MAJOR ARTICLE

Incidence and Clinical Characteristics of Herpes Zoster Among Children in the Varicella Vaccine Era, 2005–2009

Sheila Weinmann,[1] Colleen Chun,[1,2] D. Scott Schmid,[3] Michelle Roberts,[1] Meredith Vandermeer,[1] Karen Riedlinger,[1] Stephanie R. Bialek,[3] and Mona Marin[3]

[1]Center for Health Research, Kaiser Permanente Northwest, and [2]Department of Pediatrics, Northwest Permanente, Portland, Oregon; and [3]Division of Viral Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia

Background. Vaccine-strain herpes zoster (HZ) can occur after varicella vaccination. This study determined the number and proportion of HZ cases caused by vaccine-strain varicella zoster virus (VZV), assessed the positive predictive value of provider diagnosis of HZ, and computed HZ incidence rates in vaccinated and unvaccinated children.

Methods. We used electronic medical records to identify all office visits with an HZ diagnosis for children aged <18 years in a managed care plan. Providers collected skin specimens and completed a questionnaire. Specimens were tested by polymerase chain reaction to identify wild-type or vaccine-strain VZV.

Results. From May 2005 to September 2009, we enrolled 322 subjects. VZV was detected in 82% of specimens (84% wild-type, 15% vaccine-strain, 1% possible vaccine–wild-type recombinant). Among the 118 vaccinated subjects, VZV was detected in 70% (52% wild-type). The positive predictive value for provider diagnosis of "definite HZ" was 93% for unvaccinated and 79% for vaccinated children. The incidence of laboratory-confirmed HZ was 48 per 100 000 person-years in vaccinated children (both wild-type and vaccine-strain) and 230 per 100 000 person-years in unvaccinated children (wild-type only).

Conclusions. HZ incidence in vaccinated children was 79% lower than in unvaccinated children. Among vaccinated children, half of HZ cases were due to wild-type VZV.

Keywords. herpes zoster; shingles; incidence; epidemiology; varicella zoster virus; varicella vaccine; children.

Herpes zoster (HZ) is caused by reactivation of varicella zoster virus (VZV) that remains latent in the sensory nerve ganglia after primary infection. HZ occurs more commonly in elderly adults, oftentimes with postherpetic neuralgia. HZ occurs less frequently among children, typically causing mild disease with minimal pain [1, 2]. Although varicella vaccine use has significantly reduced the incidence of varicella among US children [3], and one study reported lower HZ rates in vaccinated vs unvaccinated children [4], the vaccine virus's contribution to HZ incidence rates is unknown. Similar to wild-type VZV, vaccination establishes a latent infection and can reactivate, causing HZ. Therefore, in vaccinated children, HZ can be caused by vaccine-strain VZV or by wild-type VZV [5–10] acquired either from unrecognized infection before or after vaccination or from breakthrough varicella. Attribution of the causal virus type requires laboratory confirmation and genotyping. No population-based studies of HZ in children have included laboratory confirmation, and published data on the clinical presentation of vaccine-strain HZ cases are limited.

To further characterize the epidemiology of childhood HZ in the varicella vaccine era, we determined the VZV strain of HZ cases among children aged <18 years in a managed care plan and assessed demographic and

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Correspondence: Sheila Weinmann, PhD, MPH, Center for Health Research, Kaiser Permanente Northwest, 3800 N Interstate Ave, Portland, OR 97227 (sheila.weinmann@kpchr.org).

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clinical characteristics by vaccination status and VZV type. Because the presentation of HZ may be changing in the vaccine era, we also assessed the positive predictive value (PPV) of the providers' diagnoses of HZ. We computed population-based HZ incidence rates by vaccination status, age, sex, and immunosuppressed status.

METHODS

The study was conducted at Kaiser Permanente Northwest (KPNW), a health maintenance organization serving approximately 475 000 members in Oregon and Washington, 144 000 of whom are <18 years of age. KPNW's electronic medical record (EMR) system contains information on all care received by members and covered by KPNW. One-dose varicella vaccine coverage among 24-month-olds increased from 70% in 2005 to 81% in 2009.

