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THE EPIDEMIOLOGY OF VARICELLA-ZOSTER VIRUS INFECTIONS

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Historically, varicella has been a disease predominantly affecting preschool and school-aged children in the United States. The live attenuated varicella vaccine was licensed in this country in 1995 and has been recommended for routine use in immunization of children 12 to 18 months of age.[8] As an increasing proportion of children in the United States are protected from varicella by vaccination, changes in the current epidemiology of the disease are anticipated. This article reviews the current epidemiology of varicella-zoster virus (VZV) infection and outlines issues related to possible changes in varicella epidemiology that may follow widespread use of the live attenuated varicella (Oka strain) vaccine.

EPIDEMIOLOGY OF VARICELLA

Varicella is spread by droplet or airborne transmission. Although less readily transmitted than measles, it is nonetheless highly contagious, with secondary attack rates in susceptible household contacts of greater than 85%.[22, 33] The usual incubation period is 14 to 16 days, with a range of 11 to 20 days. Second cases of chickenpox have been reported in immunocompetent persons[26] but are rare. There is immunologic evidence, however, that subclinical reinfection with VZV is common.[2] VZV

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has been detected by a sensitive polymerase chain reaction–based assay in nasopharyngeal secretions of immune household contacts of varicella.[9] It is unknown what role, if any, reinfection may play in maintenance of immunity or immune persons may play in transmission of varicella.

In the absence of vaccination, almost all persons will acquire varicella over the course of a lifetime. Thus, over time the number of cases will approximate the birth cohort; currently, an estimated 4 million cases occur annually in the United States. A striking seasonality is apparent in reported cases of varicella in the United States, with most cases reported during the winter and spring (Fig. 1). This seasonality is thought to be due primarily to high contact rates among children who attend school; because of the relatively long interval between generations of cases of varicella, peak incidence occurs later in the school year.[28] There is no evidence in available data of consistent periodicity in national varicella incidence, with epidemic years occurring at regular intervals, as has been seen for many vaccine-preventable childhood diseases in the absence of vaccination programs. There may be substantial variation, however, in incidence at the local or state level.[17]

In temperate climates varicella is a disease of preschool and school-aged children. Hope-Simpson's[22] careful observational studies of varicella transmission in households during the period 1947 to 1951 revealed that 90% of cases occurred by age 10 years 8 months. A number of population-based studies performed since the 1970s[7, 13, 20] have demonstrated a consistent pattern of age-specific incidence similar to that reported by Hope-Simpson.

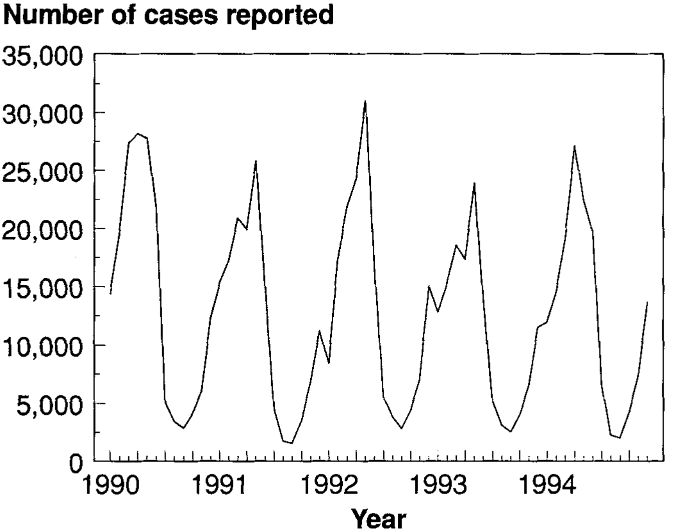

Figure 1. Number of cases of varicella reported by month to the National Notifiable Diseases Surveillance System, Centers for Disease Control and Prevention, 1990–1994. Note peaks in the winter and spring of each year.

Data from the National Health Interview Survey (NHIS), a national population-based sample survey of the noninstitutionalized civilian US population, have been summarized for the periods 1970 to 1978[20] and 1980 to 1990 (Centers for Disease Control and Prevention [CDC], unpublished data, 1993). The incidence rates reported for the two periods were remarkably consistent, with the highest incidence rates among children 5 to 9 years of age and 1 to 4 years of age (Fig. 2). A more recent study of varicella incidence[13] used a population-based telephone survey to ascertain varicella incidence in Kentucky from 1990 to 1992. The highest incidence rates were reported among children 3 to 6 years of age; the rates reported were higher than those for the corresponding age groups in the NHIS analyses.

