High incidence of shingles among children with prior chickenpox: an inadvertent consequence of the universal varicella vaccination program?

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Abstract

Active surveillance for shingles or herpes zoster (HZ) was conducted during three years, 2000-2002, in a geographically distinct high desert region known as Antelope Valley, California among 53,756 children aged 1 to 9 years during which time 92 cases were reported with an estimated 50% reporting completeness based on capture-recapture methods. The ascertainment-corrected crude (population) HZ incidence rate is 114 per 100,000 person-years (184/161,268). The cumulative (2000-2002) true HZ incidence rate is 481 per 100,000 person-years based on an ascertainment-corrected 156 cases during an observation time of 32,410 person-years among children with a previous history of natural chickenpox (varicella). By comparison, a survey conducted among school children in the same study area with nearly 100% enumeration of HZ cases yielded estimated crude and true HZ incidence rates of 72 and 144 cases, respectively, per 100,000 person-years in the pre-licensure era. The postulate is presented that high crude HZ incidence among children with a previous history of natural varicella in the post-licensure period corresponds to a dramatic 70-80% decrease in varicella cases since 1995 and concomitant loss of exogenous re-exposures (boosts) that previously helped suppress the reactivation of HZ.

Keywords: active surveillance, herpes zoster, varicella

1. Introduction

The varicella (chickenpox) vaccine was approved by the Food and Drug Administration (FDA) and licensed for use in the United States in March, 1995. Although success has been maintained with respect to the prevention of varicella [1-3], individuals in healthcare, especially experienced school nurses, are paradoxically observing increases in HZ cases among children when such cases were rare in the prelicensure era. Interestingly, initial assumptions for purposes of cost/benefit analysis of universal varicella vaccination assumed there would be no effect on the closely related herpes zoster (shingles) epidemiology.

An observation by Patti White, RN, school nurse for the Warrensburg School District in Missouri, (a location not under active surveillance) writes: "This year (2001) we have started having children in Kindergarten through third grade show up with shingles. Having worked in pediatrics for 30 years, this is definitely something new to me. At first our physicians were even misdiagnosing because 'kids don't get shingles.' As I have communicated with other nurses around the state, I have learned that other school districts are experiencing shingles outbreaks this year. One of our kids has had an extremely severe and painful case...."

From 2000 to 2002, the Varicella Active Surveillance Project (VASP) under the Los Angeles Department of Health Services in a cooperative agreement with the Centers for Disease Control and Prevention (CDC, Atlanta, GA) conducted active surveillance of herpes zoster in the high desert community known as Antelope Valley, CA. Prior to starting active HZ surveillance among 53,756 children aged 1 to 9 years in the study population, VASP estimated the expected number of cases of HZ in this cohort using the HZ incidence rate of 74 per 100,000 person-years given by Hope-Simpson among children <10 based on his general practice in Cirencester, England over the period 1947 to 1962 [4]. This crude rate is higher relative to other studies of HZ incidence conducted in the U.S. in the prelicensure era [5]. Thus, using the prelicensure HZ incidence rate of 74 per 100,000 person-years as the basis for the post-licensure rate estimate, the VASP anticipated less than 80 cases (95% C.I., 53 to 85) occurring during two years, 2000 and 2001, in the Antelope Valley assuming 100% enumeration of HZ cases and ignoring the fact that 50% to 60% of children had been vaccinated. Virtually all available sources of varicella cases from schools and healthcare providers were included in the active surveillance of varicella. With the exception of one large HMO (serving an estimated 30% of the community), these same sources also reported HZ cases. By comparison to the criterion standard established by NHIS (National Health Interview Survey), reporting completeness of cases aged 1 to 19 years via active surveillance of varicella was estimated at 50% [6]. Since a large HMO did not report HZ cases and dermatologists were not under active surveillance, VASP expected no higher than 50% reporting completeness of HZ cases, or 40 reported cases (95% CI, 22 to 45). Instead, VASP received 74 physician-diagnosed reports of herpes zoster—65 (88%) in unvaccinated and 9 (12%) in vaccinated children <10. (Table 1) Using two-source capture-recapture methods applied to unvaccinated HZ cases aged 5 to 19, a likely maximum reporting completeness estimate of 50% was confirmed. Thus, during 2000 and 2001 in the postlicensure era, the crude HZ incidence rate among children <10 was 1.85 (and the true rate was about 3) times higher than expected [7] relative to prelicensure rates determined in (a) an adolescent survey conducted among public middle school students (Appendix 1) in the study population [8] and (b) other historical studies from the U.S. and England. Since the HZ incidence rates of 138 per 100,000 among individuals 10 to 19 was as expected, this served as a control that

doi: 10.1588/medver.2004.01.00002

HZ was not generally being misdiagnosed [7]. Experienced school district nurses in the surveillance area that reported to the VASP expressed concern that they were seeing cases of HZ for the first time or observing increases in cases of HZ in school children relative to the prelicensure era. HZ disease was previously considered rare in children (1 case in 1,350 children per year) [4].

