MAJOR ARTICLE

Incidence of Herpes Zoster, Before and After Varicella-Vaccination–Associated Decreases in the Incidence of Varicella, 1992–2002

Aisha O. Jumaan,[1] Onchee Yu,[2] Lisa A. Jackson,[2] Kari Bohlke,[2] Karin Galil,[3] and Jane F. Seward[1]

[1]Centers for Disease Control and Prevention, Atlanta, Georgia; [2]Group Health Cooperative, Seattle, Washington; [3]Cubist Pharmaceuticals, Lexington, Massachusetts

(See the editorial commentary by Whitley, on pages 1999–2001.)

Background. Varicella zoster virus (VZV) causes varicella and, later in the life of the host, may reactivate to cause herpes zoster (HZ). Because it is hypothesized that exposure to varicella may boost immunity to latent VZV, the vaccination-associated decrease in varicella disease has led some to suggest that the incidence of HZ might increase. We assessed the impact that varicella vaccination has on the incidence of varicella and of HZ.

Methods. Codes for cases of varicella and of HZ in an HMO were determined in automated databases of inpatients and outpatients, on the basis of the Ninth Revision of the International Classification of Diseases. We calculated the incidence, during 1992–2002, of varicella and of HZ.

Results. The incidence of HZ remained stable as the incidence of varicella decreased. Age-adjusted and -specific annual incidence rates of varicella decreased steadily, starting with 1999. The age-adjusted rates decreased from 2.63 cases/1000 person-years during 1995 to 0.92 cases/1000 person-years during 2002; among children 1–4 years old, there was a 75% decrease between 1992–1996 and 2002. Age-adjusted and -specific annual incidence rates of HZ fluctuated slightly over time; the age-adjusted rate was highest, at 4.05 cases/1000 person-years, in 1992, and was 3.71 cases/1000 person-years in 2002.

Conclusions. Our findings revealed that the vaccination-associated decrease in varicella disease did not result in an increase in the incidence of HZ. These early findings will have to be confirmed as the incidence of varicella disease continues to decrease.

After causing varicella, the varicella zoster virus (VZV) remains dormant in the sensory ganglia and reactivates later in life to cause herpes zoster (HZ). Both varicella and HZ are characterized by a vesicular skin rash that is commonly generalized in the case of varicella and localized in the case of HZ [1]. Before the introduction of varicella vaccine in the United States during 1995, almost everyone contracted varicella by the age of 30 years [2, 3]; however, only ~10%–30% of persons infected with VZV develop HZ [4, 5]. A decrease in cell-mediated immunity is thought to play a critical role in the reactivation of the virus in healthy individuals [6].

Widespread childhood vaccination in the United States has led to a 75%–80% decrease in the incidence of varicella [7, 8], raising concern that the incidence of HZ might increase because of decreased circulation of the wild-type virus [9]. In 1965, Hope-Simpson hypothesized that external exposure to VZV may boost immunity, thereby reducing the likelihood that the virus would reactivate as HZ [10]. Subsequent studies have reported that the risk of HZ is lower in individuals exposed to varicella or to children than it is in individuals without such exposures [11–14]. Finally, modeling predicts that the vaccination-associated decrease in varicella disease would lead to an increase in the incidence of HZ, an increase that may last for as long as 50 years [15, 16]. Since 1998, the Centers for Disease Control and Prevention (CDC) has collaborated with Group Health Cooperative (GHC), an HMO in Washington State, to monitor the incidence rates of varicella and of HZ. The objectives of this project were to

Received 28 October 2004; accepted 5 January 2005; electronically published 12 May 2005.

Presented in part: 43rd Annual Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, 14–17 September 2003 (abstract G-1084).

Financial support: Group Health Cooperative (Centers for Disease Control and Prevention, under cooperative agreement for surveillance of varicella and herpes zoster [grant UR6/CCU017728]).

