

Universal Varicella Vaccination: Efficacy Trends and Effect on Herpes Zoster

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In 1995, the Varicella Active Surveillance Project (VASP) was established in Antelope Valley (California), a geographically distinct high-desert community of 300,000 residents, as one of three sites in the nation in a cooperative agreement with the Centers for Disease Control and Prevention (CDC) to collect baseline demographic and clinical data and to monitor trends in varicella (chickenpox) following introduction of varicella vaccine. Herpes zoster (shingles) was added to the active surveillance January 1, 2000. The universal varicella program has proven effective in terms of reducing the number of reported verified varicella cases by 85%, from 2,934 in 1995 to 412 in 2002. Prior to this dramatic reduction, immunologic boosting due to exogenous exposures to wild-type varicella-zoster virus (VZV) in the community (1) caused mean serum anti-VZV levels among vaccinees to increase with time after vaccination and (2) served as a mechanism that helped suppress the reactivation of herpes zoster (HZ), especially among individuals with a previous history of wild-type varicella. That immunologic boosting might play a significant role in both varicella and the closely related HZ epidemiology is evidenced by (1) a decline in vaccine efficacy by over 20%, from 95.7% (95% C.I., 82.7% to 98.9%) in 1999 to 73.9% (95% C.I., 57.9% to 83.8%) in 2001 and (2) an unexpectedly high cumulative (2000 to 2003) *true* incidence rate of 223 (95% C.I. 180–273) per 100,000 person-years (p-y) among children <10 years old with a previous history of varicella. Because capture-recapture methods demonstrate a likely lower bound of 50% underreporting, the actual rate is likely double or 446 per 100,000 p-y, approaching the HZ rate reported among older adults. Other recent studies based on VASP data have mitigated against discovery of the above trends that challenge several initial assumptions inherent to the universal varicella program, namely, (1) a single dose confers long-term immunity and (2) there is no immunologically mediated link between varicella and HZ incidence. As vaccinated children replace those with a prior history of wild-type varicella in the <10 age group, increasing HZ incidence among this cohort will be of less concern in the near future. However, previous scientific studies, including the present preliminary results from active surveillance indicate that

HZ may be increasing among adults. It may be difficult to design booster interventions that are cost-effective and meet or exceed the level of protection provided by immunologic boosting that existed naturally in the community in the precensure era.

Keywords Herpes-Zoster Incidence, Varicella Vaccination, Varicella Vaccine Efficacy, Varicella-Zoster Virus (VZV)

TRENDS IN VARICELLA VACCINE EFFICACY, 1997 TO 2001

Vaccine efficacy refers to the effectiveness of a vaccine to prevent disease. The American Committee on Immunization Practices (ACIP) states, “In clinical trials, the vaccine has proven to be effective for greater than 10 years in preventing varicella (CDC 1996).” Other reports suggest varicella vaccine confers long-lasting immunity of up to 20 years as shown in a Japanese study (Asano 1996). However, only 1 in 5 (20%) children were vaccinated in Japan so that incidence of wild-type varicella remained high, thus providing immunologic boosting to vaccinees when they contacted or were exposed to children with varicella (Brunell et al. 1988; Krause 2001). Merck & Co. explain that a boost in antibody levels has been observed in vaccinees following exposure to natural varicella, which could account for the apparent long-term persistence of antibody levels after vaccination and “the duration of protection from varicella obtained using Varivax in the absence of wild-type boosting is unknown.”

During the first years following licensure of the varicella vaccine, vaccine efficacy based on studies in clinical practices (Vazquez et al. 2001; Weibel et al. 1984) and outbreaks in daycares and school settings (Clements et al. 1999; Dworkin et al. 2002; Galil et al. 2002a) ranged from 70% to 100%. Galil et al. (2002b) reported a 44% (95% C.I., 6.9% to 66.3%) effectiveness of the vaccine in a varicella outbreak among 25 (28%) of 88 children in a daycare center between December 1, 2000, and January 11, 2001, having a high proportion of vaccinees. Lee et al. (2004) reported a 56% (85% C.I. 32.0% to 71.2%) effectiveness in an outbreak involving a primary breakthrough case followed by 54 cases in which 29 (53%) had been vaccinated in a Minnesota school with an enrollment of 319 students in 2004. Gershon (2002) suggests “the time for exploring the possibility

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of routinely administering two doses of varicella vaccine to children seems to have arrived." Similar conclusions are presented in a 2004 study by the Epidemic Intelligence Service of the Centers for Disease Control and Prevention (CDC), which reported a vaccine efficacy of 72% (95% C.I., 3% to 87%) (Tugwell et al. 2004). Wide confidence intervals have characterized most outbreak investigations due to relatively small numbers of children associated with any given local outbreak.