Interestingly, as recently as 2002, studies by Brisson et al [9] and Thomas et al [10] raised concerns regarding potential increase in HZ incidence among adults due to universal varicella vaccination of children. According to their hypothesis, which was first suggested by Dr. Hope-Simpson in 1965 [6], individuals in the prelicensure era received exogenous boosts from periodic re-exposures to children with wild-type varicella. This boosted adults' cell-mediated immunity (CMI) to varicella-zoster virus (VZV) to suppress the reactivation of HZ. While this hypothesis was applied to adults, children with a previous history of wild type varicella received the most frequent exogenous boosts of any cohort in the prelicensure era by virtue of the exposures they received in elementary school. Thus, in the postlicensure period, with 50% to 60% of children <10 vaccinated and varicella cases in 1999 and 2000 reduced by 70% to 80% of 1995 levels, I postulate that introducing varicella vaccine is associated with an earlier decline in CMI among children <10 with a previous history of varicella based on a cumulative (2000 to 2001) true HZ incidence rate that is three-fold higher than expected relative to historical rates given for the same age. It is highly improbable that ascertainment via active surveillance was better than (a) studies using automated medical records (AMR), (b) HZ data bases such as RCGP (Royal College of General Practitioners in England) and MSGP4 (another data base from England) with high ascertainment and completeness [5,11] or (c) enhanced surveillance systems such as utilized in the Shingles Prevention Study (SPS) [12]. Since no subclinical cases were identified and all HZ cases reported to VASP by schools in the Antelope Valley also sought healthcare providers under active surveillance, ascertainment-correction via capture-recapture methods helped to compensate for under-reporting of cases voluntarily submitted to VASP by healthcare providers; thus, achieving results similar to those that would have otherwise been obtained by electronically scanning computer records for ICD-9 codes indicating HZ as the primary diagnosis.

2. Methods

The Varicella Active Surveillance Project (VASP) began to collect case reports of varicella beginning in 1995 and HZ beginning in 2000 from approximately 300 reporting sites in the Antelope Valley population. With the exception of one large HMO, sites reporting HZ cases were comprised of nearly 100% of the known public and private schools and day care centers with enrollments of 12 or more children, public health clinics, hospitals, private practice physicians, and health maintenance organization offices. The methods are well described in other references [1,7,8]. A monthly Varivax Immunization Report was submitted by all 57 providers administering the vaccine since licensure in 1995. With telephone and/or fax message prompting following each reporting period, site compliance in submitting reports to VASP was virtually 100%.

Ascertainment-corrected HZ incidence rates were computed by applying two-source (schools and healthcare providers) capture-recapture methods to the number of HZ cases reported via active surveillance. The Antelope Valley population estimates are based on the 2000 census from the U.S. Census Bureau. The confidence interval (CI) for incidence of HZ and recurrent HZ is based on the Poisson or normal distribution depending on whether the number of incident cases is less than 100 or greater than or equal to 100, respectively.

Results for 2002 in this report are based on the annual report by L. Mascola and R. Civen, co-principal investigators of the Active Varicella Surveillance and Epidemiologic Studies project conducted by the Los Angeles Department of Health Services, Acute Communicable Disease Control Unit which was submitted to the Centers for Disease Control and Prevention (CDC) on June 2003 under cooperative agreement no. U66/CCU911165-10.

3. Results

Figure 1 presents annual crude HZ incidence rates among children aged <10 years, beginning with licensure of varicella vaccination in 1995. Rates extrapolated beyond 2002 assume that 5,000 school-entry children (equivalent to the birth cohort) are vaccinated each year (due to California state mandates imposed beginning in 2001) until virtually 100% of children <10 are vaccinated. I now consider in greater detail the four distinct periods characterizing HZ incidence rates by year, namely, the prelicensure era (1995 and earlier), initial uptake of vaccine (1996 through 1999), peak HZ incidence (2000 and 2001), and a period of declining incidence (2002 to 2005).

Based on the 2000 census for the Antelope Valley, there are 53,756 children aged 1 to 9 years, with a racial/ethnic composition as follows: 41% White/non-Hispanics, 14% African-Americans, 38% Hispanics, and 7% Asian/Others.

3.1 Crude Incidence Rates in the Prelicensure Era (1995 and earlier)

The cumulative (1987 to 1995) HZ incidence rate in the prelicensure era was derived from an Adolescent Survey conducted among thirteen public middle schools in the Antelope Valley. The crude (population) HZ incidence rate is 71 per 100,000 person-years among children <10 based on 18 cases occurring during an observation time of 25,472 person-years [8]. This crude rate based on a cross-sectional sample representing 37% of the public middle school population closely compares with the 74 per 100,000 person-years estimated by Hope-Simpson, based on 6 cases occurring during an observation period of 8,160 person-years, or 16 years among 510 children in his general practice in Cirencester, England [4]. These rates, in turn, are similar to those demonstrated by the more current and much larger databases of the Royal College of General Practitioners (RCGP) and the fourth morbidity survey in general practice (MSGP4) which exhibit high levels of case ascertainment and completeness. Thus, HZ incidence rates based upon low observation times (even though they have wide confidence intervals) may yield rates that are similar to much larger studies, likely

doi: 10.1588/medver.2004.01.00002

due to the social pattern and mixing of the small cohort reflecting that of the larger population.