Reprints or correspondence: Dr. Aisha O. Jumaan, CDC/ATSDR, Century Center, 2400 Century Pkwy., Rm. 3202, Atlanta, GA 30345 (ajumaan@cdc.gov).

The Journal of Infectious Diseases 2005;191:2002–7

0022-1899/2005/19112-0002$15.00

establish the baseline incidence of varicella and of HZ before vaccine licensure (1992–95) and to assess the impact that varicella vaccination had on the incidence of both diseases after licensure, during 1996–2002.

SUBJECTS AND METHODS

The study population consisted of persons enrolled in GHC at any time during 1 January 1992–31 December 2002. GHC maintains automated administrative databases that record medical information on each enrollee, including immunizations and International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-CM-9)–coded diagnoses associated with outpatient visits and/or hospitalizations [17]. For each enrollee there is also a paper medical record that contains copies of notes on outpatient and emergency-room visits, consultations with medical specialists, and hospital-admission and -discharge summaries. Incident cases of varicella and HZ were defined on the basis of the date, during the study period, of the first outpatient visit or hospitalization associated with an ICD-CM-9 code of either "052," for varicella, or "053," for HZ.

Statistical Analysis

We calculated incidence rates per 1000 person-years of HMO enrollment for the period of 1 January 1992–31 December 2002. Person-time was censored on disenrollment from GHC or death. An annual average of 350,000 persons were enrolled, contributing more than 3.9 million total person-years during the 11-year study period. We used SAS statistical software for data analysis (SAS Institute). We calculated annual incidence rates of varicella and of HZ by dividing the number of cases by the person-time in each year overall and by various age strata. To account for changes in the study population's age distribution during the 11-year period, we calculated age-adjusted incidence rates of varicella and HZ by direct standardization with the age distribution of the US population in 2000 [18]. The 95% confidence interval (CI) for the incidence rates were calculated on the basis of a Poisson distribution. Linear-trend tests of incidence rates during the period were evaluated by use of Poisson regression. $P < .05$ was considered to be statistically significant.

Vaccination-Coverage Assessment

We calculated annual vaccine-coverage rates among children 2, 6, 12, and 15 years old; for each of these 4 age-specific estimates of vaccine coverage, the denominator consisted of children who had reached the specified birthday during a particular year while enrolled in GHC, and the numerator consisted of the subset of those children who had a record of varicella vaccination on or before that birthday.

Outcome Validation

We assessed the validity of automated diagnoses of varicella and HZ over time by reviewing charts of an age-stratified random sample of persons with those diagnoses, oversampling age groups with lower incidence rates. For varicella cases diagnosed between January 1992 and May 2000, we sampled 2% of cases among those 0–9 years old, 10% among those 10–39 years old, and 15% among those ⩾40 years old; charts of 309 (98%) cases were available for review. For HZ cases diagnosed during 1992–95, we sampled 50% of cases among those <18 years old and 5% of those ⩾18 years old, for a total of 357. Cases of varicella or HZ were considered to be confirmed if a health-care provider noted a definite or probable diagnosis in the chart and if no definite diagnosis of an alternative etiology was indicated during the following month.

RESULTS

Varicella vaccine coverage increased progressively in all age groups over time. Coverage was highest among children 2 years old, ranging from <1% in 1995 to 65% in 2002, followed by coverage among children 6 years old, ranging from <0.1% to 45%. Coverage among older children (12 and 15 years old), increased modestly, to 9% and 5%, respectively, in 2002.

The proportion of automated diagnoses confirmed by chart review was higher for the age groups with the highest incidence of varicella disease. The proportion of confirmed cases of varicella was highest (100%) among children 5–9 years old and lowest (3% [1/31]) among adults ⩾60 years old. The most common alternative diagnoses among persons 0–39 years old were other viral-rash illnesses and errors in coding of varicella vaccine or immunity, whereas HZ was the most common alternative diagnosis among those ⩾40 years old. The positive predictive value of diagnosis of varicella decreased over time, ranging from an average of 85% during 1992–1994 (before vaccination) to 53% during 1999–2000 (when varicella disease was decreasing). The proportion of confirmed cases of HZ was highest (94%) among persons ⩾60 years old and lowest (60%) among children 0–4 years old. The most common alternative diagnoses among persons 0–59 years old were herpes simplex, varicella, postherpetic neuralgia, and other rash illnesses. The positive predictive value of diagnosis of HZ remained stable (⩾80%) each year during 1992–95.

