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Varicella susceptibility and incidence of herpes zoster among children and adolescents in a community under active surveillance

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Abstract

Licensure of varicella vaccine by the US Food and Drug Administration in March 1995 has given rise to concerns that include a potential shift in varicella incidence to susceptible adults and increase in herpes zoster (HZ) incidence. Baseline values prior to widespread vaccination were obtained through distribution of an adolescent survey to all 13 public middle (seventh and eighth grade) schools in the Antelope Valley, CA health district. Based on 4216 respondents aged 10–14 years, varicella susceptibility is 7.7% (95% CI, 6.9–8.5%) and true cumulative (1987–2000) HZ incidence rate is 133 per 100,000 person-years (95% CI, 95–182 per 100,000 person-years).

Keywords: Varicella susceptibility; Adolescent survey; Herpes zoster

1. Introduction

Since licensure of varicella vaccine by the US Food and Drug Administration in March 1995, universal vaccination of children, combined with herd immunity, has caused dramatic declines in varicella incidence and associated morbidity and mortality of varicella disease [1–3]. This has given rise to unresolved issues that include a potential shift in varicella incidence to susceptible adults and increase in herpes zoster incidence due to a reduction in periodic exogenous exposures to wild-type varicella which previously boosted cell-mediated immunity (CMI) to suppress reactivation [4–6].

One goal of the adolescent survey is to assess the number of adolescents still susceptible to varicella in a community with moderate vaccination coverage. Another goal is to investigate the variability of true HZ incidence rates among children and adolescents prior to widespread varicella vaccination, since there are few studies of HZ incidence in the US and only one study that provides true incidence (with pre-varicella person-time removed) among children and adolescents [7].

2. Methods

In August 2000, all 13 public middle schools in the Antelope Valley were provided a sufficient quantity of adolescent surveys designed to be included in student enrollment packages and which parents were asked to voluntarily complete and return to the school. After processing enrollments, in September 2000, the schools returned the completed surveys to the varicella active surveillance project (VASP). The one-page survey (English on front and Spanish on reverse side) requested the school name, student's name, date of birth, gender, age at varicella (if applicable), who diagnosed varicella (parent or healthcare provider), age at shingles (if applicable), date and location of varicella vaccination (if applicable or known), duration of residence (in years) in the Antelope Valley, and race/ethnicity. An initial assessment of the responses from each of the schools indicated lack of racial and socio-economic balance, so further effort in April 2001 was made to improve the representation of the sample by encouraging those schools with a poor response to issue the surveys in student classrooms. Again, parents were to complete and return the surveys. Duplicate surveys were eliminated based on exact and probabilistic matching techniques involving the student name and date of birth. Surveys that lacked the student's date of birth were excluded.

True incidence rates of HZ exclude observation time prior to varicella disease and include observation of person-time from the age of varicella disease until September 2000 (or April 2001 for surveys passed out to classrooms) or age of HZ, whichever event occurs first.

Parents reporting students having a positive history of HZ (shingles) were contacted by telephone if no age (for shingles) was specified to discern if the question regarding

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shingles was properly understood. Fifty percent of the parents who submitted surveys with an affirmative answer to shingles, including the age that shingles occurred, were contacted to confirm the response and determine if HZ was physician diagnosed.

3. Statistical methods

If we assume middle school students are comprised primarily of adolescents aged 12 and 13 years (in seventh and eighth grade), then the estimated target population is $N = 10{,}000$ based on an equal proportion of individuals aged 10–14 years from the 2000 population census. We also assume the true proportion that is susceptible to varicella is 8% ($P = 0.08$). Suppose we desire a 95% ($Z_{(1-\alpha)} = 1.96$) confidence that the estimated proportion differs from the true proportion by no more than 10% of P ($\varepsilon = 0.10$). Then the required sample size, n, assuming random selection, must satisfy:

$$n \geq \frac{Z^2_{(1-\alpha)} NP(1-P)}{(N-1)\varepsilon^2 P^2 + Z^2_{(1-\alpha)} P(1-P)}$$

or $n \geq 3064$. We must now adjust for finite population correction (f.p.c.) to reflect the fact that the survey population is finite in size and that sampling is conducted without replacement. The reduced sample size (n') is given by: $n' = n/(1+n/N) = 2345$. Future estimates should be updated to reflect the actual proportion of the population still susceptible to varicella-zoster virus (VZV).

In practice, the manner in which the adolescent survey was conducted did not lend itself to strict random sampling techniques. The adolescent survey was included in the enrollment package of students entering middle school; however, additional surveys were subsequently passed out to students in classrooms (clusters) for parents to complete and return. Each completed survey was assigned a sequential number and the survey data were entered into a data base using a computer program designed by project staff.