In contrast to HZ incidence rates determined in older age groups where most individuals have had a previous history of varicella, crude (population) incidence rates among children have been historically confounded by the presence of susceptibles who are not candidates for reactivation of HZ disease.

By investigating the percentage of children aged <10 years susceptible to varicella, confounding of the crude HZ incidence rate in children can be eliminated by considering only the observation time following varicella disease and derive the true HZ incidence rate among those children with a previous history of varicella. Based on the age-specific percentage of children susceptible to varicella given in the Kentucky Behavioral Risk Factor Surveillance System (BRFSS) study by Finger et al [13] (which closely compares to similar percentages determined in the adolescent study conducted in the Antelope Valley [8]), a mean of 52.2% of children aged <10 were susceptible to varicella (in the pre-licensure era). While 12.3% of children 10 years old remain susceptible to varicella, 52.2% is the mean of the age-specific percentages of varicella susceptibility corresponding to children by year from age 0 to 9 years, i.e., 95.5% susceptible <1-year-olds, 89.5% susceptible 1-year-olds, 79.7% susceptible 2-year-olds, …, 15.4% susceptible 9-year-olds [7,13]. Thus, since approximately 50% of the observation time in this cohort is among children prior to their onset of varicella as well as among those that remain susceptible to varicella and hence not candidates for reactivation, the crude (population) rate represents the mean of two bimodal rates: (1) 0 per 100,000 person-years among susceptibles and (2) 145 per 100,000 person-years among those with a previous history of wild-type varicella. The latter rate is also referred to as the true HZ incidence rate since pre-varicella observation time has been removed from the denominator of the incidence calculation.

The true HZ incidence rate in the Antelope Valley adolescent study is approximately double the crude rate, or 144 per 100,000 person-years among children <10 with a previous history of varicella [8]. (Table 2) This true HZ incidence rate is similar to the true rate of 133 per 100,000 person-years among children <14 determined by Donahue et al in the Boston, Massachusetts population-based study using automated medical records (AMR) [5]. These rates closely compare to HZ incidence rates in the next age group (where most individuals have a previous history of varicella) of 138 per 100,000 person-years among individuals 10-19 given by Hope-Simpson [4].

3.2 Crude Incidence Rates 1996 through 1998

Since significant uptake of varicella vaccine did not begin until 1996 [1], it is reasonable to deduce that changes in HZ incidence rates shown for 1996 through 1998 were negligible since children primarily aged 1 and 2 years were first to receive varicella vaccination and simply replaced those in the population previously susceptible to varicella. Since the incidence rate among vaccinees is given as 18 per 100,000 person-years [14], the crude HZ incidence rate only negligibly increases beyond the rate existing in the prelicensure era.

3.3 Crude Incidence Rates 1999 to 2001

By 1999 and 2000, varicella cases have been dramatically reduced by 70% to 80% of the 1995 level (Fig. 2), such that seasonality of varicella disease is markedly reduced [1]. Since children <10 are sensitive to exogenous boosts they previously received from periodic reexposures to children with wild-type varicella, *true* HZ incidence among children with a previous history of wild-type varicella increases approximately three-fold, thus resulting in a doubling of the *crude* (population) incidence rate from 72 to approximately 156 per 100,000 person-years in 2000. (Table 2)

In 2000, the true HZ incidence rate of 471 per 100,000 person-years among children <10 with a previous history of wild-type varicella is similar to that found among adults aged 40 to 50 years [4,5,7]. Data for the incidence rate shown for 2000 and 2001 are derived using ascertainment-corrected cases and corresponding incidence rates shown in Table 2.

In 2001, varicella vaccination became mandatory in California for all school entry children. This, in part, contributes to the decline in the crude HZ incidence rate following 2000.

3.4 Crude HZ Incidence Rates 2002 to 2005

In 2002 the crude incidence rate was determined to be 68 per 100,000 person-years. The remainder of the curve of crude HZ incidence was extrapolated by assuming that children <10 with a previous history of varicella are replaced by vaccinees until 100% of children <10 have been vaccinated in 2005 (approximately 9 to 10 years after licensure). This figure is supported by active surveillance of all providers of vaccine reporting doses administered by age in the Antelope Valley since licensure in March, 1995 (Fig. 3). The reported doses administered in 2001 and after exceeded the birth cohort since a “catch up” vaccination program that was mandated for entry level school children who had not been previously immunized and who did not have a prior history of varicella.

4. Discussion

By 2004 and thereafter, crude HZ incidence rate is 20 to 30 per 100,000 person-years, which is approximately the current rate among vaccinees. Since Oka-strain VZV reactivates more frequently (especially in terms of asymptomatic endogenous reactivations) than the wild-type strain [15], vaccinees may not be as sensitive to the loss of exogenous boosting as are children with latent wild-type VZV. Alternatively, the low incidence rate of HZ reported during 2000 to 2003 among vaccinees may be due to the fact that mild cases associated with vaccine (Oka) strain HZ fail to come to the attention of healthcare providers.