Crude incidence rates of varicella during 1992–1998 fluctuated, ranging from 2.00 cases/1000 person-years during 1998 to 2.44 cases/1000 person-years during 1995, and then steadily decreased, to 0.77 cases/1000 person-years during 2002 ($P <$ .001). The same pattern was observed when persons ⩾60 years old and vaccinees were excluded. We found a similar pattern for the age-adjusted rates: the highest rate was 2.63 cases/1000 person-years during 1995, and it decreased steadily, from 2.29

cases/1000 person-years during 1998 to 0.92 cases/1000 person-years during 2002 ($P < .001$) (figure 1).

The age-specific annual incidence rates of varicella fluctuated over time and then, starting in 1999, decreased steadily, among all age groups <60 years old (figure 2). Children 1–4 years old who had the highest incidence rates experienced the greatest decrease (75%), from an average rate of 14.53 cases/1000 person-years during 1992–1996 to 3.67 cases/1000 person-years during 2002. Infants (children <1 year old), who are not eligible for vaccination, experienced a decrease of 65%, from an average rate of 11.81 cases/1000 person-years during 1992–1996 to 4.11 cases/1000 person-years during 2002. Finally, adults 20–59 years old, who had the lowest incidence rates, experienced the lowest decrease (40%), from an average rate of 0.56 cases/1000 person-years during 1992–1996 to 0.34 cases/1000 person-years during 2002. We excluded persons ⩾60 years old, because varicella disease was confirmed in only 3% of them.

Crude incidence rates of HZ fluctuated over time and then increased, from 3.92 cases/1000 person-years during 1996 to 4.48 cases/1000 person-years during 2002 ($P < .001$); however, this increase disappeared after the incidence rates were adjusted for age, ranging from 4.05 cases/1000 person-years during 1992 to 3.47 cases/1000 person-years during 2000 (figure 1).

The age-specific annual incidence rates of HZ increased with age and fluctuated slightly over time, with no discernible trend (figure 3). The rates among children 0–4 years old, the age group most frequently receiving varicella vaccine, were >0.60 cases/1000 person-years for most of the years between 1992 and 2000, with the 2 lowest rates, 0.30 cases/1000 person-years and 0.38 cases/1000 person-years, occurring during 1994 and 1995, respectively, and the highest rate, 0.74 cases/1000 person-years, occurring during 1997, after which the rates decreased, to 0.48 cases/1000 person-years during both 2001 and 2002. Among children 5–9 years old, the rates were >1.52 cases/1000 person-years during 1997–2002, with the lowest observed rate being 1.08 cases/1000 person-years during 1996 and the highest observed rate being 1.64 cases/1000 person-years during 1999.

Among children 0–9 years old, incidence rates of HZ were lower (0–7 cases/year) among vaccinated children than among unvaccinated children. When 1996 and 1997 were excluded (because few children were vaccinated and these years therefore contributed little person-time), the rates of HZ during the post-vaccine years ranged from 0.0 cases/1000 person-years during 1998–1999 to 0.49 cases/1000 person-years during 2002; in contrast, the rates of HZ among unvaccinated children increased, from 0.87 cases/1000 person-years during 1996 to 1.45 cases/1000 person-years during 2002.

