Impact of Vaccination on the Epidemiology of Varicella: 1995–2009

WHAT'S KNOWN ON THIS SUBJECT: Varicella vaccine is effective, but there is concern that widespread use in young children may lead to a shift in the age of infection, with potentially more severe disease later in childhood and adolescence.

WHAT THIS STUDY ADDS: This study documents that varicella vaccine resulted in a decline of varicella incidence and hospitalization in all age groups, with no shift to older age groups.

abstract

FREE

BACKGROUND: When varicella vaccine was licensed in the United States in 1995, there were concerns that childhood vaccination might increase the number of adolescents susceptible to varicella and shift disease toward older age groups where it can be more severe.

METHODS: We conducted a series of 5 cross-sectional studies in 1994 to 1995 (prevaccine), 2000, 2003, 2006, and 2009 in Kaiser Permanente of Northern California to assess changes in varicella epidemiology in children and adolescents, as well as changes in varicella hospitalization in people of all ages. For each study, information on varicella history and varicella occurrence during the past year was obtained by telephone survey from a sample of ~8000 members 5 to 19 years old; varicella hospitalization rates were calculated for the entire membership.

RESULTS: Between 1995 and 2009, the overall incidence of varicella in 5- to 19-year-olds decreased from 25.8 to 1.3 per 1000 person-years, a ~90% to 95% decline in the various age categories (5–9, 10–14, and 15–19 years of age). The proportion of varicella-susceptible children and adolescents also decreased in all age groups, including in 15- to 19-year-olds (from 15.6% in 1995 to 7.6% in 2009). From 1994 to 2009, age-adjusted varicella hospitalization rates in the general member population decreased from 2.13 to 0.25 per 100 000, a ~90% decline.

CONCLUSIONS: In the 15 years after the introduction of varicella vaccine, a major reduction in varicella incidence and hospitalization was observed with no evidence of a shift in the burden of varicella to older age groups. *Pediatrics* 2014;134:24–30

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KEY WORDS

varicella, vaccination, epidemiology, chicken pox, vaccine impact

ABBREVIATIONS

ACIP—Advisory Committee on Immunization Practices
CI—confidence interval
KPNC—Kaiser Permanente of Northern California
VZV—varicella-zoster virus

Dr Baxter supervised data collection and analyses and drafted the initial manuscript; Dr Tran assisted with analyses and the manuscript and reviewed the manuscript; Ms Ray coordinated interviews and data collection, performed analyses, and reviewed the manuscript; Drs Black and Shinefield assisted with the original concept and design, supervised early data collection and analyses, and reviewed the manuscript; Dr Coplan assisted with original design and statistical plan and reviewed the manuscript; Mr Lewis assisted with the design and statistical plan, assisted with analyses, and reviewed the manuscript; Mr Fireman assisted with the original concept and design, worked on analyses, and reviewed the manuscript; Dr Saddier assisted with analyses and the manuscript and reviewed the manuscript; and all authors approved the manuscript.

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In the prevaccine era, varicella-zoster virus (VZV) was associated with nearly universal infection, with the highest incidence of disease in children younger than 10 years of age.[1,2] Varicella was generally considered a relatively benign disease in young healthy children, though it accounted for significant hospitalizations (~11 000–13 000 annually) and ~100 to 150 deaths every year, in all ages, in the United States. Morbidity from varicella was considerably worse in older teenagers and adults.[3] There were concerns, at the time of vaccine licensure in 1995, that decreased exposure to circulating VZV due to vaccination of only young children could increase the number of adolescents susceptible to varicella and shift the incidence of the disease to older age groups, where more severe disease might be more common. Such a shift in age was seen with mumps, for example, where prevaccine era incidence was higher in children 5 to 9 years of age, but then cases shifted to those older than 15 years of age after widespread immunization.[4] Indeed, after varicella vaccination implementation, a shift of the age distribution of varicella cases toward older age groups was observed in children and adolescents,[5] although varicella incidence rates decreased in all age groups. In addition, a mathematical model published in 1994 suggested that partial varicella vaccine coverage of the population had the potential to increase the incidence of varicella among adolescents and adults, even if it resulted in a decrease in the incidence of varicella in children.[6]