All historical studies of HZ incidence were confounded by reporting crude incidence rates in children that were approximately one-half the true rates since crude rates included observation time of children still susceptible to varicella. By utilizing only the cohort of children with a previous history of varicella, the true HZ incidence in children <10 in the prelicensure era was similar to that in the 10 to 19 age group where most individuals have a previous history of varicella. Hope-Simpson anticipated this result [4]. Thus, given true HZ incidence rates were nearly constant for the first two decades and then increased almost two-fold for the next three decades (adults 20 to 49), this formed a basis to postulate that a reduction in exoge-

doi: 10.1588/medver.2004.01.00002

nous boosts, rather than a gradual age-related decline in CMI, is responsible for the higher incidence rates associated with advancing age. Age-related decline likely predominates only in the elderly as demonstrated by sharp increases in HZ incidence occurring in the fifth or sixth decade of life and thereafter [4,5].

HZ incidence among children <10 will become less of an issue as vaccinees continue to enter this cohort. The crude HZ incidence rate decreases below the prelicensure rate 7 years postlicensure or 2002.

These results or similar outcomes based on the Antelope Valley, CA community can likely be generalized to many communities throughout the U.S. where varicella vaccination was first added to the childhood immunization schedule and administered principally to 1- and 2-year-olds, followed by state mandates issued in subsequent years requiring varicella vaccination of children upon school entry.

Presently little is known concerning HZ recurrence among vaccinees. Concerning unvaccinated individuals, data from active surveillance indicates that 7 recurrent cases occurred among 639 incident HZ cases among individuals of all ages during the two-year (2000 to 2001) study. The VASP defined recurrence as two cases of HZ separated by six or more months. The estimated rate of HZ recurrence is 2,188 (95% CI, 880 to 4,507) per 100,000 person-years based on the average at-risk person-time of 320 person-years during an average follow-up period of one year since cases reported during the first six months would not have yielded recurrent cases that may have occurred prior to the start date of the study and there was no follow up after the end date of the study concerning first HZ cases reported during the last six months.

Breakthrough disease in vaccinated children could potentially extend the period of high crude incidence rates in the post-marketing period of varicella vaccination. Breakthrough varicella is often associated with the wild-type strain and reactivation may occur at the correspondingly higher HZ incidence rate. To date, only 1 to 2% of vaccinated cases have experienced breakthrough disease in the Antelope Valley. However, vaccinated children were previously boosted via exogenous exposures to children with wild-type varicella in the community [16].

Certainly alternate hypotheses exist that are different from the foregoing ones presented. This does not change the fact that in the Antelope Valley, true HZ incidence among children <10 with a previous history of varicella is two- to three-fold higher relative to rates determined in historical studies (possessing likely higher case ascertainment and completeness) conducted in the pre-licensure era. Although a preliminary trend, this observation coincides with an increase from 2000 to 2001 of 18.6% (43/231) cases reported by schools and healthcare providers among adults aged 20 years and over, with an increase occurring in each decade with the exception of the cohort aged 70 years and over. Interestingly, the increase in HZ case reports is highest among the younger adults who received considerably more boosts in the prelicensure era than the older adults. The capture-recapture methods assume the population is closed (i.e., no migration) and that there is 100% data linkage in matching dual reported cases.

Additionally, it is assumed that the two ascertainment sources were generally independent of one another and all individuals had the same probability of being included within the list. It is impossible to perfectly satisfy all these assumptions as well as quantify the effect of the dependence of the two ascertainment sources. However, because it is the policy of schools to require a written notice from a physician to excuse a child's absence, it is suspected that schools and healthcare providers are positively dependent, with the effect of increasing the number of case matches and thus leading to an underestimate of herpes zoster incidence [17].

5. Conclusions

It has been reported, "The age-specific incidence of shingles has not changed since the vaccination program started [18,19]." However, both the state-wide 1999 and 2000 BRFSS surveillance study in Massachusetts and 1992 through 2000 Seattle Group Health Cooperative (GHC) study upon which this conclusion is based, have insufficient power and inadequate sample size to detect statistically significant changes [20]. Interestingly, both studies demonstrate an increase in herpes zoster incidence among children <10 in the post-licensure period, although not statistically significant. Since approximately 50% of children <10 have been vaccinated by 2000 in the Antelope Valley, if the decrease in exogenous boosting had negligible effect on herpes-zoster epidemiology, a decline in herpes zoster incidence rates would have been expected after 6 years of universal varicella vaccination in this cohort. Reports suggesting "no change" in the crude (population) incidence rate actually imply that the HZ incidence rate among children <10 with a previous history of natural (wild-type) varicella have increased sufficiently in the postlicensure era to offset the relatively low HZ rate experienced among vaccinees. This increase is likely more dramatic in Antelope Valley, CA where the vaccination coverage is greater than that of the two studies cited above.