The Antelope Valley Varicella Active Surveillance Project (VASP) has investigated the secondary attack rate among household contacts aged 1 to 14 years during 1997 to 2001 (Seward et al. 2004). That report states, "we analyzed the secondary attack rate by year; finding no trend, we conducted subsequent analyses for the 5 year period (Seward et al. 2004)." Below, I discuss this important trend in vaccine efficacy, which demonstrates several statistically significant changes when stratified by year.

METHODS

Since 1995, the VASP has monitored varicella cases bi-weekly from 300 different reporting sites in the Antelope Valley study population that include daycares, preschools, public and private elementary, middle, and high schools and health-care providers—including private practice physicians, public health clinics, health maintenance organizations (HMOs), and hospitals.

Detailed demographic and clinical information is obtained on each reported case by experienced staff conducting a telephone interview with the patient or patient's caretaker. The age of each household member is obtained, including varicella history and if applicable, date of receipt of varicella vaccine.

The methods applicable to varicella case collection and the investigation of vaccine efficacy by the VASP are well described in references by Seward et al. (2002, 2004).

Secondary varicella cases aged <20 years in the household contacts were considered as those occurring 10 to 21 days (inclusive) following the first (or index) case in the household. Coprimary and tertiary cases defined as those occurring 0 to 9 days and 22 or more days, respectively, following the index case were ignored.

The proportion of secondary cases that occurred among contacts exposed to the index case in the household yielded the secondary family attack rate which was computed separately among unvaccinated ($SFAR_u$) and vaccinated ($SFAR_v$) contacts. Thus, vaccine efficacy (VE) is the percentage reduction of all varicella disease incidence in the vaccinated group compared with the unvaccinated group and is given by the equation:

$$VE = 100(SFAR_u - SFAR_v)/SFAR_u \\ = 100(1 - SFAR_v/SFAR_u)$$

where $SFAR_v/SFAR_u$ is called the risk ratio (RR). The 95% confidence intervals were calculated using the log rate of the standard error of the ratio. A single vaccine efficacy or effectiveness is calculated by year for prevention of all varicella disease among household contacts exposed to an index case that exhibits breakthrough disease (and therefore was previously vaccinated) or varicella due to unvaccinated status (and generally without a previous history of varicella).

RESULTS OF VACCINE EFFICACY STUDY STRATIFIED BY YEAR

As expected, the total of 6316 varicella cases reported to VASP and verified during 1997 to 2001 exactly agrees with the CDC figure based on this same database and reported by Seward et al. (2004) in the household contact study. These cases, stratified by year in Table 1, demonstrate a dramatic decline of 68%, from 2219 in 1997 to 709 in 2001 (Maupin et al. 2002a).

Interestingly, approximately 17% of all varicella cases were due to reports comprised of 475 (7.5%) breakthrough cases (due to varicella occurring in vaccinees 42 or more days following vaccination) and 596 (9.4%) cases having a previous history of varicella (representing a second case of varicella) (Table 1) (Maupin et al. 2002a). Breakthrough cases occurring throughout the study period were generally mild (<50 lesions). The trend toward milder disease from 1997 to 2001 was evident among those who were unvaccinated—the hypothesis being that these children were exposed to either the Oka (attenuated) strain Varicella-Zoster Virus (VZV) or experienced shorter

TABLE 1
Reported breakthrough (vaccinated) cases, cases with a previous history of varicella, mild (<50 lesions) cases, and verified varicella cases of all ages by year, 1997–2001, and cumulative

Description	1997 <i>n</i> (%)	1998 <i>n</i> (%)	1999 <i>n</i> (%)	2000 <i>n</i> (%)	2001 <i>n</i> (%)	1997–2001 <i>n</i> (%)
Breakthrough cases	58 (2.6)	72 (4.0)	52 (8.9)	141 (16.9)	152 (21.4)	475 (7.5)
Cases with a previous history of varicella	184 (8.3)	169 (9.5)	78 (13.3)	80 (9.0)	85 (12.0)	596 (9.4)
<50 lesions (mild)	804 (36.2)	635 (36.7)	245 (41.7)	378 (45.2)	337 (50.4)	2,399 (38.0)
Verified cases	2219 (100)	1785 (100)	587 (100)	836 (100)	709 (100)	6316 (100)

duration exposures due to declining wild-type varicella outbreaks at school. Generally, unvaccinated primary cases were milder than secondary household cases since secondary members were usually exposed at closer proximity and for longer duration within the household relative to primary cases whose exposure source was outside the household.

The proportion of varicella cases considered as mild, defined as having <50 lesions at the peak of illness, increased significantly from 36.2% (804/2219) in 1997 to 50.4% (337/709) in 2001 ($p < .005$, $\chi^2 = 28.8$) (Table 1) (Maupin et al. 2002a).