The 95% confidence intervals (CI) reported for varicella susceptibility and herpes zoster incidence are computed based on normal approximation and Poisson distribution, respectively.

4. Results

4.1. Varicella susceptibility

Of 11,958 seventh and eighth grade students enrolled in all 13 public schools in the Antelope Valley, VASP received a total of 4216 (35%) responses providing parental recall of varicella and HZ histories of students aged 10–14 years (mean age 12.9 years). The age distribution consisted of 787 (18.7%) aged 10 or 11 years, 2935 (69.6%) aged 12 or 13 years and 494 (11.7%) were aged 14 years. The response by school widely varied from a low of 12% to a high of 94%. This represents 35% of the public middle (or intermediate) school population and 17% (4216/24,945) of the 2000 census population given for the 10–14 age group. The racial balance is consistent with that of the Antelope Valley population census and the California Basic Education Demographics Survey (CBEDS) (Table 1).

Of the total 4216 respondents, 3627 (86%) presumably had varicella and 589 (14%) indicated a negative or uncertain history. Two hundred sixty-six (6.3%) were presumably vaccinated and 323 (7.7%) were either unvaccinated or uncertain as to vaccination. Thus, the percentage of students susceptible to varicella or uncertain as to susceptibility is 7.7% (95% CI, 6.9–8.5%). Of 220 respondents that did supply a date of vaccination, 45 (20%) gave dates prior to licensure of vaccine (March 1995) and therefore were considered unvaccinated (Table 2). When stratified by age, 10% of children aged 10 and 11 years were still susceptible, declining to 7% susceptible among those aged 14 years. When stratified by race, African–Americans had a significantly higher percentage (12.8%) of susceptibles ($\chi^2 = 24.5$, $P < 0.005$) and higher percentage (10.8%) vaccinated ($\chi^2 = 21.4$, $P < 0.005$) compared to the other races. Adolescents for which parents indicated both varicella disease and receipt of varicella vaccination were classified under varicella in the first row of Table 2.

We tallied the number of parents that indicated their child had both (1) a history of varicella and (2) received varicella vaccination. Since medical professionals would be unlikely to administer varicella vaccine to children with a history of varicella, the parent's affirmative response to these two questions would indicate (a) a possible breakthrough case of varicella if date of vaccination was specified after the licensure date (March 1995) and prior to onset of varicella,

Table 1
Adolescent survey, CBEDS, and population census stratified by race

Source	African–American	Caucasian/Non-Hispanic	Hispanic	Asian/American Indian	Total
Adolescent survey	571 (14)	2021 (50)	1239 (31)	188 (4)	4019[a] (100)
CBEDS[b]	2293 (19)	5329 (45)	3818 (32)	518 (4)	11958 (100)
Population census[c]	4915 (15)	14656 (45)	10813 (33)	2375 (7)	32759 (100)

[a] Of 4216 responses, 197 indicated race as "other" or did not answer.
[b] 2000–2001 California Basic Education Demographics Survey for 13 public schools with seventh and eighth grades.
[c] 2000 population census for individuals aged 10–14 years.

Table 2
Adolescent survey responses regarding varicella disease, receipt of vaccination, and percentage susceptible stratified by race and combined races

	Varicella?		Receipt of varicella vaccination?		Percent susceptible (95% CI)	Total number of respondents *n* (%)
	"Yes"	"No" or "unknown"	"Yes"	"No" or "unknown"		
African–American	437 (77)	134 (23)	61 (10.8)	73 (12.8)	12.8 (10–15.5)	571 (100)
Caucasian/Non-Hispanic	1775 (88)	246 (12)	117 (5.8)	129 (6.4)	6.4 (5.3–7.4)	2021 (100)
Hispanic	1086 (88)	153 (12)	66 (5.3)	87 (7.0)	7.0 (5.6–8.5)	1239 (100)
Asian/American Indian/other	255 (85)	46 (15)	19 (6.3)	27 (9.0)	9.0 (5.7–12.2)	301 (100)
Unspecified race	74 (88)	10 (12)	3 (3.6)	7 (8.3)	8.3 (2.4–14.2)	84 (100)
Combined race	3627 (86)	589[a] (14)	266 (6.3)	323[b] (7.7)	7.7 (6.9–8.5)	4216 (100)

[a] Of the 589 responses, 92 indicated "unknown."
[b] Of the 323 responses, 123 indicated "unknown."