The paradoxical increase in the crude (population) HZ incidence rate among children <10 is quickly resolved following 2003, thus shifting concern of healthcare professionals from children to adults. The Amajor epidemic of herpes zoster@ suggested by Brisson et al [9] and supportive case control study by Thomas et al [10] deserve more attention as it is seen that exogenous exposures to wild-type varicella in the community previously played a significant role in boosting CMI to VZV to suppress reactivation of HZ. Increases in reactivation among adults due to reduction in exogenous exposures are implied by vaccine trials in which recipients demonstrate boosting of CMI to VZV [21,22]. Since adults manifest a longer residual cell-mediated immunity compared to that of children following an exogenous exposure, sensitive surveillance systems will be required to detect a preliminary increasing HZ rate among adults.

Results from active HZ surveillance in the Antelope Valley study population 2000 to 2003 were presented by R. Civen et al [23]. According to this report, crude or population-based HZ rates demonstrated no statistically significant difference by year, sex, race, or by month in the three years. The crude rates, however represent the mean of three very different HZ rates among children (a) still susceptible to varicella who cannot experience onset of shingles (0 cases per 100,000 person-years), (b) with a previous history of natural varicella demonstrating a true HZ incidence rate of 480 per 100,000 person-years, and (c)

doi: 10.1588/medver.2004.01.00002

who received varicella vaccination having a mean HZ incidence rate of 20 to 30 cases per 100,000 person-years. Reporting the mean incidence rate of 56 per 100,000 person-years for the tri-modal distribution of three distinct cohorts masks the important high trend in HZ in the post-licensure period among children with a previous history of natural varicella as highlighted in the current manuscript (Fig. 4). Interestingly, the reported result "there was no statistically significant difference in the overall HZ incidence rates" may support the hypothesis that the true HZ incidence rate among children with a previous history of natural varicella has risen in the absence of exogenous boosting, effectively yielding a relatively constant crude incidence rate despite the expectation of a significantly lower HZ rate among children in a community with widespread varicella vaccine coverage. This appears to be supported by the conclusion in the poster presentation that "significantly fewer persons with HZ had a history of reported varicella vaccination than varicella infection [23]." Additionally, reported HZ incidence rates by age in the poster presentation assume 100% enumeration of all HZ cases which is rarely true. While HZ cases ascertained via active surveillance can be validly compared from year-to-year in the active surveillance project, the HZ rates actually reflect different percentages of reporting completeness of cases by age. Thus, rates estimated via active surveillance that are uncorrected by the percentage of reporting completeness are uninterpretable and cannot be reliably compared with rates determined in other studies that capture a high percentage of the true cases.

Cost/benefit analyses have yet to fully explore alternative interventions of booster vaccinations taking into account the effects of universal vaccination on the closely related HZ epidemiology [11,24,25]. As of the last update on April 15, 2003, the Vaccines for Children (VFC) Program *CDC Vaccine Price List* indicates varicella vaccine cost to the private sector is 66% higher than the $35 modeled, or $58.11 per dose. Based on the model by Lieu et al, the mean varicella vaccine and administration (discounted) costs approach $146 million and thus create an annual net medical cost deficit of $66 million for varicella, resulting in a benefit-cost ratio of 0.55:1, costing the health payer $16.50 per case of chickenpox prevented (instead of a cost of $2 per case as initially derived assuming $35 per dose) [25,26]. It has been estimated that universal varicella vaccination will have the impact of causing an additional 14.6 million to 21 million cases of herpes zoster among adults during the next 50 years at a substantial cost burden that finally resolves in 30 or more years when a majority of the adult population with a previous history of varicella is replaced by vaccinated individuals [24,25].

Currently under trial in the U.S. is an intervention whereby a booster varicella (or "shingles") vaccination is administered to older adults (60 and over) to substitute for boosting, or possibly improve boosting, that naturally occurred (a) when incidence of wild-type varicella was high in the community and (b) following an adult's outbreak of HZ [12]. This intervention fails to ameliorate the greatest potential for increased burden of HZ disease among adults aged <50 years who experienced considerably more exogenous re-exposures (boosts) than the elderly in the prelicensure era.

Acknowledgements

A special thanks to the healthcare providers, school nurses, child care center directors, and other professionals and members of the Antelope Valley community who reported cases of HZ during 2000 to 2003. A special thanks to Patti White, RN, whose personal concern for the school children under her care and long-term commitment in pediatrics serve as a model for her profession that is worthy of emulation.