DISCUSSION

In this first large longitudinal study that has examined the incidence of varicella and of HZ, before and after introduction of varicella vaccination, the incidence rates of varicella decreased after an increase in varicella vaccine use among children, whereas those of HZ did not change. To date (7 years after introduction of the vaccine), a 65% decrease in the incidence of varicella disease has not appeared to have had an impact on the incidence of HZ. In some countries, varicella vaccine programs have either

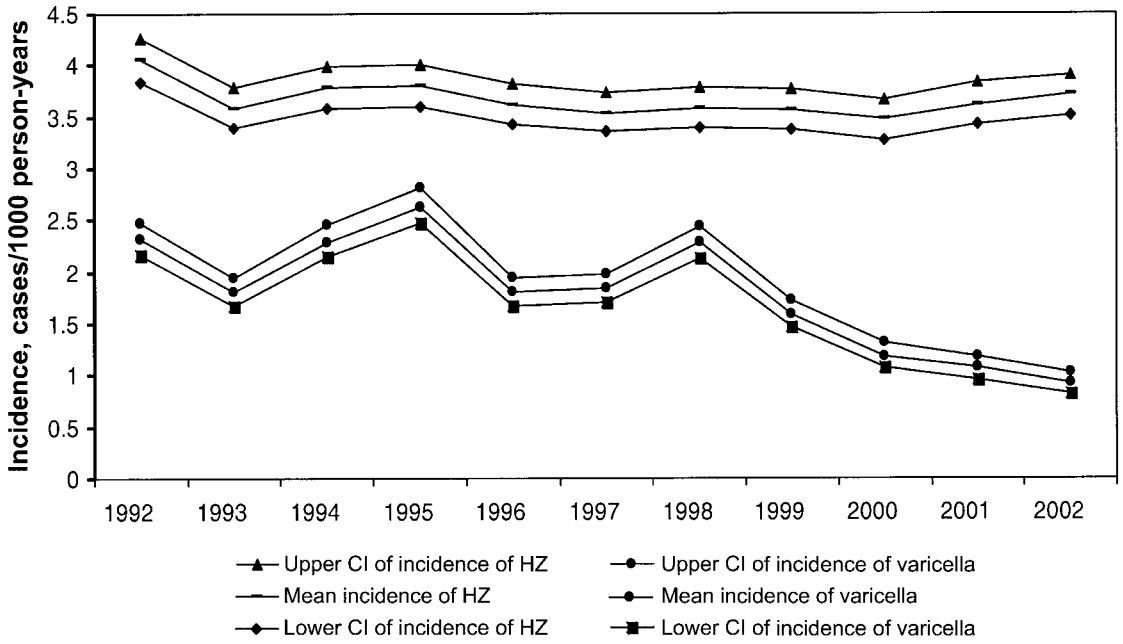

Figure 1. Age-adjusted (to the US population in 2000) incidence rates (and 95% confidence intervals [CI]) of varicella and of herpes zoster (HZ), 1992–2002.