Laboratory Confirmation and VZV Strain Investigation

Potential study subjects were patients aged 0–17 years diagnosed with HZ and assigned *International Classification of Diseases, Ninth Revision* (*ICD-9*) code 053 by a primary care provider (PCP) between May 2005 and September 2009. Patients were recruited by PCPs during office visits. Inpatients with suspected HZ were reported by the treating physician. To ensure complete ascertainment of cases, we screened computerized outpatient and emergency room medical records for *ICD-9* code 053 daily. If the PCP had not enrolled a potential subject, we first confirmed the HZ diagnosis by reviewing the medical record. The study nurse then telephoned the family to invite participation. Children with an HZ diagnosis were excluded if a laboratory test confirmed an alternate diagnosis, no lesions were still present, parents were non–English speakers, or no parent/guardian was available to provide consent.

For all subjects, PCPs completed a questionnaire reporting date of rash onset, whether rash appearance was characteristic of HZ, rash distribution, number of lesions, and certainty of their diagnosis ("definite," "possible," or "not sure"). For subjects enrolled during an office visit, the PCPs collected skin lesion specimens for laboratory testing as previously described [7], and the study nurse interviewed a parent by phone as soon as possible after the visit to collect data on the clinical features of the child's HZ episode, medication use, and history of varicella or HZ. The study nurse mailed a follow-up questionnaire (to be completed after the illness resolved) regarding disease course, complications, and medications. For subjects not enrolled at the office visit, the study nurse visited the home to collect specimens, conduct the parent interview, and leave the follow-up questionnaire.

Varicella vaccination status was confirmed from the KPNW EMR and the state immunization databases. We reviewed medical charts for vaccinated subjects to determine into which extremity varicella vaccine was administered. We obtained information on preexisting medical conditions and immunosuppressive therapy from the EMR.

All specimens were tested at the National VZV Laboratory at the Centers for Disease Control and Prevention (CDC) using 4 fluorescent resonant energy transfer polymerase chain reaction (PCR) protocols to determine the type of VZV; β-actin protein was measured to detect cellular material verifying an adequately collected specimen [11]. Laboratory employees were blinded to the subjects' vaccination status. We considered adequate specimens to be those testing PCR positive or PCR negative but actin positive.

We used descriptive analysis to examine the demographic and HZ clinical characteristics by vaccination status and VZV type. We used χ^2 and Fisher exact tests to test for differences and considered P values $\leq .05$ to be statistically significant. We used logistic regression to examine factors associated with presence of pain (yes/no) and self-reported severity (severe vs mild/moderate); analysis was restricted to children aged ≥4 years who could describe their symptoms. Potential predictors included age at diagnosis as a continuous variable, sex, race, ethnicity, varicella vaccination status, VZV strain type, and history of varicella; all were included in multivariable models regardless of statistical significance in univariate analysis. We removed from the model covariates that were not statistically significant and assessed model fit using Akaike information criteria [12].

To assess the accuracy of PCPs' clinical diagnoses of HZ as "definite" or "possible," we calculated PPVs and 95% confidence intervals (CIs) overall and by vaccination status, using the PCR results as the gold standard. We calculated CIs using the exact method for binomial distributions.

HZ Incidence Rate Investigation

HZ cases used for incidence rate calculations were those among all KPNW health plan members aged <18 years who had an *ICD-9* code of 053 recorded in the outpatient, inpatient, or emergency room EMR or in claims data during the study period. To ensure that only new cases were used to calculate incidence, we included only those who had no HZ *ICD-9* code 053 in the previous 180 days. We did not include subjects whose only HZ-related *ICD-9* codes were 053.12 (postherpetic trigeminal neuralgia) and 053.13 (polyherpetic polyneuropathy), because these may not represent incident HZ cases. We calculated incidence rates using total person-years of observation of the health plan members aged <18 years; person-years for vaccinated subjects began 21 days after vaccination; prior person-time was counted as unvaccinated. We selected age groupings (1–2, 3–9, and 10–17 years) for comparison of incidence rates with an earlier KPNW report [13].