References

[1] Seward JF, Watson BM, Peterson CL, et al. Varicella Disease After Introduction of Varicella Vaccine in the United States, 1995–2000, *JAMA* 2002; 287(5):606–11.
[2] Wise RP, Salive ME, Braun MM, et al. Postlicensure Safety Surveillance for Varicella Vaccine. *JAMA* 2000 Sept.; 284(10):1271–79.
[3] Vazquez M, LaRussa PS, Gershon AA, Steinberg SP, Freudigman K, Shapiro ED. The effectiveness of the varicella vaccine in clinical practice. *N Engl J Med* 2001; 344:955–60.
[4] Hope-Simpson RE. The nature of herpes zoster: A long-term study and a new hypothesis. *Proc R. Soc. Med.* 1965. 58:9–20.
[5] Donahue JG, Choo PW, Manson JE, Platt R. The Incidence of Herpes Zoster. *Arch Intern Med*, 1995 Aug; 155:1605–9.
[6] Goldman GS. Using Capture-recapture Methods to Assess Varicella Incidence in a Community under Active Surveillance. *Vaccine* Oct. 2003; 21(27-30):4250–55.
[7] Goldman GS. Incidence of Herpes Zoster among Children and Adolescents in a Community with Moderate Varicella Vaccination Coverage. *Vaccine* Oct. 1, 2003; 21(27-30):4243–49.
[8] Goldman GS. Varicella Susceptibility and Incidence of Herpes Zoster among Children and Adolescents in a Community under Active Surveillance. *Vaccine* Oct. 1, 2003; 21(27-30):4238–42.
[9] 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(19-20):2500–7.
[10] Thomas SL, Wheeler JG, Hall AJ. Contacts with varicella or with children and protection against herpes zoster in adults: a case–control study. *Lancet*, July 2, 2002; http://image.thelancet.com/extras/01art6088web.pdf.
[11] Edmunds WJ, Brisson M, Rose JD. The epidemiology of herpes zoster and potential cost-effectiveness of vaccination in England and Wales. *Vaccine*, 2001; 19:3076–90.
[12] Oxman MN. Immunization to reduce the frequency and severity of herpes zoster and its complications. *Neurology* 1995; 45(Suppl 8):S41–6.
[13] Finger R, Hughes JP, Meade BJ, Pelletier AR, Palmer CT. Age-specific incidence of chickenpox. *Public Health Rep*, 1994 Nov-Dec; 109(6):750–5.
[14] Vaccination and Immunization Education: a teleconference series. Strategic Institute for Continuing Health Care Education. Strategic Implications International, 1998:45.
[15] Krause PR, Klinman DM. Varicella vaccination: Evidence for frequent reactivation of the vaccine strain in healthy children. *Nature Medicine* 2000 April; 6(4):451–4.
[16] Galil K, Lee B, Strine T, Carraher C, Baughman AL, Eaton M, Montero J, Seward J. Outbreak of Varicella at a Day-Care Center despite Vaccination. *N Engl J Med* 2002; 347(24):1909–15.
[17] Hook EB, Regal RR. Capture-recapture methods (Letter). *Lancet* 1992; 339:742.
[18] Varicella Vaccines in the USA: Visit by Jane Seward. Hot Topics Article in NCIRS (National Centre for Immunisation Research and Surveillance) Newsletter, December 2002. The Children's Hospital at Westmead. Cnr Hawkesbury Rd. & Hainsworth St., Westmead, Locked Bag 4001, Westmead NSW 2145. 1:3. http://www.ncirs.usyd.edu.au/newsltrs/newsletter_01.pdf (last accessed Dec. 8, 2003).
[19] Roche P. Blumer C, Spencer J. Varicella –Zoster Virus, Communicable DiseasesIntelligence,Dec.2002; (4):576–580. http://www.cda .gov.au/pubs/cdi/2002/cdi2604/pdf/cdi2604.pdf (last accessed Dec. 8, 2003).

doi: 10.1588/medver.2004.01.00002

[20] Yih WK, Clements K, Lett S, Jumaan A, Seward J. The Incidence of Varicella and Herpes-Zoster in Massachusetts as Measured by the Behavioral Risk Vactors Surveillance System (BRFSS) During a Period of Increasing Varicella Vaccine Coverage 1998-2000. Presented at 37th National Immunization Conference, March 19, 2003, Chicago, Ill.
[21] Levin MJ, Muray M, Zerbe GO, White CJ, Hayward AR. Immune responses of elderly persons 4 years after receiving a live attenuated varicella vaccine. *J Infect Dis* 1994; 170:522–8.
[22] Takahashi M, Okada S, Miyagawa H, et al. Enhancement of immunity against VZV by giving live varicella vaccine to the elderly assessed by VZV skin test and IAHA, gpELISA antibody assay. *Vaccine* Sept. 2003. 21(25-26):3845–53.
[23] Civen RH, Maupin TJ, Xiao H, Seward JF, Jumaan AO, Mascola L. #896 A population-based study of herpes zoster (HZ) in children and adolescents post-varicella licensure. October 9-12, 2003, 41st Annual Meeting of the Infectious Disease Society of America.
[24] Brisson M, Edmunds WJ. Varicella vaccination in England and Wales: cost-utility analysis. Arch Dis Child, Oct. 2003; 88(10):862–869.
[25] Goldman GS. Cost-benefit analysis of universal varicella vaccination in the U.S. taking into account the closely related herpes-zoster epidemiology. Vaccine, available online Jan. 2004.
[26] Lieu TA, Cochi SL, Black SB, et al. Cost-effectiveness of a routine varicella vaccination program for US children. JAMA Feb. 1994; 271(5):375–81.

Appendix 1. Probability of two-fold increase in true HZ incidence rate.

In the prelicensure (adolescent survey) study, the probability of observing a case of HZ is p=0.001445 (18 cases/12,457 person-years or 145 per 100,000 person-years) among children aged <10 years with a previous history of natural varicella. If this probability is assumed to be unchanged in the postlicensure (active surveillance) study, the expectation would have been 57 cases in 39,676 person-years. Thus, the interest is in computing the probability of observing 122 cases during 39,676 person-years of observation time in this same age group (or 307 per 100,000 person-years).