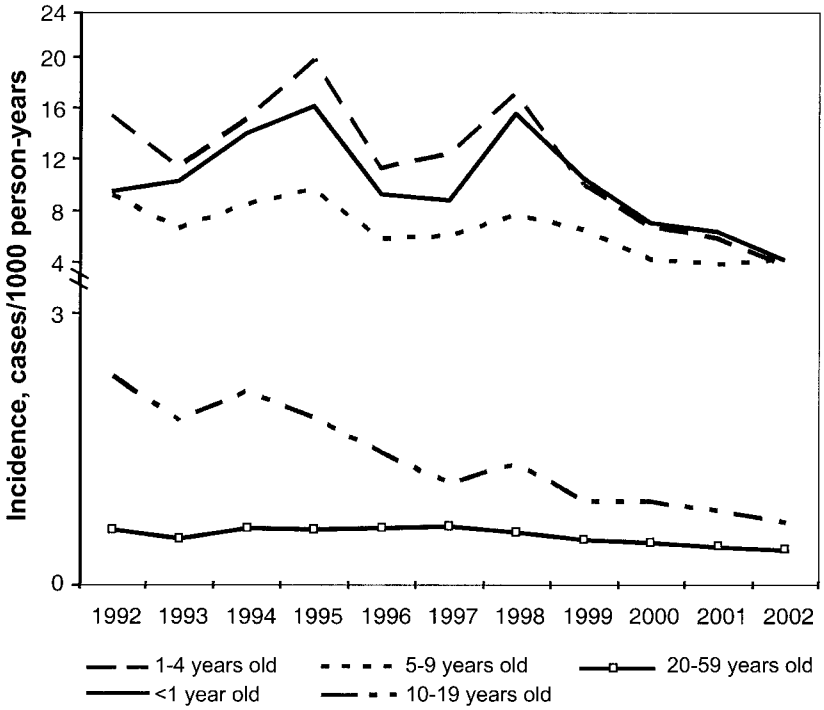

Figure 2. Age-specific incidence rates of varicella, 1992–2002

not been instituted or have been abandoned, in part because of concerns about potential increases in the incidence of HZ after routine varicella vaccination.

Because varicella rates in the present study are based only on cases in which persons sought health care in person, they are lower than those obtained from studies based on self-report [3, 19–21]. Assuming that the number of varicella cases approximates that of the annual birth cohort in GHC, we estimated that our data captured only 18% of the varicella cases occurring during the prevaccine period (1992–94); however, because health-seeking behavior for treatment of varicella is unlikely to have changed in this population during the 11-year study period, the trend observed should not be affected by underascertainment.

Published studies have reported various unadjusted incidence rates of HZ, ranging between 1.3 cases/1000 person-years and 4.8 cases/1000 person-years [10, 22–24]. The US study with the lowest rate used a more stringent case definition [23]. The unadjusted rates reported in the present study are within the range (3.2–4.8 cases/1000 person-years) of published rates observed in other countries [10, 22, 24, 25]. However, because the risk of HZ increases with increasing age, comparison of incidence rates across studies and years should be done after age adjustment to a standard population. Two previous studies have reported increases in unadjusted rates of HZ; one study reported a 36% increase, from 1.15 cases/1000 person-years to 1.50 cases/1000 person-years, between 1945 and 1959 [23], and the other reported a 57% increase, from 1.08 cases/1000 person-years, during 1970–1974 to 1.70 cases/1000 person-years, during 1990–1994 [26]. In the present study, crude rates of HZ increased 37%, from 3.92 cases/1000 person-years during 1996 to 4.48 cases/1000 person-years, during 2002; this increase was due to an increase in the elderly population in GHC and disappeared after the rates were adjusted for age. We used the US population in 2000 to claculate age-adjusted HZ incidence rates for the 2 studies that provided data by age group, and we compared them with the overall adjusted rate (3.90 cases/1000 person-years) observed in the present study, which resulted in rates of 3.27 cases/1000 person-years ($P < .01$) [27] and 3.14 cases/1000 person-years ($P = .60$) [10]; these rates, however, are similar to the overall adjusted rate of 3.20 cases/1000 person-years that was observed in the present study, after adjustment for miscoding of HZ cases.

The incidence rates of HZ among children should be interpreted with caution, because the risk of HZ is conditional on a person's having either had varicella disease or been given varicella vaccine, and age-specific rates of varicella and of vaccination may vary across populations. Furthermore, diagnosis of HZ in children may be challenging, because HZ can be confused with other conditions, such as herpes simplex, a possibility that may explain the wide range in rates of HZ that have been observed in the present study. In the present study, children <10 years old who were vaccinated had HZ rates that were lower than those in children who were unvaccinated; this