Varivax ([OKA/Merck] varicella vaccine live) was licensed in the United States and recommended for routine use by the Advisory Committee on Immunization Practices (ACIP) in 1995. Vaccine uptake increased gradually up to the early 2000s and coverage has been ~90% among children 19 to 35 months of age since 2007. The first dose is currently routinely administered to healthy children in the second year of life in the United States. At the time of licensure, catch-up of first dose vaccination up to age 12 years was also recommended.[7] Despite estimates of 1 dose effectiveness of 80% to 90%, varicella in vaccinated children (breakthrough disease) was noted with multiple outbreaks occurring in the early to mid-2000s,[8–10] leading to a recommendation for a second dose of the vaccine at 4 to 6 years of age by the ACIP in 2006.[11] Recent studies have revealed that varicella incidence has declined further since implementation of the second dose[12,13] and effectiveness of the 2-dose series has been estimated to be as high as 98%,[14] confirming findings from clinical trials.[15] In a previous cohort study conducted from 1995 to 2009, we reported an effectiveness of ~90% over 14 years postvaccination for the first dose, with no cases noted after the second dose.[16]

In light of concerns about disease shifts, we conducted a series of 5 cross-sectional surveys in 1995 (prevaccine), 2000, 2003, 2006, and 2009 to examine the changes in the epidemiology of varicella in children and adolescents over a period of ~15 years after the introduction of the varicella vaccine. We also examined changes in the incidence of varicella-associated hospitalization in all age groups of the population over this time period.

METHODS

Setting

The study was conducted at Kaiser Permanente of Northern California (KPNC), a nonprofit, integrated health care delivery system that had a membership of ~2.3 million in 1994, 2.9 million in 2000, and 3.1 million in 2003, 2006, and 2009. The annual birth cohort changed from ~25 000 births in 1994 to ~40 000 births in 2000, 38 000 births in 2003, 36 000 births in 2006, and 35 000 births in 2009. The member population reflects the general population in the Northern California region, although the poor are underrepresented.[17] KPNC provides services in more than 15 counties and operates more than 40 outpatient clinics and 18 hospitals throughout Northern California. Laboratory results and diagnostic data from hospital discharges and ambulatory settings, including emergency departments, are archived in databases. KPNC databases contain individual patient records and are readily linked by using the patient's unique medical record number that remains with the patient for life. The institutional review board of KPNC approved this study.

Study Design

This serial cross-sectional survey was conducted at baseline in 1995 (prevaccine) and then in 2000, 2003, 2006, and 2009. Each survey included a random sample of ~8000 children and adolescents 5 to 19 years of age who were members of KPNC regardless of vaccination status. The age-stratified sampling was designed to randomly select ~1000 members 5 to 9 years of age, 1000 members 10 to 14 years of age, and 6000 members 15 to 19 years of age. To ensure completeness of the information, survey participants in 2000, 2003, 2006, and 2009 were sampled from those who were continuously enrolled at KPNC (ie, without any gap in KPNC membership) from 1995 (when the vaccine was first available at KPNC) or birth, whichever was later, until the time of the survey. Trained telephone interviewers surveyed study participants (when living independently) or parents/guardians, using a structured, standardized questionnaire to obtain information about the occurrence of varicella in the past year (varicella incidence) and whether the study participant had ever had varicella before the survey year (varicella history). To ensure greater consistency of response across age categories, interviewers attempted to interview parents/guardians, even if the children were older adolescents. No medical confirmation of the diagnosis of varicella was required. Information on

varicella vaccination status was ascertained via the telephone survey in 1995 or via the KPNC immunization database for the subsequent surveys.

In addition to the cross-sectional surveys of children and adolescents, to assess the impact of childhood varicella vaccination, either directly or due to herd immunity, on the incidence and severity of varicella in the general pediatric and adult population, we measured changes in varicella-associated hospitalization rates in the entire KPNC population (including all age groups) by using computerized hospital records. The analysis was performed in 1994 (the baseline year of this analysis before vaccine introduction), 2000, 2003, 2006, and 2009.

Data Analysis

Two time periods were considered for each participating child or adolescent: the 12-month period preceding the interview (the survey year) and the entire period before the survey year (ie, before the 12-month period preceding the interview).

Annual incidence rates of parent- or self-reported varicella were determined as the ratio of the number of cases of varicella reported during the survey year among children and adolescents in a given age category over the person-time contributed by all individuals in that age category. For this calculation, each surveyed member contributed 1 year of person-time to an age category, corresponding to the 1-year survey period in which the occurrence of varicella was queried.