Immunosuppressed status was defined as (1) having an immunosuppressive medical condition from the time of diagnosis

Table 1. Characteristics of Patients With Herpes Zoster by Varicella Zoster Virus Type and Varicella Vaccination Status[a], Kaiser Permanente Northwest, 2005–2009

			Wild-type HZ Cases (n = 214)					
	Vaccine-Strain HZ Cases (n = 38)		Vaccinated (n = 43)		Unvaccinated (n = 171)		PCR-Negative Subjects (n = 55)	
Characteristic	No.	%	No.	%	No.	%	No.	%
Sex								
Male	18	47.4	17	39.5	84	49.1	35	63.6
Female	20	52.6	26	60.5	87	50.9	20	36.4
Age at HZ diagnosis, y[b]								
1–2	22	57.9	2	4.7	0	0	7	12.7
3–9	10	26.3	8	18.6	20	11.7	18	32.7
10–17	6	15.8	33	76.7	151	88.3	30	54.6
Race								
White	31	81.6	26	60.5	134	78.4	46	83.6
Black	0	0	0	0	5	2.9	0	0
Asian/Pacific Islander	1	2.6	4	9.3	7	4.1	4	7.3
Native American/Alaska Native	0	0	1	2.3	5	2.9	2	3.6
Multiracial[c]	5	13.2	7	16.3	10	5.9	0	0
Unknown[d]	1	2.6	5	11.6	10	5.9	3	5.5
Ethnicity								
Hispanic	5	13.2	8	18.6	22	12.9	5	9.1
Non-Hispanic	33	86.8	34	79.1	140	81.9	48	87.3
Unknown	0	0	1	2.3	9	5.3	2	3.6
Years since varicella diagnosis[b]								
0–2	2	50.0	1	4.6	0	0.0	0	0.0
3–9	1	25.0	8	36.4	53	32.3	11	42.3
10–17	1	25.0	13	59.1	109	66.5	15	57.7
Unknown	0	0.0	0	0.0	2	1.2	0	0.0
Years since varicella vaccine[b,e]								
<1	16	42.1	1	2.3	NA	NA	5	14.3
1	6	15.8	3	7.0	NA	NA	3	8.6
2–5	7	18.4	12	27.9	NA	NA	12	34.3
6–9	6	15.8	13	30.2	NA	NA	7	20.0
10–12	3	7.9	14	32.6	NA	NA	8	22.9
Immunosuppressed[f]								
Yes	0	0.0	1	2.3	3	1.8	1	1.8
No	38	100	42	97.7	168	98.3	54	98.2

Abbreviations: HZ, herpes zoster; NA, not applicable; PCR, polymerase chain reaction.

[a] Two possible recombinant vaccine/wild-type cases not included in table.

[b] $P \leq .05$ for χ^2 or Fisher exact tests between vaccine-strain HZ cases, wild-type vaccinated HZ cases, and wild-type unvaccinated HZ cases. Unknowns were excluded.

[c] Of 22 multiracial: 9 Asian/Pacific Islander/white; 5 Native American/Alaska Native/white; 5 black/white; 1 Native American/Alaska Native/black; 1 Native American/Alaska Native/black/white; 1 Native American/Alaska Native/Asian/white.

[d] Twelve of 19 of those with unknown race self-reported their ethnicity as Hispanic; the remaining had unknown ethnicity.

[e] Median of 436 days (range, 78–4457 days) between vaccination date and HZ rash onset date.

[f] Patients with immunosuppressive medical conditions or treated with immunosuppressive medications.

through the duration of the study, (2) receiving systemic corticosteroids from the second medication dispensing date until 90 days after the last dispensing date, or (3) receiving other immunosuppressive medications during the time covered by the prescription plus the next 90 days.

We calculated crude incidence overall and by varicella vaccination status, year, age group, sex, and immunosuppressed status. We then adjusted the crude rates by the proportion of cases with adequate specimens that were positive for VZV by PCR. CIs were computed using the Poisson distribution

Table 2. Herpes Zoster Rash Characteristics and Clinician Diagnostic Certainty by Varicella Zoster Virus Type and Varicella Vaccination Status[a], Kaiser Permanente Northwest, 2005–2009

Characteristic and Diagnostic Certainty	Vaccine-Strain HZ Cases (n = 35)		Wild-Type HZ Cases (n = 210)				PCR-Negative Subjects (n = 55)	
			Vaccinated (n = 42)		Unvaccinated (n = 168)			
	No.	%	No.	%	No.	%	No.	%
Characteristic HZ rash								
Yes	32	91.4	38	90.5	165	98.2	47	85.5
No	2	5.7	3	7.1	3	1.8	8	14.6
Unspecified	1	2.9	1	2.4	0	0.0	0	0.0
Dermatomal distribution								
Cranial	1	2.9	1	2.4	3	1.8	7	12.7
Cervical[b]	9	25.7	5	11.9	16	9.5	6	10.9
Thoracic[b]	5	14.3	26	61.9	113	67.3	24	43.6
Lumbar[b]	13	37.1	8	19.1	23	13.7	8	14.6
Sacral	2	5.7	2	4.8	5	3.0	2	3.6
Dermatome unspecified	6	17.1	4	9.5	17	10.1	13	23.6
Diagnostic certainty[b]								
Definite	23	65.7	23	54.8	136	81.0	22	40.0
Possible	9	25.7	19	45.2	30	17.9	30	54.6
Not sure	2	5.7	0	0.0	1	0.6	3	5.5
Unspecified	1	2.9	0	0.0	1	0.6	0	0.0

Abbreviations: HZ, herpes zoster; PCR, polymerase chain reaction.