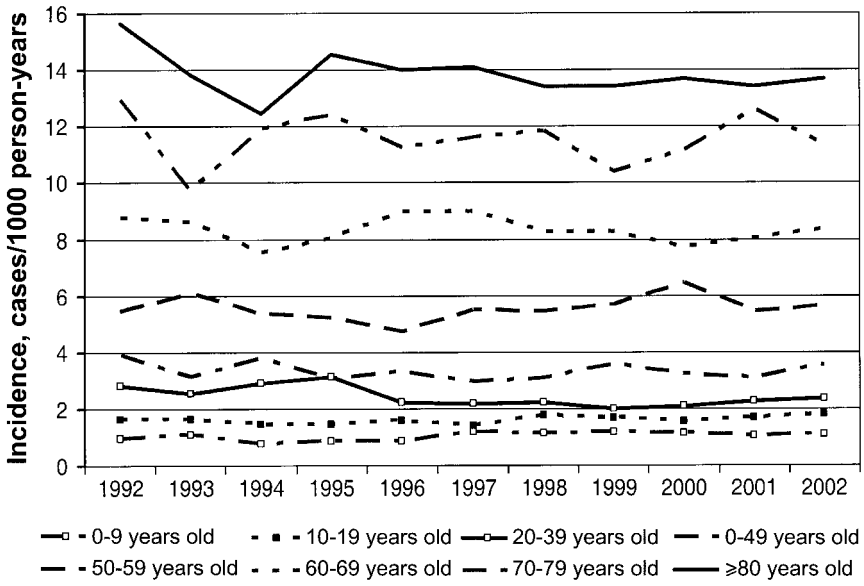

Figure 3. Age-specific incidence rates of herpes zoster, 1992–2002

finding supports the hypothesis that the varicella vaccine virus is less likely than the wild-type to reactivate and thereby cause HZ. The increase in the rate of HZ among unvaccinated children may be a result of an increasing proportion of children in the denominator who, because of the maturing of the vaccination program, are truly at risk for HZ. Before vaccination, many children <5 years old would not have been at risk for HZ, because they had not had varicella; yet, with universal vaccination at 12–18 months, the majority will be vaccinated and thus be removed from the denominator whereas the remaining will be more likely to have had varicella.

Some researchers have suggested that the risk of HZ in persons exposed to varicella cases or to children is lower than that in those not so exposed [11, 13, 14]. Thomas et al. found that the risk of HZ in persons exposed to ⩾3 varicella cases was ~20% of that in those not so exposed. Two other studies have reported that the risk of HZ in pediatricians is lower than both that in the general population [13] and that in dermatologists and psychiatrists [14]; however, the first of these 2 reports studied small numbers of persons [13], and the second of them had low response rates and found no differences between dermatologists and psychiatrists, 2 groups who are considered to have different rates of exposure to varicella cases [14]. In these 2 studies, protection was observed in groups whose exposure to varicella was greater than that likely to be experienced by the general population. Two additional studies have reported that household exposure to children (relative risk [RR], 0.75 [95% CI, 0.63–0.89]) [4] and occupational exposure to children (RR, 0.70 [95% CI, 0.58–0.85]) [12] are associated with a lower incidence of HZ. However, persons who are at a higher risk for HZ because of other medical health problems may be less likely to live with and/or work with children. Persons ⩾50 years old are less likely to live with children (in one study [4], 6% live with children), indicating that protection afforded by exposure to children, if it exists, will benefit only a small portion of adults ⩾50 years old, the group that is at highest risk for HZ. Finally, mathematical models predict an increase in the incidence of HZ, which may be detected as soon as 5 years [16] to 7 years [4] after the implementation of a routine vaccination program; this increase is predicted to last up to 50 years and to decrease thereafter, as vaccinated cohorts replace those who have a history of varicella disease [4, 16].

Exposure to varicella may afford protection against HZ. This postulation is supported by other studies [28, 29]; for example, Arvin et al. have reported that 71% of adults with household exposure to varicella experience a boost in cellular immune responses [28], and Gershon et al. have reported that vaccinated leukemic children who had household exposure to varicella were less likely to develop HZ than were those who did not have such exposure [29]. Yet, other issues—including factors that contribute to boosting, the duration of protection after exposure, and other factors influencing reactivation—remain to be investigated.