Choo and colleagues[7] recently studied varicella incidence in a large managed care population. Although reported trends were generally consistent with national data from the 1970s and 1980s, incidence among children under 5 years of age was much lower than that reported previously. This likely reflects an incomplete record of mild cases that did not come to medical attention; rates in older persons were comparable to those found in other studies.

Because varicella is less infectious than other diseases such as measles, social changes that affect contacts among children influence its epidemiology more than they do other, more infectious diseases.[40] In England and Wales, morbidity reports from the Royal College of General Practitioners demonstrate an increased incidence in varicella among children under 5 years of age in the early 1980s.[25] Three decades ago,

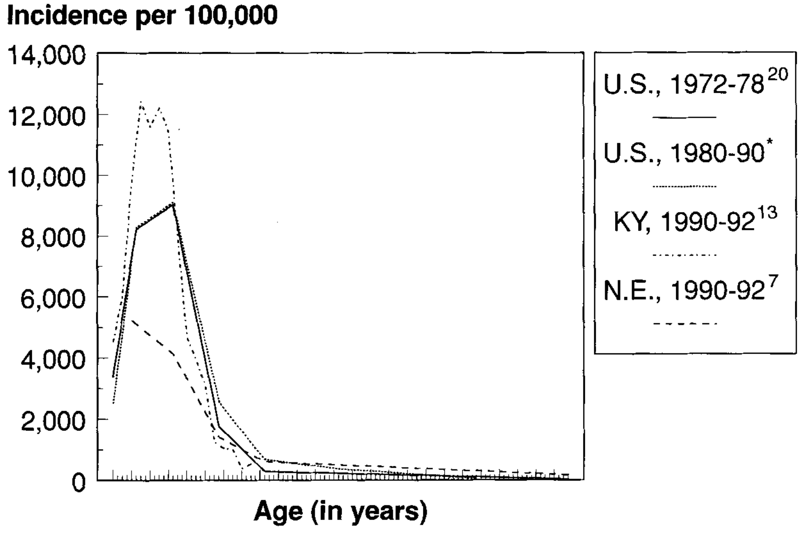

Figure 2. Varicella incidence rate (per 100,000 person-years) by age group as reported in selected studies. All rates are plotted at the midpoint of the age group; age groups differ by study. *CDC, unpublished data, 1993.

varicella was typically introduced into a household by a school-aged child who would then infect younger siblings.[33] With an increasing number of preschool-aged children now participating in organized group child care, many children 1 to 4 years of age now acquire varicella in day-care settings. It is plausible that the average age of varicella acquisition has fallen; this might account for the higher incidence rate reported among preschool-aged children in Kentucky.[13] More data are needed on the impact of group child care on the epidemiology of varicella.

Seroprevalence studies reflect the age distribution reported for varicella incidence. Preliminary analysis of sera collected as part of the third National Health and Nutrition Examination Survey (1988–1994) demonstrates that 34% of 4- to 5-year-olds, 18% of 6- to 10-year-olds, 6% of 11- to 19-year-olds, and 4% of 20- to 29-year-olds are susceptible to varicella.[37] Likewise, studies of US Navy and Marine Corps recruits found that 8% of recruits were susceptible to varicella; although not statistically significant for all race, ethnicity, and gender categories, seronegativity rates were higher among nonwhites than whites. More than 20% of recruits enlisting from outside the United States were found to be susceptible to varicella.[36]

The number of varicella hospitalizations in the United States has been estimated at from 4000 to 9000 annually. Ascertaining the reason for hospitalization from hospital discharge diagnoses, in the absence of additional information from the clinical record, is difficult due to lack of standard procedures for ordering discharge diagnoses. This lack of standardization may account for some of the variation, as do different data sources and estimates of incidence.

Amler and colleagues[1] used the National Center for Health Statistics Hospital Discharge Survey from the years 1970 to 1978 to estimate an annual average incidence of 6458 hospitalizations due to varicella. Almost half of these were of persons under 5 years of age, but compared with the proportion of cases by age group, the risk of hospitalization was highest among those 20 years of age and older.

Guess and colleagues[18] estimated an annual total of 3837 varicella-related hospitalizations by analyzing hospitalizations with varicella-related codes as the principal discharge diagnosis in the Commission on Professional and Hospital Activities (CPHA) National Sample File for January 1979 to June 1982. Records that included diagnoses of or histories of malignancy (including leukemia) were excluded; these accounted for less than 2% of the total.