[a] Two possible vaccine + wild-type recombinant cases not included in table.

[b] $P \leq .05$ for χ^2 or Fisher exact tests between vaccine-strain HZ cases, wild-type vaccinated HZ cases, and wild-type unvaccinated HZ cases. Unspecified excluded.

method [14]. We evaluated linear trends in annual incidence rates, overall and by varicella vaccination status, using Poisson regression analysis.

The KPNW and CDC institutional review boards approved the study protocol. For the laboratory confirmation and VZV strain investigation, we obtained for all study subjects written informed parental consent and written assent from subjects age 8 years and older.

RESULTS

Laboratory Confirmation and VZV Strain Investigation

We identified 551 children aged 0–17 years with an HZ diagnosis and contacted 461 (84%). Of these 461, 74 (16%) were deemed ineligible (rash healed, 36; non-HZ diagnosis confirmed, 14; HZ not clinically confirmed, 3; nonincident HZ, 1; non-English-speaking parent, 7; parent unavailable, 13). Of the remaining 387 children, 65 (17%) declined participation and 322 (83%) were enrolled.

Similar proportions of enrolled and nonenrolled subjects were female (50% vs 55%). Enrolled subjects were more likely to be 1–2 years old (11% vs 3%) or 3–9 years old (17% vs 13%) and less likely to be 10–17 years old (72% vs 84%). More enrolled subjects had received varicella vaccination (38% vs 26%).

Among enrolled participants, 96% completed the initial questionnaire; 59% returned the follow-up questionnaire. The provider questionnaire was completed for 98% of enrolled subjects. PCPs collected 35% of specimens, and the study nurse collected 65%. Although no specific diagnostic criteria were conveyed to PCPs by study investigators, rash deemed characteristic for HZ was typically vesicular and dermatomal. Some specimens were collected after the vesicles had evolved to scabs.

Specimens were collected from all 322 enrolled subjects; 309 (96%) were adequate. VZV was identified in 254 (82%), of which 214 (84%) were wild-type, 38 (15%) were vaccine-strain, and 2 (0.8%) were possible vaccine/wild-type virus recombinants. Of 254 subjects with VZV-positive specimens, 83 (33%) were vaccinated and 171 (67%) were unvaccinated. Of the 83 vaccinated subjects, 43 (52%) had wild-type HZ, 38 (46%) had vaccine-strain HZ, and 2 (2%) had HZ from possible recombinant VZV. Among vaccinated subjects, the proportion of vaccine-strain HZ did not change over the study period ($P = .72$). A history of clinical varicella was reported by 4 of 38 (11%) subjects with vaccine-strain HZ, 22 of 43 (51%) vaccinated subjects with wild-type HZ, and 164 of 171 (96%) of unvaccinated subjects with wild-type HZ. Five percent of subjects reported a previous HZ episode.

Subjects with vaccine-strain HZ and vaccinated and unvaccinated subjects with wild-type HZ did not differ by sex, race, or

Table 3. Parental- and Self-Reported Clinical Features of Herpes Zoster Rash by Varicella Zoster Virus Type and Varicella Vaccination Status[a], Kaiser Permanente Northwest, 2005–2009