The present study has several limitations. First, we relied on automated medical-encounter data, which led to underestimation of incidence rates, although such underestimation should remain constant over time. Second, relying on ICD-CM-9 codes for clinical diagnoses may result in misclassification of varicella cases and HZ cases. Although the predictive value for diagnosis of varicella decreased over time, such misclassification would overestimate the incidence of varicella and minimize the impact of vaccination. Third, although the incidence of HZ remained

constant during the study period, the study may have been concluded too early to detect an increase attributable to a decrease in exposure to varicella. In the population considered by the present study, the uptake of varicella vaccine was slightly lower than the national average, and the study covered only the first 7 years after varicella vaccine was introduced [30]. Finally, the population in the present study may not be representative of those who do not have health insurance, although this should not affect the trends observed.

We will continue to monitor the incidence of HZ as the rate of varicella disease continues to decrease. Other studies have reported the results of boosting VZV-specific cell-mediated immunity by administering another dose of VZV vaccine ⩾5 years after the first dose [31–33]. Future public-health interventions focusing on VZV may include a vaccine to prevent or modify HZ.

Acknowledgments

We thank Mary McCauley for editorial assistance and John Zhang for help with the analysis.

References

1. Dworkin RH, Nagasako EM, Johnson RW, Griffin DR. Acute pain in herpes zoster: the famciclovir database project. Pain **2001**; 94:113–9.
2. Kilgore PE, Kruszon-Moran D, Seward JF, et al. Varicella in Americans from NHANES III: implications for control through routine immunization. J Med Virol **2003**; 70(Suppl 1):S111–8.
3. Wharton M. The epidemiology of varicella-zoster virus infections. Infect Dis Clin North Am **1996**; 10:571–81.
4. Brisson M, Gay NJ, Edmunds WJ, Andrews NJ. Exposure to varicella boosts immunity to herpes-zoster: implications for mass vaccination against chickenpox. Vaccine **2002**; 20:2500–7.
5. Schmader K. Herpes zoster in older adults. Clin Infect Dis **2001**; 32: 1481–6.
6. Miller AE. Selective decline in cellular immune response to varicella-zoster in the elderly. Neurology **1980**; 30:582–7.
7. Seward JF, Watson BM, Peterson CL, et al. Varicella disease after introduction of varicella vaccine in the United States, 1995–2000. JAMA **2002**; 287:606–11.
8. Centers for Disease Control and Prevention (CDC). Decline in annual incidence of varicella—selected states, 1990–2001. MMWR Morb Mortal Wkly Rep **2003**; 52:884–5.
9. Brisson M, Edmunds WJ, Gay NJ, Miller E. Varicella vaccine and shingles. JAMA **2002**; 287:2211–2.
10. Hope-Simpson RE. The nature of herpes zoster: a long-term study and a new hypothesis. Proc R Soc Med **1965**; 58:9–20.
11. Thomas SL, Wheeler JG, Hall AJ. Contacts with varicella or with children and protection against herpes zoster in adults: a case-control study. Lancet **2002**; 360:678–82.
12. Thomas SL, Hall AJ. What does epidemiology tell us about risk factors for herpes zoster? Lancet Infect Dis **2004**; 4:26–33.
13. Terada K, Hiraga Y, Kawano S, Kataoka N. Incidence of herpes zoster in pediatricians and history of reexposure to varicella-zoster virus in patients with herpes zoster [in Japanese]. Kansenshogaku Zasshi **1995**;69: 908–12.
14. Solomon BA, Kaporis AG, Glass AT, Simon SI, Baldwin HE. Lasting immunity to varicella in doctors study (L.I.V.I.D. study). J Am Acad Dermatol **1998**; 38:763–5.