For each age category, vaccination coverage was determined as the proportion of children and adolescents surveyed in that age category who had a recorded varicella vaccination before the interview. History of varicella was based on parental or self-report of varicella before the survey year. Children or adolescents with a reported case of varicella in the survey year were systematically classified as varicella history negative before the report of varicella. To track changes in those children without any protection from varicella, we defined a child or adolescent as "varicella-unprotected" in the absence of either a history of varicella before the survey year or a record of varicella vaccination before the interview.

Varicella-associated hospitalizations were identified through the presence of a diagnosis code of varicella (International Classification of Diseases, Ninth Revision code 052.×) listed as a primary diagnosis among hospital discharge diagnosis codes, as in previous studies.[18] The hospital diagnosis of varicella in adults older than 60 years of age was confirmed by medical record review. Person-time was calculated by multiplying the number of members by 1 year. Hospitalization rates were presented both as age-specific rates and overall rates age-adjusted to the year 2000 KPNC population distribution. Poisson regression was used to assess changes in hospitalization rates over time while adjusting for age.

RESULTS

Study Sample

Between May and November of each survey year, of the ~9400 to 10 400 people contacted, ~8400 to 8900 (82%–95%) KPNC members 5 to 19 years of age were eligible and completed the telephone survey. Those who could not complete the survey included ~200 to 1100 (2%–11%) who were not reachable, ~250 to 800 (3%–8%) who refused to participate, and ~50 (0.5%) who were not eligible. Reasons for ineligibility included language barriers and individuals who were deceased, in foster care, or traveling out of state.

Demographics

Across the study years, the sample population was well-balanced with respect to gender (Table 1). Most (96.5%) of the sample population attended day care or school. Over the years, the proportions of the Asian, Hispanic, and white participants in the study samples were relatively stable, whereas there was a slight decrease of African Americans and a slight increase of multiracial participants. The majority of parents/guardians had more than a high school education.

Varicella Vaccination Coverage

From 2000 to 2009, varicella vaccination coverage increased rapidly from 51% to 98.8% in the 5- to 9-year age group, 11% to 94.7% in the 10- to 14-year age group, and 3% to 53.6% in the 15- to 19-year age group, respectively. In the 2009 survey, 90.6% of all history-negative children and adolescents 5 to 19 years of age were recorded as being vaccinated, with an even higher proportion (99.3% and 98.5%) among the 5- to 9-year age group and 10- to 14-year age group, respectively. These findings suggest that vaccination coverage was high in the younger age groups and that catch-up vaccination programs have been effective at reaching susceptible children and adolescents.

Unvaccinated Children Without Varicella Over Time

The overall proportion of varicella-unprotected children and adolescents 5 to 19 years of age decreased gradually from 18.0% in 1995 to 5.8% in 2009. The decrease was observed in all age categories, including in 15- to 19-year-olds (15.6% in 1995 vs 7.6% in 2009; Table 2). Thus, in the 2009 survey sample, we did not observe an increase in the proportion of children and adolescents without any protection from varicella compared with 1995, the prevaccine era.

Among all sampled children and adolescents 5 to 19 years of age, the proportion of individuals reporting having ever had varicella (whether before or during the survey year) was 84.6% in 1995, 79.5% in 2000, 70.7% in 2003, 59.4% in 2006, and 37.9% in 2009. The reduction was seen in all age categories. In particular, a dramatically smaller proportion of children 5 to 9 years of

age reported having ever had varicella in 2009 (4.9%) than in 1995 (76.0%). Also, a substantially smaller proportion of young adolescents 10 to 14 years of age reported having ever had varicella in 2009 (13.6%) than in 1995 (87.5%). In the 15 to 19 years of age category, 48.1% reported ever having had varicella in 2009 compared with 85.7% in 1995.

Varicella Incidence Rates Over Time

Table 3 summarizes the reported annual varicella incidence rates in the 5- to 9-, 10- to 14-, and 15- to 19-year age groups for the 5 surveys.

The incidence rates of reported varicella declined significantly in all age categories since varicella vaccination was introduced in 1995. The rate of reported varicella in the 5- to 9-year age group in 2009 was 4% of the rate in 1995, a 96% reduction in disease incidence. In the 10- to 14-year age group, the incidence of reported varicella in 2009 was 9% of that in 1995, a 91% reduction in disease incidence. In the 15- to 19-year age group, the incidence in 2009 was 5% of that in 1995, a 95% reduction. Overall, in children and adolescents 5 to 19 years of age, the incidence of varicella decreased by ∼90% to 95% (ie, a ∼10- to 20-fold decrease) in all age groups between 1995 and 2009.