			Wild-type HZ Cases (n = 209)					
	Vaccine-Strain HZ Cases (n = 38)		Vaccinated (n = 42)		Unvaccinated (n = 167)		PCR-Negative Subjects (n = 54)	
Clinical Feature	No.	%	No.	%	No.	%	No.	%
Time for all lesions to scab over[b]								
<1 wk	8	21.1	16	38.1	54	32.3	28	51.9
≥1 wk	27	71.1	23	54.8	98	58.7	21	38.9
No follow-up questionnaire, all lesions not scabbed at time of initial questionnaire	3	7.9	3	7.1	15	9.0	5	9.3
Time until new lesions stopped appearing[b]								
<1 wk	30	79.0	28	66.7	121	72.5	35	64.8
≥1 wk	6	15.8	13	31.0	36	21.6	17	31.5
No follow-up questionnaire, all lesions not scabbed at time of initial questionnaire	2	5.3	1	2.4	10	6.0	2	3.7
Symptoms during rash[c]								
Pain								
Yes	29	76.3	32	76.2	141	84.4	40	74.1
No	9	23.7	10	23.8	26	15.6	14	25.9
Itchiness[d]								
Yes	29	76.3	41	97.6	144	86.2	45	83.3
No	9	23.7	1	2.4	23	13.8	9	16.7
Tingling or hypersensitivity								
Yes	22	57.9	31	73.8	138	82.6	33	61.1
No	10	26.3	8	19.1	28	16.8	14	25.9
Unspecified	6	15.8	3	7.1	1	0.6	7	13.0
Self-reported severity of symptoms[c]								
Mild	15	39.5	9	21.4	46	27.5	16	29.6
Moderate	14	36.8	23	54.8	81	48.5	26	48.2
Severe	7	18.4	10	23.8	38	22.8	9	16.7
Unspecified	2	5.3	0	0.0	2	1.2	3	5.6
Acyclovir use during illness episode								
Yes	17	44.7	17	40.5	56	33.5	23	42.6
No	21	55.3	24	57.1	108	64.7	29	53.7
Unspecified	0	0.0	1	2.4	3	1.8	2	3.7

Completeness of follow-up survey was 27 of 38 (71.1%) for vaccine-strain, 29 of 42 (69.0%) for vaccinated wild-type, 97 of 167 (56.4%) for unvaccinated wild-type, and 31 of 54 (56.4%) for PCR-negative subjects.

Abbreviations: HZ, herpes zoster; PCR, polymerase chain reaction.

[a] Two possible vaccine + wild-type recombinant cases not included in table.

[b] Responses were taken from follow-up survey. If follow-up survey was incomplete/not returned and all lesions had scabbed over, or stopped appearing at the time of initial survey, responses were taken from initial survey.

[c] Responses taken from follow-up survey. If follow-up survey was incomplete/not returned, responses were taken from initial survey.

[d] $P \leq .05$ for χ^2 or Fisher exact tests between vaccine-strain HZ cases, wild-type vaccinated HZ cases, and wild-type unvaccinated HZ cases. Unknown and unspecified excluded.

ethnicity (Table 1). However, vaccinated subjects with vaccine-strain HZ were significantly younger at diagnosis than the other groups ($P < .0001$). The median age at diagnosis for vaccinated subjects was 9 years (range, 1–17), including 2 years (range 1–14) for vaccinated subjects with vaccine-strain HZ and 13 years (range, 2–17) for vaccinated subjects with wild-type HZ. For unvaccinated subjects with wild-type HZ, the median age at diagnosis was 14 years (range, 3–17). Characteristic HZ rash was reported for almost all subjects with no difference by vaccination status (Table 2). Subjects with vaccine-strain HZ were

more likely to have lumbar (37%, $P = .004$) and cervical (26%, $P = .03$) dermatomal involvement, whereas vaccinated and unvaccinated subjects with wild-type HZ mainly had thoracic involvement (63% and 67%, respectively; $P < .0001$).

Among the 30 subjects with vaccine-strain HZ and known vaccination location, 16 (53%) had rash on the extremity where vaccine had been administered, 7 (23%) had rash on a different dermatome ipsilateral to the vaccination, 4 (13%) had rash on the corresponding dermatome contralateral to the vaccination, and 3 (10%) had rash on a different dermatome contralateral to the vaccination. Among all 38 vaccine-strain HZ subjects, only one (3%) had bilateral rash. Among the 11 vaccinated subjects with wild-type HZ and known vaccination location, 2 had the HZ rash in the vaccinated extremity.

Although some clinical features suggested a milder presentation among subjects with vaccine-strain HZ, except for itchiness, clinical features did not differ significantly between subjects with vaccine-strain HZ and vaccinated and unvaccinated subjects with wild-type HZ (Table 3). Among those returning the follow-up questionnaire, a minority reported any symptoms after the rash resolved (26% vaccine-strain, 19% vaccinated wild-type, 19% unvaccinated wild-type); the most common symptom in all groups was pruritus (data not shown).