15. Brisson M, Edmunds WJ, Gay NJ, Law B, De Serres G. Modelling the impact of immunization on the epidemiology of varicella zoster virus. Epidemiol Infect **2000**; 125:651–69.
16. Garnett GP, Grenfell BT. The epidemiology of varicella-zoster virus infections: the influence of varicella on the prevalence of herpes zoster. Epidemiol Infect **1992**; 108:513–28.
17. World Health Organization. Manual of the international statistical classification of diseases, injuries and causes of death, based on the recommendations of the Ninth Revision Conference, 1975. Geneva: WHO, **1997**.
18. US Census Bureau. All across the USA: population distribution and composition, 2000. In: Population profile of the United States: 2000. Available at: http://www.census.gov/population/pop-profile/2000/chap02.pdf. Accessed 6 May 2005.
19. Zaia JA, Levin MJ, Preblud SR, et al. Evaluation of varicella-zoster immune globulin: protection of immunosuppressed children after household exposure to varicella. J Infect Dis **1983**; 147:737–43.
20. Finger R, Hughes JP, Meade BJ, Pelletier AR, Palmer CT. Age-specific incidence of chickenpox. Public Health Rep **1994**; 109:750–5.
21. Yawn BP, Yawn RA, Lydick E. Community impact of childhood varicella infections. J Pediatr **1997**; 130:759–65.
22. Chidiac C, Bruxelle J, Daures JP, et al. Characteristics of patients with herpes zoster on presentation to practitioners in France. Clin Infect Dis **2001**; 33:62–9.
23. Ragozzino MW, Melton LJ3, Kurland LT, Chu CP, Perry HO. Population-based study of herpes zoster and its sequelae. Medicine **1982**; 61:310–6.
24. McGregor RM. Herpes zoster, chicken-pox, and cancer in general practice. Br Med J **1957**; 32:84–7.
25. Opstelten W, Mauritz JW, de Wit NJ, van Wijck AJ, Stalman WA, van Essen GA. Herpes zoster and postherpetic neuralgia: incidence and risk indicators using a general practice research database. Fam Pract **2002**; 19:471–5.
26. Jumaan AO, Seward JF, Wooten K, Singelton J. Varicella and herpes zoster surveillance in the US, 1970–1994 [abstract 899]. In: Programs and abstracts of the 41st Annual Meeting of the Infectious Disease Society of America (San Diego, 2003). Alexandria, VA: Infectious Diseases Society of America, **2003**.
27. Donahue JG, Choo PW, Manson JE, Platt R. The incidence of herpes zoster. Arch Intern Med **1995**; 155:1605–9.
28. Arvin AM, Koropchak CM, Wittek AE. Immunologic evidence of reinfection with varicella-zoster virus. J Infect Dis **1983**; 148:200–5.
29. Gershon AA, LaRussa P, Steinberg S, Mervish N, Lo SH, Meier P. The protective effect of immunologic boosting against zoster: an analysis in leukemic children who were vaccinated against chickenpox. J Infect Dis **1996**; 173:450–3.
30. Centers for Disease Control and Prevention, National Immunization Program. Estimated vaccination coverage with individual vaccines and selected vaccination series among children 19–35 months of age by state: US, National Immunization Survey, Q1/2002–Q4/2002. Available at: http://www.cdc.gov/nip/coverage/NIS/02/tab3_antigen_state.xls. Accessed 6 May 2005.
31. Levin MJ, Cai GY, Manchak MD, Pizer LI. Varicella-zoster virus DNA in cells isolated from human trigeminal ganglia. J Virol **2003**; 77: 6979–87.
32. Levin MJ, Murray M, Rotbart HA, Zerbe GO, White CJ, Hayward AR. Immune response of elderly individuals to a live attenuated varicella vaccine. J Infect Dis **1992**; 166:253–9.
33. Levin MJ, Barber D, Goldblatt E, et al. Use of a live attenuated varicella vaccine to boost varicella-specific immune responses in seropositive people 55 years of age and older: duration of booster effect. J Infect Dis **1998**; 178(Suppl 1):S109–12.