More recently, the Michigan Inpatient Database for the years 1983 to 1987 has been used to derive population-based estimates of varicella hospitalizations. Applying those rates to national data, Wharton et al[38] estimated that 9300 hospitalizations due to varicella occur annually. The database, collected annually by CPHA for the Michigan Health Data Corporation, includes Michigan residents discharged from hospitals in Michigan as well as from hospitals in contiguous states (Ohio, Indiana, and Wisconsin); nonresidents of Michigan hospitalized in the state were excluded. The study included all hospitalizations with varicella-related diagnoses, with two exceptions: hospitalizations that included any codes for zoster, and those in which the principal diagnosis was major trauma.

Although the estimates do differ, all studies agree that there is marked variation in age-specific hospitalization rates. This reflects both the varying incidence by age group used in calculations and the increased risk of hospitalization among the very young as well as adolescents and adults (Fig. 3).

During the late 1970s, there were approximately 100 varicella-related deaths each year in the United States. This death rate decreased in the early 1980s, coincident with the availability of acyclovir, varicella-zoster immune globulin, and recommendations for the prevention of Reye's syndrome. In the late 1980s, however, the number of deaths rebounded to previous levels (Fig. 4). The reason for this increase is unknown, but a review of other diagnoses for deaths from 1987 to 1990 suggests that the increases are occurring among persons not reported to have malignancy or other causes of immunodeficiency, including HIV (CDC, unpublished data, 1993).

It has long been observed that the epidemiology of varicella varies remarkably between temperate and tropical climates. In tropical areas, varicella typically occurs among older persons, with many cases occurring among adults who are at risk of developing more severe disease. People raised in tropical areas often develop varicella soon after relocating to temperate zones as has been observed in Tamil refugee populations in Denmark[27] as well as in US military recruits from Puerto Rico.[29]

Reasons for this dramatic difference in epidemiology are unclear.

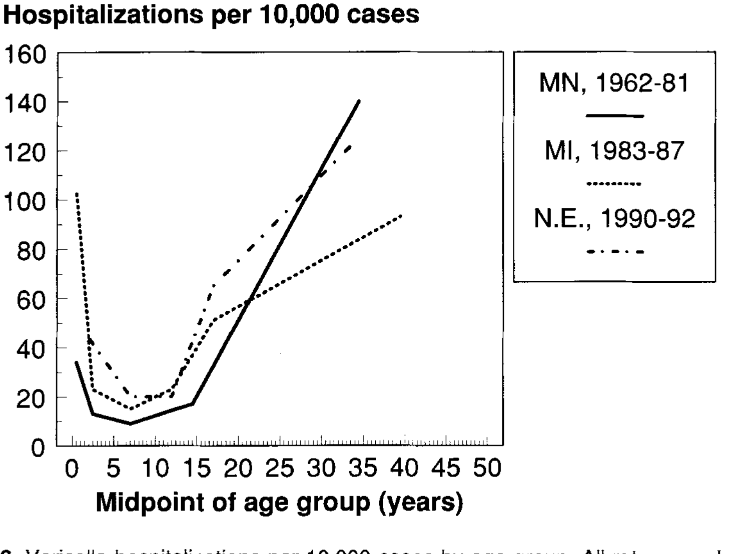

Figure 3. Varicella hospitalizations per 10,000 cases by age group. All rates are plotted at the midpoint of the age group; age groups differ by study.[7, 18, 38]

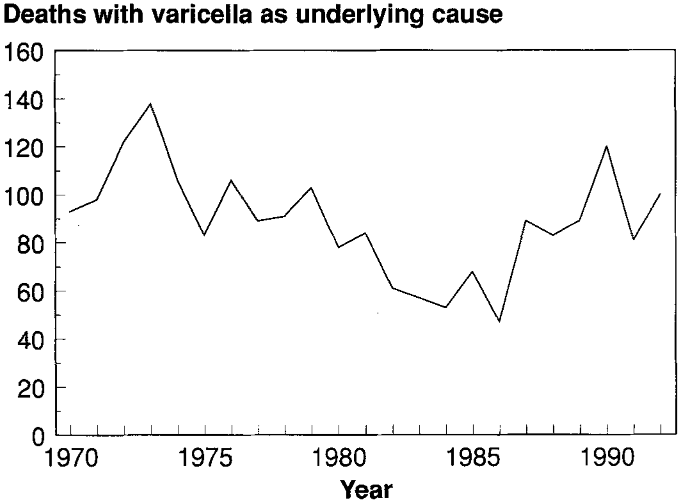

Figure 4. Deaths with varicella as underlying cause, United States, 1970–1992, National Center for Health Statistics, Centers for Disease Control and Prevention.