TABLE 1 Demographic Characteristics of Study Participants

Characteristics	1995		2000		2003		2006		2009	
	N	%	*N*	%	*N*	%	*N*	%	*N*	%
Total	8355	100	8412	100.0	8879	100.0	8926	100.0	8496	100.0
Gender										
Boy	4099	49.1	4185	49.8	4448	50.1	4554	51.0	4249	50.0
Girl	4256	50.9	4227	50.3	4415	49.7	4372	49.0	4247	50.0
Unreported[a]	—	—	—	—	16	0.2	—	—	—	—
Day care/school status										
In day care/school	7949	95.3	7895	93.9	8389	94.5	8523	95.5	8202	96.5
Not in day care/school	388	4.7	509	6.1	472	5.3	382	4.3	272	3.2
Unreported[a]	—	—	—	—	2	0.2	21	0.2	22	0.3
Race/ethnicity										
Asian	1080	13.1	1226	14.7	1374	15.5	1307	14.6	1278	15.0
African American	895	10.8	768	9.2	841	9.5	788	8.8	682	8.0
Hispanic	1233	14.9	1228	14.8	1173	13.2	1300	14.6	1206	14.2
White	4111	49.7	4110	49.4	4268	48.1	4170	46.7	3934	46.3
Multiracial	862	10.4	929	11.2	1023	11.5	1181	13.2	1200	14.1
Other	94	1.1	51	0.6	50	0.6	87	1.0	90	1.1
Unreported[a]	—	—	—	—	150	1.7	93	1.0	106	1.3
Parents' years of school										
Mother										
≤12 y	3092	37.7	2706	32.9	2573	29	2415	27.1	2318	27.3
>12 y	5109	62.3	5527	67.1	6096	68.7	6366	71.3	5893	69.4
Unreported[a]	—	—	—	—	210	2.4	145	1.6	285	3.4
Father										
≤12 y	2937	36.7	2660	33.0	2629	29.6	2754	30.9	1991	23.4
>12 y	5069	63.3	5403	67.0	5843	65.8	5894	66.0	6323	74.4
Unreported[a]	—	—	—	—	407	4.6	278	3.1	182	2.1

[a] Not all categories were documented for all survey members. Some participants declined to answer a particular question.

Varicella Hospitalizations in the Entire Population (All Age Categories)

The age-specific rates of hospitalization for varicella over time are presented in Fig 1. Hospitalization rates decreased in all age categories, including in adults. Overall age-adjusted varicella hospitalization rates per 100 000 person-years decreased from 2.13 in 1994 to 0.87 in 2000, 0.46 in 2003, 0.52 in 2006, and 0.25 in 2009, corresponding to a ∼90% reduction (ie, ∼10-fold decrease) between 1994 and 2009. On average, the rate of hospitalizations with a primary diagnosis of varicella decreased 13% annually between 1994 and 2009 (incidence rate ratio, 0.87; 95% confidence interval [CI]: 0.84–0.90, $P < .001$).

DISCUSSION

In the KPNC membership 5 to 19 years of age, there was a decline by ∼90% to 95% (∼10- to 20-fold) in the incidence of varicella between vaccine introduction in 1995 and 2009 in all age categories (5–9, 10–14, and 15–19 years), irrespective of vaccination status. This finding is consistent with what has been

TABLE 2 Proportion of Varicella-Unprotected Children and Adolescents 5 to 19 Years of Age by Age Category and Survey Year, KPNC, 1995–2009

Survey Year	5–9 Years				10–14 Years				15–19 Years			
	Unvac Hx (−)[a]	Number Surveyed	%[b]	95% CI	Unvac Hx (−)[a]	Number Surveyed	%[b]	95% CI	Unvac Hx (−)[a]	Number Surveyed	%[b]	95% CI
1995	387	1125	34.4	31.6–37.3	157	1085	14.5	12.3–16.9	915	5879	15.6	14.6–16.6
2000	125	1123	11.1	9.4–13.1	133	1108	12.0	10.1–14.2	692	5985	11.6	10.7–12.5
2003	43	1263	3.4	2.5–4.6	109	1270	8.6	7.0–10.4	804	7132	11.3	10.5–12.1
2006	22	1181	1.9	1.2–2.8	57	1136	5.0	3.8–6.5	596	6350	9.4	8.7–10.1
2009	7	1076	0.7	0.3–1.3	14	1082	1.3	0.7–2.2	459	6049	7.6	6.9–8.3

[a] Unvac Hx (−) (unvaccinated history-negative individuals): Individuals with no record of varicella vaccination and reported to have no history of varicella disease were considered susceptible to varicella. Varicella disease history was based on parental or self-report of varicella disease before the survey year. Vaccination status was obtained from the KPNC immunization database.
[b] %: The proportion of individuals susceptible to VZV infection (first column) among individuals surveyed in this age category (second column).