During 1997 to 2001, each of 1860 index cases, of which 213 (11.5%) were vaccinated, had one or more secondary household contacts aged <20 years. These index cases exposed 2155 unvaccinated and 526 vaccinated contacts (Table 2).

Vaccine efficacy increased from 86.7% (95% C.I., 75.0% to 92.9%) in 1997 to a high of 95.7% (95% C.I., 82.7% to 98.9%) in 1999 (Table 2). After 1999, vaccine efficacy declined to 73.9% (95% C.I., 57.9% to 83.8%) in 2001 as varicella incidence continues at a dramatically reduced level relative to the preclosure era (Table 2).

Table 2 summarizes that in 1997 secondary vaccinated cases ($SFAR_v = 9.6\%$) were about 1/8th as contagious as unvaccinated cases ($SFAR_u = 72.3\%$) with a RR of 0.133 (95% C.I., 0.071 to 0.250). In 2001, vaccinated contacts ($SFAR_v = 12.5\%$) are about 1/4th as contagious as unvaccinated contacts ($SFAR_u = 47.8\%$) with a RR of 0.26 (95% C.I., 0.16 to 0.42).

DISCUSSION OF TREND IN VACCINE EFFICACY

The increase in vaccine efficacy from 86.7% in 1997 to 95.7% in 1999 (Table 2) was likely attributed to the additional residual boosting to vaccinees that resulted from contact with children having natural disease. In 1997 and 1998 the incidence of varicella was still high in the community and displayed the characteristic seasonality (Seward et al. 2002).

Although the 20% decline in vaccine efficacy from 1999 to 2001 is not statistically significant at the 95% confidence level ($z = 1.96$), it is significant at 94% ($z = 1.88$). By July/August 2002, the vaccine efficacy declined to 58.4% (95% C.I., 13.7% to 79.9%) which was statistically significantly lower than the 1999 efficacy.

The vaccine efficacy estimated in 2001, although lower than estimates in the earlier years of varicella vaccination, likely better reflects the efficacy under the current disease-transmission circumstances associated with moderate to widespread vaccination.

The overall cumulative (1997–2001) vaccine efficacies of 87.4% (95% C.I., 83.0% to 90.6%) using household contacts aged <20 years and 78.9% (95% C.I., 69.7% to 85.3%) using contacts aged 1 to 14 years by Seward et al. (2004) are not statistically significantly different. However, the overall vaccine efficacy figure reported by Seward et al. (2004) is comparatively lower because it is computed based on transmission in households resulting from only unvaccinated primary cases and neglects transmission especially occurring in the later years of the study period that resulted from breakthrough (vaccinated) primary cases. A vaccine efficacy based solely on unvaccinated primary cases is artificial and lacks meaning when in reality (a) unvaccinated primary cases were themselves infected by exposures to both unvaccinated and vaccinated children outside their immediate household and (b) as vaccination coverage became more widespread over the study period, the proportion of vaccinated primary cases (ranging from 3.4% in 1997 to 32.9% in 2001) increasingly influenced secondary household transmissions (Table 2).

In addition to reporting a skewed vaccine efficacy limited to those households with only unvaccinated primary cases, Seward et al. (2004) reports a single, overall 5-year vaccine efficacy result that (a) mitigates against discovery of a more than 20% decline in varicella vaccine efficacy by 2001 as vaccination

TABLE 2
Secondary family attack rate (SFAR) among contacts aged <20 years and vaccine efficacy by year, 1997–2001

Year	Primary cases all ages		Cases outside range $N = 269$		Unvaccinated household contacts $N = 2155$		Vaccinated household contacts $N = 526$			Vaccine efficacy % (95% C.I.)	
	Total N	Vaccinated n (%)	Coprimary 0–9 days	Tertiary >21 days	Secondary cases	Remaining susceptibles	SFAR _u %	Secondary cases	Remaining susceptibles		SFAR _v %
1997	639	22 (3.4)	52	45	594	228	72.3	7	66	9.6	86.7 (75.0–92.9)
1998	526	30 (5.7)	40	33	481	184	72.3	4	84	4.5	93.7 (83.2–97.7)
1999	182	20 (11.0)	17	13	127	71	64.1	2	71	2.7	95.7 (82.7–98.9)
2000	261	58 (22.2)	21	16	152	90	62.8	12	120	9.1	85.5 (73.9–92.0)
2001	252	83 (32.9)	28	4	109	119	47.8	20	140	12.5	73.9 (57.9–83.8)
1997–2001	1860 ^a	213 (11.5)	158	111	1463	692	67.9	45	481	8.6	87.4 ^b (83.0–90.6)

^aThere were 3,707 index cases reported to VASP of which 1860 (50.2%) had one or more secondary contacts aged <20 years.