(b) inability to understand the question regarding receipt of varicella vaccine or (c) possibly incorrect memory recall or confusion of varicella vaccination with other traditional vaccinations. Over one-fourth of the responses by Hispanics (27.7%) and African–Americans (25.2%) incorrectly indicated that students with a history of varicella received varicella vaccination. By contrast, only 3.9% of the responses by Caucasians indicated this inconsistency. Of the 518 respondents indicating both varicella and vaccination, 298 (57.5%) gave no date of vaccination, thus the percentage of breakthrough cases was indeterminable in the adolescent study. Based on active surveillance in 2000, of the 837 verified varicella cases reported of all ages, 141 (16.8%) cases occurred 42 or more days after vaccination and were considered possible breakthrough cases. When stratified by age, 25.4% of breakthrough cases were in children 1–4, 18.0% were in children 5–9, and 9.5% were in those aged 10–14 years.

Parents indicated that the students had resided in the Antelope Valley a mean of 8.8 years. African–Americans had the lowest mean of 6.5 years and those Caucasian/Non-Hispanic had the highest mean of 10 years. A majority, 52%, indicated having resided in the Antelope Valley for 10 or more years, 25% resided 5–9 years and 24% resided less than 5 years.

Of those respondents indicating they experienced varicella, approximately half were physician diagnosed and half were diagnosed by the parent.

The adolescent survey indicated that 51% of varicella cases occurred before the age of 5 years; 46% occurred between the ages of 5–9 years; and 3% occurred on or after age 10 years.

4.2. Herpes zoster

A total of 39 (0.9%) cases of HZ occurred in respondents during the 14-year period from 1987 to 2000. Crude incidence is 72/100,000 person-years (39 cases/54,222 person-years) among the cohort aged <15 years and the true incidence is 1.8 times higher, or 133/100,000 person-years (95% CI, 95–182 per 100,000 person-years) (39 cases/29,249 person-years) among those with a previous history of varicella (Table 3). Of 20 (51%) parents contacted regarding their affirmative answer to HZ, 19 (95%) indicated HZ was physician diagnosed; one (5%) parent indicated familiarity with HZ symptoms and therefore did not seek physician confirmation. Restricting the data to the pre-licensure era, the cumulative (1987–1995) true HZ incidence rate is 145 per 100,000 person-years (95% CI, 86–228 per 100,000) (18 cases/12,457 person-years) among children <10 years.

Table 3
Adolescent survey responses regarding shingles (herpes zoster) disease and cumulative (1987–2000) true and crude incidence rates of HZ among children <15 years

No. of herpes zoster cases (*n*)	39
Total number of respondents (*N*)	4216
Post-varicella observation time (person-years)	29249
Total observation time (person-years)	54222
True HZ incidence rate (cases per 100,000 person-years)	133
Crude Hz incidence rate (cases per 100,000 person-years)	72

5. Discussion

The 4216 respondents in the adolescent study exceeded the goal sample size of 2335. The cumulative varicella susceptibility of 7.7% (95% CI, 6.9–8.5%) among individuals aged <15 years in the Antelope Valley, CA health district is consistent with the 7% VZV susceptibility among 12–19 years old measured by serological testing (National Health and Nutrition Examination Survey, NHANES III, 1988–1994) and similar to the cumulative 8.8% theoretically susceptible reported by Finger et al. in the 1991–1992 Kentucky Behavioral Risk Factor Surveillance System (BRFSS)-based study [8]. Of the 4216 respondents aged 10–14 years in the Antelope Valley, CA adolescent survey, if we exclude individuals that cannot be stratified by age of immunity due to unspecified (unknown) age of varicella onset or date of varicella vaccination, 114 (2.7%) and 84 (1.9%), respectively, the cumulative age-specific percentages of varicella susceptibility can be determined among the remaining cohort of 4018 (95.3%). Since only the cohort aged 10–14 years was available in the Antelope

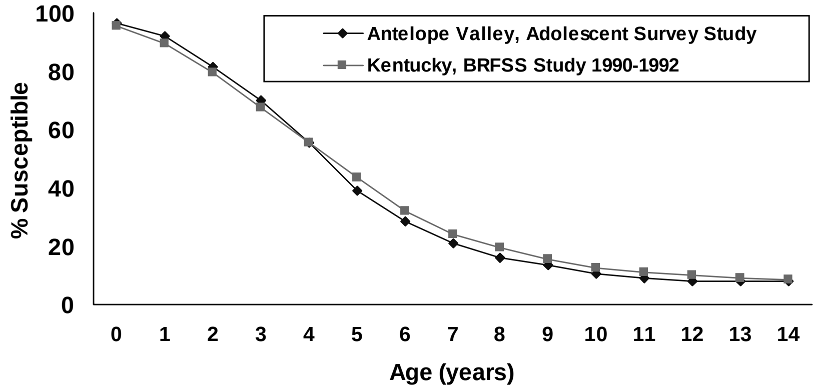

Fig. 1. Comparison of age-specific percentages of varicella susceptibility.