To calculate the probability, consider a binomial trial with n=39,676 and probability p=0.001445, the probability of observing 122 cases would be

$$\binom{39676}{122}0.001445^{122}\times 0.99855^{39554}\approx\frac{e^{-57.331}\times 57.331^{122}}{122!}$$

$$\approx 4.2785x10^{-14}\approx 0$$

If the chance of observing a case of HZ postlicensure is assumed to remain the same as in the prelicensure period, then the probability of observing 122 cases during an observation time of 39,676 person-years would be virtually zero. Thus, it can be concluded that the cases post-licensure have significantly increased.

Hypothesis Testing: To further argue about the significance of the postlicensure study, the following statistical hypotheses can be formulated:

Null Hypothesis: There is no difference between the two studies in terms of the chance of observing cases. Mathematically, H0: $p = 0.001445$.

Alternative Hypothesis: The chance of observing HZ cases is greater in the postlicensure study than in the prelicensure study. Mathematically, H1: p>0.001445.

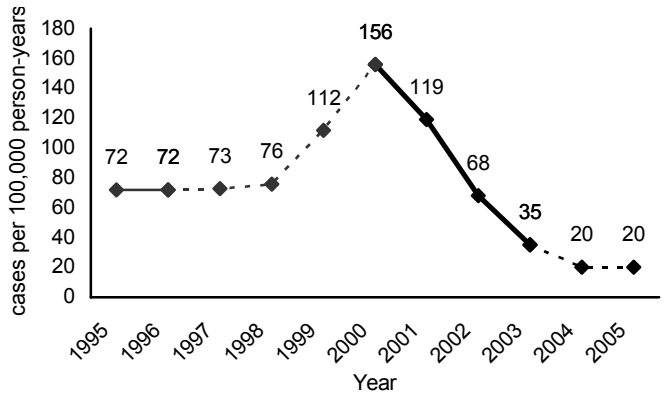
Let X be the random variable that follows a binomial distribution with 39676 trials and the probability of success is some p (0<p<1). Under the null hypothesis, p=0.001445,

$$P(X\geq 122)=P\left(\frac{X-np}{\sqrt{np(1-p)}}\geq\frac{122-39676\cdot 0.001445}{\sqrt{39676\cdot 0.001445\cdot(1-0.001445)}}\right)$$

$$P(Z\geq 4.604)\approx 0.0000$$

where Z follows the standard normal distribution. The Central Limit Theorem has been applied in the computation above. Since the probability value, P, is extremely small, the null hypothesis can be rejected and the conclusion is p>0.001445, i.e., the chance of observing HZ cases is greater in the postlicensure study than in the prelicensure era.

Figure 1. Crude HZ incidence rate among children <10 by year following varicella vaccine licensure in March, 1995.[a]



[a]Crude HZ incidence rates for 1996 to 1999 and 2003 to 2005 are extrapolated.

Figure 2. Verified cases of varicella reported via active surveillance by Year, 1995-2002

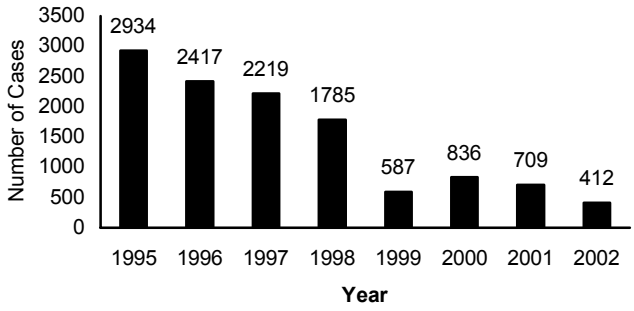
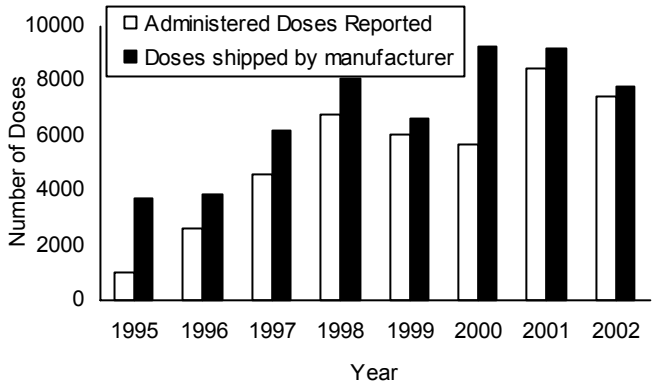
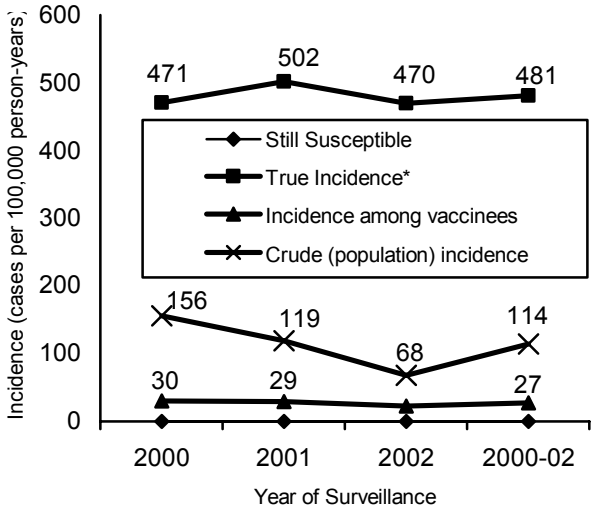