^bThere were minor changes in cumulative vaccine efficacy when children <1 were excluded: 87.8% among contacts aged 1–19 years and 87.9% among contacts aged 1–14 years exposed to index cases of all ages (with breakthrough or wild-type varicella).

coverage among children <10 years old increased in the community from <20% in 1997 to >50% in 2001 and (b) largely reflects the weighting of the majority (66% or 2924/4439) of primary and secondary cases that occurred during 1997 to 1998. During these years, the hypothesis is that although incidence of wild-type varicella was still high in the community, an immunologic boost to vaccinees caused their attack rates to decline with longer time since vaccination. Vaccine efficacy declined after 1999 due to dramatic reductions in exogenous exposures to wild-type varicella and concomitant increasing trends in (1) breakthrough disease associated with vaccinees and (2) generally milder varicella cases occurring in unvaccinated susceptibles, perhaps attributed to lower intensity and duration of exposure to disease in both the community and within the household.

Secondary vaccinated cases (i.e., those with "breakthrough" disease) having onset less than 42 days after vaccination were considered as unvaccinated. Without this adjustment involving 10 of 55 secondary breakthrough cases, the cumulative vaccine efficacy is slightly lower, 84.9% (95% C.I., 80.2% to 88.4%).

A limitation of the study was that varicella cases reported to VASP were not laboratory confirmed. Although receipt of varicella vaccine was confirmed by the healthcare provider in 75% to 85% of vaccinated cases, the remaining cases relied on parental recall, potentially resulting in misclassification of vaccination status. A small proportion of unvaccinated children classified as susceptible, including some vaccinated children who had a previous (unnoticed) history of varicella will actually demonstrate serology for wild-type VZV, potentially affecting the SFAR and computed vaccine efficacy.

UNIVERSAL VARICELLA VACCINATION PROGRAM'S EFFECT ON HERPES ZOSTER, 2000 TO 2003

Introduction

A few years after licensure of the varicella vaccine (on March 17, 1995) by the U.S. Food and Drug Administration (FDA) (Hardegree and Donlon 1995), physicians expressed concern that it was unknown if periodic reexposures to natural varicella in the community played a significant role in helping to suppress the reactivation of herpes zoster (HZ) (Spingarn and Benjamin 1998; Wack 1998). The universal varicella vaccination program, combined with mandates adopted in many states requiring school-entry children to be vaccinated, resulted in high coverage rates, allowing the concerns related to increasing HZ incidence to be investigated.

The crude HZ incidence rate determined in historical studies was dependent on the proportions of children still susceptible to varicella (and hence not candidates for HZ) and those with previous histories of varicella. In the postlicensure period, the HZ incidence rate was additionally affected by the increasing proportion of vaccinated children. The VASP sought to (1) compare the true HZ incidence rate among children with a previous history of varicella to the rate among vaccinees and (2) compare *true* HZ incidence rates in the pre- and postlicensure periods.

Note the importance of using methodology that compares only *true* (rather than *crude* or population) HZ incidence rates in pre- and postlicensure periods—prelicensure studies had no vaccinees and postlicensure studies would have a declining number of susceptibles as varicella vaccination became more widespread.

Methods Pertaining to HZ Incidence Calculation among Children and Adolescents

It was not until January 2000, or 5 years postlicensure, that HZ disease was added to the Antelope Valley VASP. By the end of 2000, approximately 50% of children aged <10 had been vaccinated; due to herd protection, varicella cases had declined to 80% of the 1995 level (Maupin et al. 2001).

The population of the study community by age was determined from the 2000 U.S. Census for the Antelope Valley. The number of vaccinees by age was determined from reports that the VASP collected monthly from the 40 providers at the start of licensure in March, 1995. Estimates of the number of susceptibles in the population were obtained via an adolescent survey of middle school students. Finally, the number of children with previous histories of natural varicella was obtained by subtracting the number still susceptible and the number vaccinated from the population census figure. The methodology applicable to HZ case collection is well described in Maupin et al. (2001, 2002a) and the cumulative (2000 to 2001) HZ incidence rates previously presented by Goldman (2003a) have been updated with two additional years of data collection.

Unfortunately there were no prelicensure baseline HZ data collected in a consistent methodology to use in straightforward comparisons with HZ data gathered later in the postlicensure period. The Antelope Valley VASP, however, did conduct a retrospective cohort study among adolescents in public middle schools that estimated both varicella susceptibility and prelicensure HZ incidence rates in the study population (Goldman 2003b). This and only a few other historical studies are available as surrogates for baseline comparisons of HZ incidence rates among children and adolescents (Goldman 2003a; Hope-Simpson 1965; Donahue, Manson, and Platt 1995).