No serious HZ-related complications were reported. However, 2 subjects were hospitalized. The first was an unvaccinated 12-year-old male admitted for evaluation of right leg pain; on day 7 of pain, he developed HZ on the right buttock. He had varicella at age 13 months. The second was a vaccinated 10-year-old male with a brain tumor who was hospitalized to receive intravenous acyclovir. Both subjects tested PCR positive for wild-type VZV.

In a multivariable model including children aged ≥4 years, pain during the HZ episode was predicted by age (odds ratio [OR] = 1.09; 95% CI, 1.03–1.16 for each year of age) and female sex (OR = 1.94; 95% CI, 1.08–3.47). In a second multivariable model, self-reported "severe" HZ was predicted by age only (OR = 1.10; 95% CI, 1.03–1.18 for each year of age). Neither vaccination status nor VZV type was associated with pain during the HZ episode or severity of HZ.

The 2 subjects with HZ with possible recombinant VZV were a 22-month-old who developed HZ 10 months after his one varicella vaccination and an 11-year-old who developed HZ 3 months after the second varicella vaccination and 9 years after the first vaccination. Both subjects presented with typical HZ rash and self-reported severity as "mild." Both were classified as "possible HZ" by their PCPs. Neither was immunocompromised or had a history of varicella or HZ; however, both had a history of atopic dermatitis.

The overall PPV of a "definite" PCP diagnosis of HZ was 89.2% (95% CI, 85.0%–92.6%). The overall PPV of a "possible" PCP diagnosis of HZ was 66.7% (95% CI, 57.6%–74.8%). When stratified by varicella vaccination status, the PPV for "definite" diagnosis was higher for unvaccinated subjects (93.2%; 95% CI, 88.7%–96.2%) than for vaccinated subjects (79.3%; 95% CI, 68.6%–87.6%); the PPV for "possible" diagnosis was also higher for unvaccinated (76.9%; 95% CI, 63.2%–87.4%) than for vaccinated subjects (58.8%; 95% CI, 46.3%–70.5%). There was no statistically significant variation by age group.

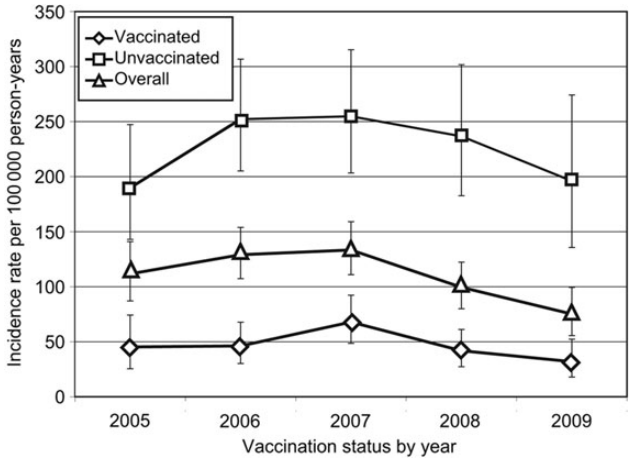

Figure 1. Herpes zoster incidence rates per 100 000 person-years adjusted for laboratory confirmation rates, by year and varicella vaccination status, persons aged 0–17 years, Kaiser Permanente Northwest, 2005–2009.

HZ Incidence Rate Investigation

Figure 1 shows adjusted HZ incidence rates. The overall incidence of laboratory-confirmed HZ was 112 per 100 000 person-years (Table 4); incidence decreased during the study period to a low of 75 per 100 000 person-years in 2009 ($P = .003$). Adjusted for vaccination status and age, this decrease remained statistically significant ($P = .05$). When HZ incidence was calculated by vaccination status, there was no significant change over time ($P = .35$ unvaccinated; $P = .10$ vaccinated).

Vaccinated children overall had a 79% lower incidence of HZ than unvaccinated children (48 vs 230/100 000 person-years, $P < .001$). These lower incidence rates were present in the 3–9 and 10–17 age groups. However, among children aged 1–2 years, incidence was higher among vaccinated children ($P = .01$; Figure 2). Incidence was higher in females than males ($P = .007$) and among immunosuppressed than nonimmunosuppressed children ($P = .008$; Table 4).