Figure 3. Vaccine doses administered and shipped by year in Antelope Valley, CA, 1995-2002



doi: 10.1588/medver.2004.01.00002

Figure 4. Trimodal distribution of HZ incidence rates among children aged 1 to 9 years in the Antelope Valley by year, 2000–2002



*True HZ incidence is among only those children with a previous history of natural varicella.

Note: The crude (population) HZ incidence rate approximates the mean of two widely different HZ incidence rates among vacinees and those with a previous history of varicella (since few in the population are still susceptible to varicella).

Table 1. Unvaccinated cases of HZ reported by schools and healthcare providers by month and age category in the Antelope Valley, 2000 and 2001

Year	Month	0 to 9 n (%)	10 to 19 n (%)	20+ n (%)	All Ages n (%)
2000	Jan.	5 (14)	4 (11)	27 (75)	36 (100)
	Feb.	2 (10)	2 (10)	16 (80)	20 (100)
	Mar.	4 (17)	3 (13)	17 (70)	24 (100)
	Apr.	3 (18)	2 (12)	12 (70)	17 (100)
	May	4 (14)	4 (14)	21 (72)	29 (100)
	Jun.	1 (4)	3 (13)	19 (83)	23 (100)
	Jul.	4 (12)	2 (6)	27 (82)	33 (100)
	Aug.	4 (13)	5 (16)	22 (71)	31 (100)
	Sep.	5 (19)	3 (12)	18 (69)	26 (100)
	Oct.	3 (12)	1 (4)	22 (84)	26 (100)
	Nov.	1 (6)	1 (6)	14 (88)	16 (100)
	Dec.	2 (9)	4 (18)	16 (73)	22 (100)
2001	Jan.	0 (0)	1 (5)	18 (95)	19 (100)
	Feb.	2 (7)	3 (10)	25 (83)	30 (100)
	Mar.	3 (12)	0 (0)	22 (88)	25 (100)
	Apr.	6 (21)	2 (7)	20 (72)	28 (100)
	May	1 (3)	3 (10)	27 (87)	31 (100)
	Jun.	2 (6)	4 (11)	29 (83)	35 (100)
	Jul.	2 (6)	8 (25)	22 (69)	32 (100)
	Aug.	3 (10)	2 (7)	24 (83)	29 (100)
	Sep.	1 (4)	3 (11)	23 (85)	27 (100)
	Oct.	2 (7)	4 (14)	22 (79)	28 (100)
	Nov.	2 (9)	2 (9)	19 (82)	23 (100)
	Dec.	3 (10)	3 (10)	23 (80)	29 (100)
2000 to 2001	Total	65 (10)	69 (11)	505 (79)	639 (100)

Table 2. Crude (population) incidence rates and true incidence rates among vaccinated children and children with a previous history of varicella, 1995, 2000, 2001, 2002 and cumulative 2000 to 2002

Description	1995	2000	2001	2002[d]	2000 to 2002
Children aged 1-9 years	53,756 (100)	53,756 (100)	53,756 (100)	53,756 (100)	161,268 (100)
Vaccinated children	806 (1.5)	26,878 (50)	34,941 (65)	43,005 (80)	104,824 (65)
Susceptible children	26,475 (49.3)	10,751 (20)	8,064 (15)	5,219 (9.7)	24,034 (15)
Children with a previous history of varicella	26,475 (49.3)	16,127 (30)	10,751 (20)	5,532 (10.3)	32,410 (20.1)
HZ cases among vacc. children	0	8[b]	10[b]	10[b]	28
HZ cases among unvacc. children	38	76[b]	54[b]	26[b]	156
Total HZ Cases	38[a]	84[b]	64[b]	36[b]	184
Crude (Pop.) Incidence Rate[c]	72[a]	156[b]	119[b]	68[b]	114
True Incidence Rate among children with a previous history of varicella[c]	144[a]	471	502	470	481
True Incidence Rate among vacc. children[c]	0[a]	30	29	23	27

[a]Based on adolescent survey.

[b]Based on active surveillance of herpes zoster. Cases are ascertainment-corrected based on 50% under-reporting.

[c]cases per 100,000 person-years

[d]Figures for 2002 based on Freedom of Information Act (FOIA) request: Mascola L, Civen R. Active Varicella Surveillance and Epidemiologic Studies, Cooperative Agreement No. U66/CCU911165-10; Annual Report, 2003, June:1–32.

doi: 10.1588/medver.2004.01.00002