HZ Incidence Rates in the Prelicensure Era

An adolescent survey was utilized by the VASP in 2000 to determine varicella susceptibility and incidence of herpes zoster. Data collected were name, date of birth, age of varicella (chickenpox), varicella vaccination date, age of herpes zoster (shingles), gender, race/ethnicity on 4216 (35%) adolescents aged 10 to 14 years attending public middle schools (grades 7/8) in the Antelope Valley (Goldman 2003b). The respondents represented a cross-sectional sample with a racial and socioeconomic balance similar to that of the larger population of students (Goldman 2003b; Maupin et al. 2002b). Varicella susceptibility by age in the Antelope Valley compared closely with that reported in the Kentucky Behavioral Risk Factor Surveillance System (BRFSS) study of 1990 to 1992 (Finger et al. 1994).

By ignoring outcomes of varicella and herpes zoster reported during the previous 5 years among middle school students 10 to

14 years old, it was possible to investigate varicella susceptibility and herpes zoster incidence among these same students aged 5 to 9 years in the precensure era. This analysis determined a cumulative (1987 to 1995) crude (population) incidence rate of 71 (95% C.I., 42 to 112) per 100,000 patient-years (p-y) based on 18 HZ cases occurring during an observation time of 25,470 p-y. The *true* HZ incidence rate was approximately double or 145 (95% C.I., 86 to 228) per 100,000 p-y among children aged <10 years (Goldman 2003b). The true rate is obtained by removing observation time associated with children still susceptible to varicella and hence not candidates for reactivation of HZ (Goldman 2003b).

The crude HZ incidence rate of 71/100,000 p-y among children <10 in the Antelope Valley agrees closely with 68/100,000 p-y reported by Guess et al. (1986) and 74/100,000 p-y reported by Hope-Simpson (1965). The true rate of 145/100,000 p-y in the Antelope Valley is similar to the true rate of 133/100,000 p-y reported by Donahue, Manson, and Platt (1995).

In the adolescent survey, parents had excellent recall of their children's cases of HZ due to the fact that prior to their visit to

a physician, the symptoms of HZ (shingles) were unknown and shingles was considered to be a rare event in children. Therefore unlike active surveillance where ascertainment-adjustment is necessary due to 50% underreporting of cases voluntarily submitted to VASP by the reporting sites, the methodology of the adolescent survey likely produced nearly 100% enumeration of cases in the cross-sectional sample.

Results from Active HZ Surveillance

If we were to assume 100% enumeration of HZ cases reported to VASP via active surveillance, there is no statistically significant difference between pre- and postlicensure HZ incidence rates among children aged 1 to 9 years. Children aged 1 to 9 years having a previous history of wild-type varicella with a cumulative (2000 to 2003) *true* HZ incidence rate of 223/100,000 p-y (95% C.I., 180 to 272 per 100,000 p-y) were 16.2 (95% C.I., 10.1 to 26.0) times as likely of reactivating as vaccinees with a rate of 14/100,000 p-y (95% C.I., 9 to 21 per 100,000 p-y) (Table 3). Interestingly, the above bimodal results among

TABLE 3
Herpes-zoster cases and crude and true incidence rates (cases per 100,000 p-y) among children 1–9 years old by year, 2000–2003, Antelope Valley

Description	Precensure 1987–1995	Post-licensure period				Cumulative 2000–2003
		2000 ^c	2001 ^c	2002 ^d	2003 ^d	
A. Children aged 1 to 9 years, N (%)	—	53,756 (100)	53,756 (100)	55,560 (100)	57,365 (100)	220,437 (100)
B. Children with a previous history of varicella, n (%)	—	16,127 (30)	10,751 (20)	8,334 (15)	6,884 (12)	42,096 (19.1)
C. Vaccinated children, n (%)	—	26,878 (50)	34,941 (65)	41,670 (75)	48,760 (85)	152,249 (69.1)
D. Susceptible children, n (%)	—	10,751 (20)	8,064 (15)	5,556 (10)	1,721 (3)	26,092 (11.8)
E. Cases with a previous history	—	38	27	13	16	94
F. Cases vaccinated	—	4	5	6	6	21
G. Total cases	—	42	32	19	22	115
Crude (population) rate = G/A (95% C.I.)	71 (42–112) ^a	78 (56–106)	60 (41–84)	34 (21–53)	38 (24–58)	52 (43–63)
True rate among vaccinees = F/C (95% C.I.)	—	15 (4–38)	14 (5–33)	14 (5–31)	12 (5–27)	14 (9–21)
True rate among children with a previous history = E/B (95% C.I.)	145 (86–228) ^b	236 (167–323)	251 (169–371)	156 (83–267)	232 (133–377)	223 (180–273)
Ascertainment-corrected true rate among children with a previous history = 2E/B	145 (86–228) ^b	471	502	312	465	446

^aIncidence rate based on 18 cases observed during 25,400 p-y among children aged <10 years (Goldman 2003b).