DISCUSSION

In this first population-based study of laboratory-confirmed childhood HZ, overall HZ incidence was 79% lower among vaccinated than among unvaccinated children. Wild-type virus

Table 4. Herpes Zoster Incidence Rates Per 100 000 Person-years, Crude and Confirmation-Adjusted by Year, Age Group, Sex, Vaccination Status, and Immunosuppressed Status, Kaiser Permanente Northwest, 2005–2009

Characteristic	Person-years	HZ Diagnosis Among KPNW Members (≤17 y of Age) (n = 554)	Crude Incidence Rate of HZ Among KPNW Members (≤17 y of Age) per 100 000 Person-years	KPNW Study Participants Positive for VZV by PCR/No. of Adequate Specimens (%) (n = 309)	Confirmation-Adjusted Incidence Rate per 100 000 KPNW Member Person-years
Overall	406 552	554	136	254/309 (82.2)	112 (102–123)
Year of HZ diagnosis					
2005	62 796	94	150	44/59 (74.6)	112 (87–141)
2006	95 814	155	162	67/84 (79.8)	129 (107–154)
2007	92 785	141	152	72/82 (87.8)	133 (111–159)
2008	90 189	107	119	47/56 (83.9)	100 (80–122)
2009	64 968	57	88	24/28 (85.7)	75 (56–99)
Varicella vaccination status					
Vaccinated	260 186	179	69	80/115 (69.6)	48 (40–57)
Not vaccinated	146 366	375	256	174/194 (89.7)	230 (206–256)
Year of HZ diagnosis for vaccinated					
2005	33 964	21	62	11/15 (73.3)	45 (26–74)
2006	56 115	47	84	16/29 (55.2)	46 (30–68)
2007	59 652	51	85	27/34 (79.4)	68 (49–92)
2008	62 729	42	67	15/24 (62.5)	42 (27–61)
2009	47 725	18	38	11/13 (84.6)	32 (18–52)
Year of HZ diagnosis for unvaccinated					
2005	28 832	73	253	33/44 (75.0)	190 (143–247)
2006	39 699	108	272	51/55 (92.7)	252 (205–307)
2007	33 133	90	272	45/48 (93.8)	255 (203–315)
2008	27 460	65	237	32/32 (100)	237 (183–302)
2009	17 243	39	226	13/15 (86.7)	196 (136–274)
Age group					
1–2 y	37 898	40	106	25/32 (78.1)	82 (56–117)
3–9 y	149 809	85	57	38/56 (67.9)	39 (29–50)
10–17 y	209 993	429	204	191/221 (86.4)	177 (159–195)
Sex					
Male	207 661	264	127	120/155 (77.4)	98 (85–113)
Female	198 890	290	146	134/154 (87.0)	127 (112–144)
Immunosuppressed					
Yes	2281	9	395	4/5 (80.0)	316 (129–644)
No	404 271	545	135	250/305 (82.2)	111 (101–122)

Abbreviations: HZ, herpes zoster; KPNW, Kaiser Permanente Northwest; PCR, polymerase chain reaction; VZV, varicella zoster virus.

caused half of HZ cases among vaccinated children. A higher HZ incidence among vaccinated than unvaccinated 1- to 2-year-olds has not been previously reported. Our study also suggests that vaccine-strain and wild-type VZV may be recombining rarely in some subjects. PCP diagnosis of HZ was good overall, although less reliable in vaccinated subjects.

Our finding of a lower HZ incidence rate among vaccinated children is consistent with other population-based studies [4, 15] and is the first to demonstrate lower incidence in vaccinated children aged 10 and older. Civen et al described a 4- to 12-times lower HZ risk among vaccinated children aged <10 years compared to children with prior varicella [4]. In the same age group, Jumaan et al reported a 3-fold lower HZ risk among vaccinated vs unvaccinated children [15]. Another study indicated that varicella vaccine prevented HZ among HIV-infected children [16], a population group >15 times more likely than the general population to develop HZ [17].