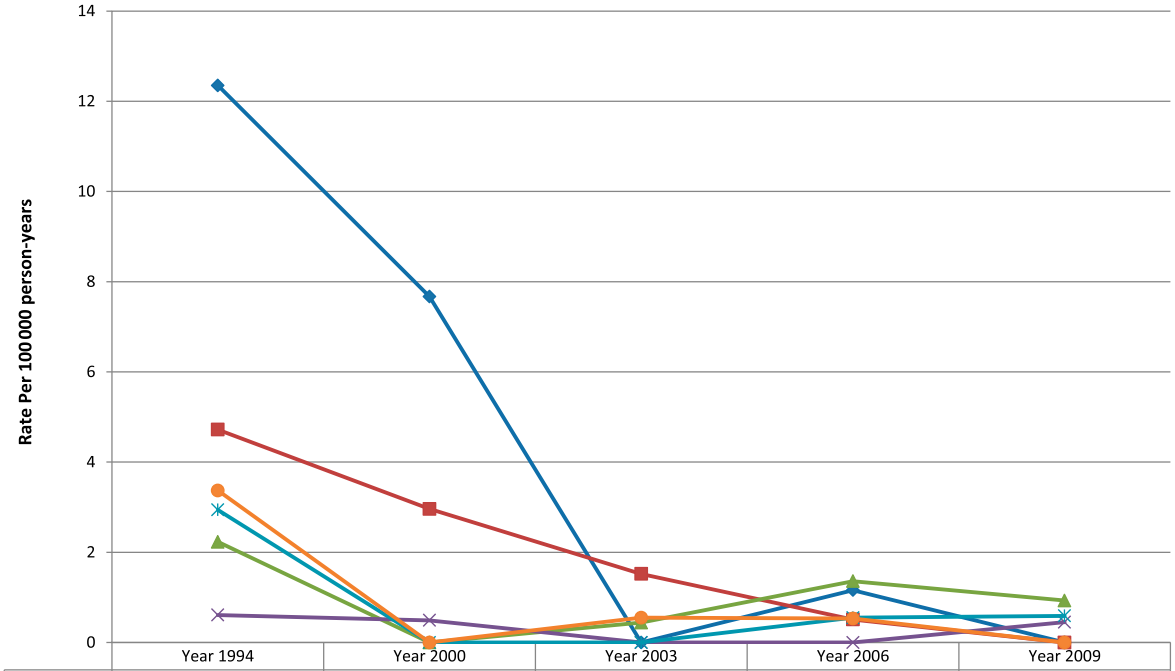
reported by the Centers for Disease Control and Prevention from US surveillance systems[5,19,20] and in published surveillance data from Europe.[21,22] In the 2009 survey, varicella vaccine coverage at KPNC was high among young children and adolescents because of high compliance with vaccine recommendations, and a successful catch-up program in history-negative teenagers. As a result, few children and adolescents were still without any protection from varicella in 2009.

In addition to the first dose catch-up for adolescents, KPNC broadly implemented the June 2006 ACIP recommendation for a second dose of varicella vaccine, which resulted in 40% of all 2009 survey participants having received a second dose of varicella vaccine (with either a monovalent varicella vaccine or a combined measles, mumps, rubella, varicella vaccine). The coverage for second dose of varicella vaccine as assessed from the KPNC immunization database (without regard to previous history of varicella) was 73% in the 5- to 9-year-olds, 51% in the 10- to 14-year-olds, and 24% in the 15- to 19-year-olds. Of note, study data suggested that, in 2009, the 15- to 19-year-old category was a combination of unvaccinated adolescents who had varicella in the past (approximately half), adolescents vaccinated by the catch-up program, and adolescents entering this age category after having been vaccinated in the second year of life. No increase in varicella-unprotected rates was observed over the study period despite the dramatic decrease in varicella incidence and the likely decrease in VZV circulation. The varicella-unprotected rates steadily decreased in all age categories over time, even in the 15- to 19-

TABLE 3 Reported Annual Incidence Rates of Varicella by Age Category and Survey Year, KPNC, 1995–2009

Survey year	5–9 Years of Age			10–14 Years of Age			15–19 Years of Age		
	Cases	Children	Rate[a]	Cases	Children	Rate[a]	Cases	Children	Rate[a]
1995	116	1125	103.1	21	1085	19.4	72	5879	12.3
2000	19	1123	16.9	8	1108	7.2	7	5984	1.2
2003	8	1263	6.3	5	1270	3.9	7	7131	1.0
2006	12	1181	10.2	6	1136	5.3	6	6350	0.9
2009	5	1076	4.6	2	1082	1.8	4	6049	0.7

[a] Rate per 1000 person-years.