The seasonality seen in temperate climates is not generally seen in the tropics. It has been suggested that heat, humidity, and lack of exposure to the agent in confined spaces during the winter months may account for the different age distribution. In rural India, however, unexpectedly low rates of household transmission were found, even though most families lived in small houses.[35] It is intriguing that in Singapore varicella appears to have occurred, since the 1960s, in two very large epidemics separated by more than 20 years; serosurvey data obtained during the most recent epidemic, which began in 1988 and affected predominately those 15 to 24 and 5 to 14 years of age,[39] suggested that high levels of immunity existed among those old enough to have been infected during the previous epidemic in 1965. In contrast, more than 50% of 15- to 24-year-olds and more than 75% of 5- to 14-year-olds remained susceptible, even after several years of increased varicella incidence.[31]

This pattern of widely spaced large epidemics may not be typical of tropical areas. A recent serologic survey in the Caribbean island of St. Lucia demonstrated a gradual rise in seroprevalence with increasing age.[14] In contrast to varicella, the prevalence of immunity to mumps was indistinguishable from that in England and the Netherlands, with an average age of infection between 3 and 4 years of age.[10] The latter finding suggests that the distinctive age distribution of varicella seen in tropical climates is agent-specific rather than attributable to nonspecific factors, such as absence of crowding indoors in the winter.

EPIDEMIOLOGY OF ZOSTER

Herpes zoster (HZ) represents reactivation of VZV that has established latency following primary infection. The increased risk of HZ in persons with malignancies and HIV infection is thought to be due to loss of cell-mediated immunity (CMI) for VZV. Decreasing CMI associated with aging is thought to be responsible for the increasing rates of HZ observed among the elderly.[4] Primary varicella acquired in utero or before the first birthday is a risk factor for childhood HZ (see the article by Allan M. Arbeter in this issue), presumably because of immaturity of the immune system.[3, 6, 12, 19]

The most striking feature of the epidemiology of HZ is the increase in incidence observed with increasing age. Hope-Simpson[23] estimated an incidence rate of 74 per 100,000 persons per year among children less than 10 years of age. This rate increases dramatically with increasing age, to 1010 per 100,000 persons per year among those 80 to 89 years of age.

More recent population-based studies in the United States document similar trends (Fig. 5). Guess and colleagues studied the incidence of HZ in persons under 20 years of age in Rochester, Minnesota from 1960 to 1981 using a comprehensive centralized diagnostic file. This file contained diagnoses by almost all health care providers, including outpatient and emergency room visits. The lowest incidence rates were found among children less than 5 years of age (20 per 100,000 person-years) and highest among those 15 to 19 years of age (63 per 100,000 person-years).[19] A similar estimate of incidence among children and adolescents was obtained by Donahue and colleagues from records of the Harvard Community Health Plan, a large health maintenance organization (HMO), during the period 1990 to 1992. In this population,

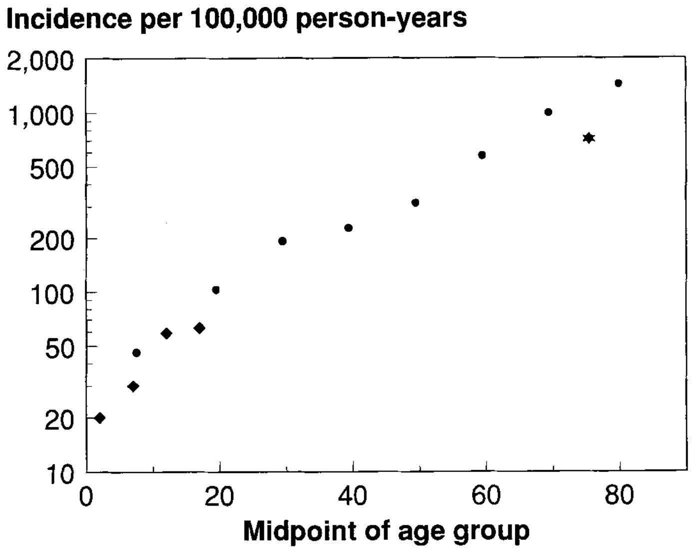

Figure 5. Zoster incidence (per 100,000 person years) by age group. All rates are plotted at the midpoint of the age group; age groups differ by study. Upper limit of oldest age group assumed to be 85 years. (*Data from* references 11 [*circles*], 19 [*diamonds*], and 34 [*star*].)