^bIncidence rate based on 18 cases observed during 12,457 p-y among children aged <10 years with a previous history of varicella (Goldman 2003b).

^cPopulation figures based on 2000 census.

^dPopulation figures estimated based on 2000 census.

TABLE 4

Verified HZ cases and crude and true HZ incidence rates (cases per 100,000 p-y) among individuals 10–19 years old by year, 2000–2003, Antelope Valley

Description	Cumulative 1987–2000	Postlicensure period				Cumulative 2000–2003
		2000	2001	2002	2003	
A. Adolescents 10–19 years	—	60,421	60,421	60,421	60,421	241,684
B. Adolescents with a previous history of varicella	—	54,654	54,104	53,554	53,004	215,316
C. Vaccinated adolescents	—	2,746	3,296	3,846	4,396	14,284
D. Susceptible adolescents	—	3,021	3,021	3,021	3,021	12,084
E. Number of HZ cases among those with a prior history of varicella	—	33	30	38	30	131
Crude (population) rate = E/A (95% C.I.)	—	55 (38–77)	50 (34–71)	63 (45–86)	50 (34–71)	54 (45–65)
True rate among adolescents with previous history = E/B (95% C.I.)	133 (95–182) ^a	60 (42–85)	55 (37–79)	71 (50–97)	57 (38–81)	61 (51–72)
Ascertainment-corrected True rate among adolescents with previous history = 2E/B	133 ^a	120	110	142	114	122

^aIncidence rate derived from adolescent study based on 39 cases observed during 29,249 p-y among those aged <15 years (Goldman 2003b).

vaccinated and unvaccinated cohorts are masked by inspecting only the cumulative (2000 to 2003) crude (population) rate of 52 (95% C.I., 43 to 63) per 100,000 p-y, which is dependent upon the proportions of children still susceptible, vaccinated, and those with a previous history of varicella.

The cumulative (2000 to 2003) *true* HZ incidence rate is 61/100,000 p-y among individuals aged 10 to 19 years. There is no statistically significant difference in post-licensure HZ incidence rates by year which range from 55 to 71 per 100,000 p-y. When ascertainment-corrected (using 50% reporting completeness), the adjusted rates in this age category compare to those reported in other prelicensure studies (Table 4) (Goldman 2003b; Hope-Simpson 1965).

Justifying Ascertainment-Corrected HZ Incidence Rates

Nearly complete ascertainment of cases in the prelicensure era was achieved by means of (1) the Antelope Valley adolescent survey, (2) Hope-Simpson serving as a physician investigating cases of HZ in the town of Cirencester, England (with a mean of 510 children), and (3) computerized medical records accessed by Donahue et al. By contrast, varicella and herpes-zoster cases reported to VASP via active surveillance in the postlicensure period require ascertainment-correction due to underreporting of cases.

The ascertainment-corrected varicella incidence rates estimated by VASP using capture-recapture methods compared to within 5% to 10% of the national average incidence rates by age reported by the National Health Interview Survey (NHIS), which served as a criterion (or “gold”) standard by which to check the capture-recapture estimate (Goldman 2003c). Varicella cases ascertained via active surveillance were underreported by 50%. The close agreement between the NHIS inci-

dence rates and the adjusted varicella incidence stratified by age category, disease severity, or number of lesions suggests that the capture-recapture assumption of uniform reporting probabilities is plausible. Because the same 300 surveillance sites that reported varicella cases also reported HZ cases, the same 50% underreporting might be expected in regard to ascertainment of HZ cases.

Consider that during 2000 and 2001, schools reported 54 HZ cases and healthcare providers reported 91 cases of HZ among unvaccinated children and adolescents aged 5 to 19 years. Of these 145 case reports, 19 were duplicates. Although all 54 cases that were reported by schools sought attention from healthcare providers participating in the active surveillance project, only 19 (35%) were reported to the VASP by healthcare providers. Capture-recapture methods estimate the reporting completeness in this example is 50% (95% C.I., 34% to 65%) as expected based on similar findings with the reporting of varicella disease (Goldman 2003a, 2003c).

Because schools often require an absence to be documented by a physician, the number of dual reports of HZ cases by the school and healthcare ascertainment sources is likely higher than it would be had such documentation not been required. Hook and Regal discuss the fact that when two ascertainment sources are positively dependent as implied above, the capture-recapture estimate in that instance is useful in that it represents a likely lower-bound estimate (Hook and Regal 1992a). So despite the characteristically wider confidence intervals associated with capture-recapture estimates applied to HZ disease, the estimate derived represents a likely lower bound.