Valley study, determination of the age-stratified percentage susceptible relies on parental recall of varicella experience beginning in 1986–1990 for those aged <1 year (age 0). These percentages are compared to those derived in the BRFSS-based study [8] in Fig. 1. The similar results may indicate that the limitations of these two studies, including use of parental recall, may have had no significant effect on the percentage of varicella susceptibility among children and adolescents.

The percentage susceptible that we calculated in this study is biased high since those uncertain as to varicella vaccination were all assumed to be unvaccinated. If high varicella vaccine coverage levels can be achieved and maintained among school entry children, only a relatively small percentage of children and adolescents may enter adulthood still susceptible to varicella with the potential of increased morbidity and mortality of varicella disease.

The high vaccination rate among African–Americans may indicate some selective sampling bias or a true difference relative to other ethnic groups.

Interestingly, active surveillance of varicella in the Antelope Valley population indicates the mean age of first cases of varicella (i.e. excluding both breakthrough cases of varicella reported among those vaccinated and second varicella cases occurring among those individuals reporting a previous history of varicella) has increased from 6.9 years in 1995 to 8.1 years in 2000. However, since decline in incidence was observed across all age groups, the burden of varicella disease (in 2000) was lower than in the pre-licensure era.

The cumulative (1986–2000) true HZ incidence rate of 133/100,000 person-years (95% CI, 95–182 per 100,000 person-years) among children age <15 years in the Antelope Valley population, based on 39 cases occurring during an observation period of 29,249 person-years, compares with the cumulative (1990–1992) rate of 133/100,000 person-years (95% CI, 98–176 per 100,000 person-years) in the population-based Harvard Community Health Plan Study [7] conducted among children <14 years, based on 49 cases occurring during an observation period of 36,842 person-years. These rates are similar to the cumulative (1947–1962) rate of 138/100,000 person-years among 455 individuals aged 10–19 years reported in the 16-year study conducted in a medical practice in Cirencester, England, based on 10 cases occurring during an observation period of 7280 person-years [9].

The cumulative HZ incidence obtained in the Antelope Valley study represents the mean of the incidence rate among children <10 years in the pre-licensure era (1987–1995) and the incidence rate among children 10–14 years in the post-licensure period (1996–2000). The fact that HZ incidence in the Antelope Valley, CA study compares favorably with the only other historical study reporting true incidence [7], suggests that individuals aged 10–14 years in the post-licensure period have not as yet been influenced by increasing varicella vaccination levels. While CMI to varicella-zoster virus in this cohort has persisted sufficiently to suppress reactivation, significant decline in exogenous exposures has occurred only during the past 2 years (since 1999). Decline in CMI resulting in reactivation may occur sooner than suggested by laboratory measurements of CMI to VZV in individuals. Such measurements conducted in the pre-licensure era were confounded and enhanced due to boosting that individuals received from periodic exogenous exposures to natural varicella in the community.

The similar true HZ incidence rates reported in the Antelope Valley, CA and Boston, MA communities [7], despite differences in study methodology, suggest that the limitations inherent to these studies may have had no significant effect on true HZ rates in children and adolescents. Additionally, considering the HZ incidence reported by Hope-Simpson [9], studies of HZ incidence rates based on low observations times (while they exhibit wide confidence intervals) may accurately characterize the population due to the mixing of age groups and societal behaviors within the study sample that are representative of the population.

In the near future, it will be interesting to investigate post-licensure incidence rates of HZ among children <10 years with a previous history of varicella. Introducing varicella vaccine may reduce the exogenous boosts this cohort receives in elementary school and result in an earlier decline in CMI.

Limitations of this study include the fact that only a cross-sectional sample of the adolescent population was surveyed, although both racial and socio-economic balance was similar to that of the population. Due to the retrospective nature of this study, parents would likely recall the age of children with recent episodes of varicella disease more accurately than early episodes of disease. None of the cases were laboratory confirmed. Since HZ in children and adolescents is relatively mild compared to older adults, many cases may not come to the attention of parents, school nurses, or healthcare providers. Ascertainment of only more serious cases of HZ among children and adolescents by healthcare providers and other age-related biases could further confound observations of incidence rate and advancing age.

Parents appeared to have excellent recall of age of onset and dermatome affected by herpes zoster in their children. Of those parents interviewed by telephone concerning an affirmative response to herpes zoster, all but one parent indicated that prior to seeking healthcare, symptoms of herpes zoster (shingles) were largely unknown. Parents' learning experience at the physician's office, combined with the fact that shingles was considered to be a rare event in children, likely contributed to enhanced memory of the event.

Since shifts in varicella incidence to older age groups or increases as low as 20% in HZ disease among adults with a prior history of wild-type varicella could potentially counterbalance the medical cost-effectiveness of varicella vaccination [6,10,11], careful post-licensing active surveillance of both varicella and herpes zoster diseases will assist public health authorities in evaluating vaccine use strategies.

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