	Year 1994	Year 2000	Year 2003	Year 2006	Year 2009
0–4	12.35	7.67	0	1.16	0
5–9	4.72	2.96	1.52	0.51	0
10–14	2.23	0	0.44	1.36	0.93
15–19	0.61	0.49	0	0	0.45
20–24	2.94	0	0	0.55	0.59
25–29	3.37	0	0.55	0.53	0
All ages	2.23	0.87	0.46	0.51	0.25

FIGURE 1
Rates of hospitalization with a primary diagnosis for varicella at KPNC, by age group, 1994–2009.

year-old category, and continued to do so in 2009 as compared with 2006.

In the 2009 survey, the age-specific incidence rates of varicella were lower than those in any previous survey, with a substantial decrease in all age groups in 2009 compared with 2006. Implementation of a second dose after 2006 may have provided further protection and may explain the decrease between 2006 and 2009. In the 2009 survey, the varicella incidence rates remained low in vaccinated and unvaccinated children 5 to 19 years old, suggesting that the vaccine provides good protection both directly and through herd immunity.

The overall ∼90% decline in varicella hospitalization rates in all age categories of the entire KPNC membership between 1994 and 2009 emphasizes the impact of varicella vaccination through both direct protection and herd immunity, and is consistent with published results from varicella surveillance in the United States.[20,23–26] The continued decrease in the varicella hospitalization rates observed between 2006 and 2009 may be related to lower VZV circulation as a result of both the continued first dose catch-up program in older children and adolescents, and the implementation of a second dose of varicella vaccine after 2006.

This study has a number of limitations. Although parental report of varicella history has been shown to be reliable for young children, history of varicella as reported by parents/guardians or the subject may be less reliable in adolescents, and for younger children as varicella becomes less common.[27,28] The accuracy of a report of varicella in the past year may also be subject to recall bias, especially if the case of varicella occurred earlier in that time period. In addition, as varicella disease has become rare and much milder in the vaccine era, parents may have been less able over time to accurately recognize a varicella case. They may both have missed mild varicella cases or have identified as varicella various types of rashes (eg, insect bites, allergy, or contact dermatitis) unrelated to VZV infection. Furthermore, reporting varicella in the past year may be influenced by vaccination status, although it is unknown in which direction this might bias the results. Vaccinated individuals (or their parents) could have been more likely to identify or recall an episode of varicella than unvaccinated individuals. Altogether, misclassification of varicella history and varicella incidence in the year before the interview may have occurred in this survey where this information was solely based on parental or self-report, especially for adolescents.

Varicella vaccination information was based on the KPNC immunization database. Misclassification may have occurred if vaccination was not recorded properly or if the child was vaccinated outside KPNC. However, because only children continuously enrolled since birth (or at least since 1995) were included in the survey sample, misclassification of vaccination status should be minimal.

In addition, use of primary hospital discharge diagnoses may have underestimated rates of varicella hospitalization, if the infection was only listed as a secondary diagnosis. In 1 study,[25] use of secondary codes resulted in 20% more cases diagnosed by electronic records.

CONCLUSIONS

Over the 15 years since the introduction of varicella vaccine, varicella incidence data from the baseline (1995), 2000, 2003, 2006, and 2009 surveys did not indicate a shift in the burden of varicella to older age groups among children and adolescents 5 to 19 years of age. Varicella incidence decreased by ∼90% to 95% (∼10- to 20-fold) in all age categories between 1995 and 2009, irrespective of vaccination status, and no increase in susceptibility rates was observed in any age category compared with the prevaccine era.

In parallel, varicella hospitalization rates decreased by ∼90% in all age categories between 1994 and 2009, emphasizing the impact of the varicella vaccination program in all age groups, including adolescents and adults. This study confirms that varicella vaccination has the ability to dramatically decrease varicella burden, both directly and possibly through herd immunity.

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