The ascertainment-corrected cumulative true HZ incidence rate of 446/100,000 p-y among children aged 1 to 9 years with a previous history of natural varicella is 3 times higher

by comparison to the true precensure rate of 145/100,000 p-y (Table 3). The ascertainment-corrected crude rate of 104/100,000 p-y is paradoxically high 9 years post licensure and suggests the possibility of increased burden of HZ disease among children in the Antelope Valley community with moderate vaccination coverage (>80% of children <10 vaccinated).

Discussion of Effects on HZ

Studies conducted by the Massachusetts Department of Public Health BRFSS and Group Health Cooperative (GHC) (a) have lower vaccination coverage than the communities under active surveillance and (b) use a small sample size. Due to insufficient statistical power, it is invalid to draw the conclusion that these studies “show no change in HZ incidence to date” (Roche, Blumer, and Spencer 2002; Burgess 2002; Seward 2002). The BRFSS telephone survey, for example, was based on a sample size of 4916 and 3123 respondents aged 1 to 19 years in 1999 and 2000, respectively.

Yet, since 2000, Antelope Valley VASP had been reporting preliminary results by age and vaccination status from a population-based study of HZ among the 318,000 residents of the Antelope Valley, 118,685 of which were aged <20 years (Maupin et al. 2001, 2002a). HZ cases among adults aged 20 years and older reported principally by healthcare providers increased 18% from 237 HZ cases in 2000 to 279 in 2001 with increases in nearly every 10-year age group from 20–29 through 60–69. Young adults that previously received the most exogenous boosting in the precensure era generally experienced the greatest percentage increase in case reports relative to the older adults. A total of 370 HZ cases reported among adults in 2002 represented an increase of 32.6% and 56.1% over those cases reported in 2001 and 2000, respectively (Civen and Mascola 2004). Another study by Yih et al. (2005) shows a preliminary increase among adults.

The assumption made by Civen et al. (2003, 2004)—that active surveillance achieves 100% case ascertainment—is rarely correct and uncorrected incidence rates are a function of the case ascertainment and therefore are not comparable with other studies (Deming 1991; Thacker and Berkelman 1988; McCarty et al. 1993; LaPorte et al. 1993; Hook and Regal 1992b). The postlicensure crude incidence rates of 40/100,000 p-y among children <10 (>80% of which had been vaccinated) and 45/100,000 p-y among individuals 10 to 19 reported by Civen et al. (2004) seemingly lead to the conclusion that there is negligible difference between HZ incidence rates among vaccinated and unvaccinated cohorts and mitigate against discovery that the HZ incidence rate among children with a previous history of varicella is unexpectedly high (relative to available precensure rates and relative to the rate in the 10 to 19 age category). Yet, when these same data are ascertainment corrected and stratified by vaccination status, the analysis leads to incidence rates similar to those given in Tables 3 and 4. The expected low rates among vaccinees serve as a control that HZ was not generally being misdiagnosed.

Although cell-mediated immunity (CMI) to VZV in 10 to 19 cohort has apparently persisted sufficiently to suppress reactivation during 2000 to 2003, significant decline in exogenous exposures has occurred only during the past 4 years, since 1999 and the duration of protection due to boosts to CMI exceeds this time period in this older cohort (Brisson et al. 2002; Thomas, Wheeler, and Hall 2002).

Scientific Literature Suggests Link between Incidence of Varicella and HZ

As early as 1965, Hope-Simpson, based on observations of varicella and HZ in his medical practice in Cirencester, England, suggested that there were two mechanisms involved in boosting immunity to suppress the reactivation of HZ: (1) periodic exogenous exposures to natural varicella and (2) asymptomatic endogenous reactivations (Hope-Simpson 1965). Hope-Simpson writes, “The peculiar age distribution of zoster may in part reflect the frequency with which the different age groups encounter cases of varicella and because of the ensuing boost to their antibody protection have their attacks of zoster postponed.”

Japanese pediatricians aged 50 to 69 who were reexposed to VZV demonstrated HZ incidence rates 1/2 to 1/8 that of the general population (Terada et al. 1995). In 1983, Arvin et al. noted a boost in CMI in 71% of adults who were exposed to varicella patients in the family (Arvin, Koropchak, and Wittek 1983). In a more recent study of HZ in physicians, pediatricians (who have a greater incidence of exposure to VZV) were reported to have lower rates of HZ than psychiatrists (who had the lowest VZV exposure rates) (Solomon et al. 1998). In a community under active varicella surveillance with moderate vaccination coverage and reported varicella cases dramatically reduced by 80% of the 1995 level due to herd protection, Goldman (2003a) reports cumulative (2000 to 2001) incidence that is two- to three-fold higher than expected among children aged <10 years with a previous history of natural varicella. This high incidence continued during 2002 and 2003. In 2002, epidemiological evidence in England and Wales demonstrated higher incidence of HZ among adults living without children compared to those living with children (Brisson et al. 2002). Finally, in a case-control study in South London, United Kingdom, it was suggested that reexposure to VZV via contact with children seems to protect latently infected individuals against HZ (Thomas, Wheeler, and Hall 2002).

