as the leading causes of serious RTI in children, including croup, bronchiolitis and pneumonia (Chanock and Parrott, 1965; Glezen and Denny, 1973; Glezen *et al.*, 1982; Kim *et al.*, 1961; Parrott *et al.*, 1962). Type 4 has been linked only to mild upper RTI in children and adults.

Early serological surveys indicate at least 60% of children have been infected by parainfluenza Type 3 by the age of two and 80% by age four (Parrott, 1961). These estimates were confirmed in a longitudinal study of 119 children Glezen *et al.* (1981) who estimated 75% of children have had parainfluenza Type 3 by age two. Rates for Type 1 and Type 2 appear to be somewhat lower, but by age five about half of all children have been infected by Type 2 and 75% by Type 1 (Parrott, 1961). Parainfluenza Type 3 is often acquired in hospitals by children admitted for other reasons (Mufson *et al.*, 1973).

As a group, parainfluenza viruses are estimated from large, multi-year epidemiologic studies, to cause 4% of RTI (Monto, 1994). Kellner *et al.* (1988) found evidence of parainfluenza in 12 of 519 infants hospitalized by with RTI. Of two hundred young adults with common colds, four yielded evidence of parainfluenza by virus culture and seven by serology (Makela *et al.*, 1998). Of 254 cases of community-acquired pneumonia, 10% were found to be associated with parainfluenza.