incidence rates increased dramatically among older persons, with incidence greater than 1000 per 100,000 person-years among persons 75 years of age and older.[11] Similarly high rates among the elderly have been recently reported in a population-based study of community-dwelling persons more than 64 years of age in North Carolina. In this population (mean age 73.6 years, range 65–104 years of age), 69 of 3206 participants reported HZ within 3 years of the interview, for an incidence of 710 cases per 100,000 per year.[34]

There is some suggestion of an increase in age-specific incidence rates over time, but these changes may be due to differences in populations studied or in case ascertainment among studies over time. The first population-based study of HZ incidence in the United States was performed by Ragozzino and colleagues,[32] who reviewed the Rochester, Minnesota diagnostic file for the period 1945 to 1959. They found an incidence rate of 131 per 100,000 person-years, directly age-adjusted to a standard population (US whites, 1970). Although the authors identified no changes in case ascertainment, they found an increase in age-adjusted incidence from 112 per 100,000 person-years in the period 1945 to 1949 to 120 per 100,000 person-years in 1950 to 1954 and 150 per 100,000 person-years in 1955 to 1959. In Donahue's recent study, based on records of the Harvard Community Health Plan during the period 1990 to 1992, an age-adjusted rate of 287 per 100,000 person-years was reported (adjusted to the 1970 US white population). Because these differences are age-adjusted to a standard population, differences in age structure cannot account for the increases. It may reflect improved ascertainment in an HMO population without financial barriers to seeking care or a real increase in incidence over time. Even excluding cases associated with HIV infection (5%) and cancer (11%), the incidence rate was still approximately 50% higher than that reported by Ragozzino and colleagues.[11]

Recently, differences in HZ incidence among the white and black elderly have been reported. In a study of community-dwelling elderly, Schmader and colleagues found a highly significant difference in self-reported HZ among white and black residents of North Carolina. Although the proportion of persons reporting ever having HZ increased with increasing age among both whites and blacks, lifetime incidence of HZ among African-Americans remained less than half that reported by whites. Race remained a significant protective factor after adjusting for age, cancer history, gender, education, and urban or rural residence; only age and cancer history were significant risk factors for HZ.[34]

The significance of these observations is uncertain, but there is evidence that exposure to varicella may decrease the risk of HZ, at least in one very high-risk population. In a longitudinal study of children with acute lymphoblastic leukemia who had received one or more doses of varicella vaccine, Gershon and colleagues[16] demonstrated that both receipt of more than one dose of varicella vaccine and household exposure to varicella protected these high-risk children from HZ. The role of exposure to varicella in maintenance of immunity among immunologically normal persons is unknown, but it is possible that societal changes over the last few decades have resulted in less frequent exposure of the elderly to varicella, which might result in increasing incidence in this population if exposure is important in maintenance of immunity. Likewise, if there were differences in varicella exposure by race (if, for example, the black elderly had more frequent contact with their grandchildren than did whites in Schmader's study), that could potentially account for the observed difference.

FUTURE ISSUES AND THE IMPACT OF VARICELLA VACCINE

Routine immunization of children at 12 to 18 months of age with live attenuated varicella vaccine is expected to dramatically reduce morbidity and severe complications due to varicella among vaccinated children. Because older persons are at greater risk of serious complications than children, failure to achieve high vaccine coverage among children could conceivably result in increased complications, if unvaccinated children reach adolescence or adulthood before contracting varicella (see the article by M. Elizabeth Halloran in this volume).[30] This issue was explored by Halloran and colleagues[21] in a mathematical model of transmission of varicella. Under a range of assumptions regarding vaccine coverage, duration of protection, boosting, and transmissibility, routine varicella vaccination of children was found to reduce both overall morbidity and hospitalizations, even with a shift in remaining cases to older persons. The impact of this shift may be mitigated by catch-up immunization of susceptible older children and adults. Surveillance for varicella will be essential for monitoring the effectiveness of current immunization strategies.

Likewise, more information is needed on the impact of routine immunization on the incidence of HZ. Garnett and Grenfell[15] have used mathematical modeling techniques to evaluate this question. Their analysis suggests that if exposure to varicella plays a role in maintenance of immunity and prevention of reactivation, widespread use of varicella vaccine in children could result in increased incidence of HZ. Administration of varicella vaccine has been demonstrated to boost CMI to varicella in the elderly.[5] This boost in immunity may become even more important in the future, as disease incidence declines; with decreasing risk of exposure to varicella, vaccination of adults might be needed. Ongoing surveillance for changes in the epidemiology of both varicella and zoster is needed, as routine childhood immunization programs are implemented. Efforts are currently underway to enhance surveillance for varicella in the United States.

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