CONCLUSIONS

Virtually all historical studies demonstrate HZ incidence increases with advancing age. This curve has been attributed to a gradual decline in immunity due to aging. These studies were confounded by reporting crude (population) incidence rates in children that were approximately one-half the *true* rates because approximately 50% of the children were still susceptible to varicella and hence not candidates for reactivation (Goldman 2003b; Finger et al. 1994). By computing true incidence rates among only the cohort of children with a previous history of wild-type

varicella, the true HZ incidence rate among children aged <10 years in the prelicensure era was similar to that in the next age category, 10 to 19, where most individuals had a previous history of varicella. Hope-Simpson (1965) anticipated this result by suggesting that the “peculiar curve” of HZ incidence might be due to the different frequency of exposures to wild-type varicella that each group had experienced—older adults receiving fewer boosts and manifesting higher HZ incidence relative to younger adults who generally have greater exposure to children with natural varicella (Fuller-Thomson and Minkler 2001).

The available scientific literature indicates that many investigators, starting with Hope-Simpson (1965) and including Arvin et al. (1983; 1992; 1996), Garnett and Grenfell (1992), Gershon et al. (1996), Krause and Klinman (2001, 2000), Solomon et al. (1998), Terada et al. (1995), Brisson, Gay, and Edmunds (2002, 2003), and Thomas, Wheeler, and Hall (2002, 2004), believe that immunological boosting (including via wild-type VZV exposure) can decrease the likelihood of varicella reactivation, which in turn would be expected to decrease the likelihood of HZ. A logical consequence would be that a reduction in such boosting would lead to a relative increase in HZ incidence rates.

It is suspected that HZ disease in children is underreported because children may not be excluded from school attendance and thus, parents/guardians are not under any obligation to obtain a physician’s note of excuse for the illness. Ascertainment bias may also arise as a result of parents/guardians seeking health-care more often for younger children than older children and adolescents. In communities with high vaccination coverage, adolescents and adults have only experienced reduced exposures to natural varicella for 4 years—since 1999. Thus, in the 10 to 19 cohort, it is plausible that CMI to VZV has not as yet declined substantially to cause increased HZ reactivation and individuals in this cohort are likely to have already had boosts to their immunity because of prior re-exposure.

Based on studies by Goldman (2003a) and others (Brisson et al. 2002; Thomas, Wheeler, and Hall 2002), it is plausible that HZ incidence is increasing among children with a previous history of natural varicella. A statistically significant increase in HZ incidence during the period 1998–2003 has been recently reported among adults (Yih et al. 2005).

Although a recent national analysis indicates a clinically and statistically significant reduction in varicella-related hospitalizations for children and adults associated with childhood varicella immunization in the U.S. (Davis, Patel, and Gebremariam 2004), it must be considered that HZ results in three times as many hospitalizations (32,000 versus 11,000) and approximately five times (560 versus 100) as many fatalities as varicella. Thus, a significant portion of VZV hospitalizations (approximately 75%) in the prelicensure era was attributed to HZ. An HZ-to-varicella cost ratio of 4.5 was reported in a Canadian province based on an analysis of direct costs during 1992 to 1996 (Baker 1999). For these reasons, a relatively small increase in the estimated 800,000 annual HZ cases occurring in the U.S. could potentially offset the medical cost savings associated with reductions in 4 million varicella cases and associated morbidity for many years.

The potential intervention to provide a booster varicella (or shingles) vaccination to adults aged 60 years and older (Oxman 1995) will fail to ameliorate the greatest potential for increased burden of HZ disease among adults aged <50 (parents) who, in the prelicensure era received considerably more exogenous exposures (boosts) than the elderly (Fuller-Thomson and Minler 2001). No cost-benefit analysis performed to date has justified a \$10 billion expense to provide a “booster” varicella vaccination to each of the 200 million adults in the United States (using \$50 per dose). Likely such booster vaccination would require repeating after an interval that is currently unknown.

Additional studies conducted in different communities with high vaccination rates will help elucidate the duration of immunity afforded by varicella vaccination and the roles of both mechanisms of immunologic boosting: periodic exogenous exposures and asymptomatic endogenous reactivations.

The United States is the first to implement a universal varicella vaccination program where, in time, naturally occurring varicella and its booster effect will be nearly eradicated. It will be difficult to design booster interventions that are cost-effective and meet or exceed the level of protection provided by immunologic boosting that existed naturally in the community in the prelicensure era (Goldman 2005).

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