The difference in HZ incidence between vaccinated and unvaccinated children probably underestimates the true difference in likelihood of VZV reactivation between the wild-type and vaccine VZV strains. Given the decline in varicella incidence reported during the first 10 years with routine varicella

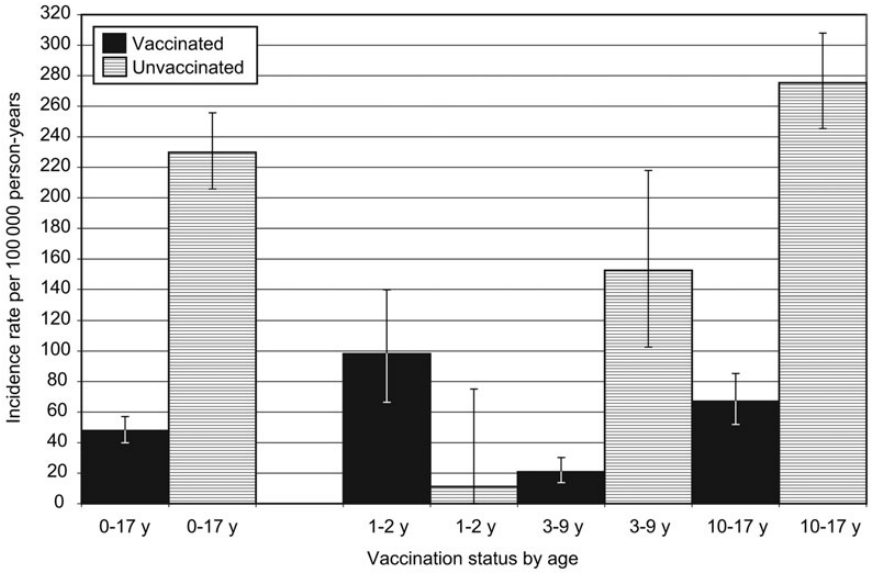

Figure 2. Herpes zoster incidence rates adjusted for laboratory confirmation rates by age and varicella vaccination status, persons aged 0–17 years, Kaiser Permanente Northwest, 2005–2009.

vaccination [3], many unvaccinated children, especially those <10 years old, likely had not had varicella and therefore were not at risk for HZ. Our reported HZ incidence rates among unvaccinated children would likely be higher if those with no history of varicella had been excluded [18, 19]. That half of cases in vaccinated children were due to wild-type VZV suggests that the incidence of vaccine-strain HZ is about half that reported here among vaccinated children.

Few studies have reported HZ incidence rates among individuals aged <20 years. In the absence of a varicella vaccination program, the reported incidence rates among 0- to 19-year-olds varied from 42 to 160 and 220 per 100 000 person-years in the United States [20], Iceland [1], and France [21], respectively. A reported rate among US 0- to 14-year-olds was 46 [18]. Our overall confirmation-adjusted HZ rate of 112 per 100 000 person-years is on the lower end of this range, suggesting no adverse effect of the varicella vaccination program on HZ epidemiology in children. More detailed comparison of rates across studies is challenging due to differing methodologies and differing likelihood of exposure to VZV in different time periods. Our study's confirmation-adjusted HZ incidence rate of 230 per 100 000 person-years among unvaccinated 0- to 17-year-olds is higher than these prevaccine-era rates; however, due to high vaccination levels in younger children at KPNW, this rate was calculated predominantly among adolescents who likely had natural varicella. This rate is similar to that described by Civen et al [4] among children aged <10 years with a history of varicella (238.5/10 000 person-years during 2000–2006) and the rate described in young adults aged 20–29 (258/100 000 person-years during 1947–1962) [22]. Our rate may also reflect relatively complete HZ ascertainment through use of EMR data and echoes the comparatively higher background HZ incidence previously described in this age group in 1997–2002 at KPNW [13].

The HZ incidence rates we report for 1- to 2-year-olds and 10- to 17-year-olds are similar to rates reported for 0- to 2-year-olds and adolescents in the previous study conducted at KPNW in the early years of the varicella vaccination program [13]. However, the incidence in our study for 3- to 9-year-olds is much lower than in the earlier study (39/100 000 vs 139–176/100 000 person-years). This decline in HZ incidence is coincident with increased varicella vaccine uptake in this age group and the decreased risk of HZ in vaccinated children.

Our finding of a higher incidence of HZ among vaccinated compared with unvaccinated 1- to 2-year-olds should be interpreted with caution. With high varicella vaccine coverage, more 1- to 2-year-olds are infected with vaccine-strain VZV than likely would have been infected with wild-type VZV. Almost all (92%) HZ cases in this age group were due to vaccine-strain VZV. In contrast, unvaccinated 1- to 2-year-olds are probably less likely to have been exposed to wild-type VZV than older age groups, so fewer would be at risk for HZ before the age of 3 years. Without an incidence rate for unvaccinated previously VZV-infected 1- to 2-year-olds, we cannot conclude that HZ incidence due to vaccine-strain VZV is higher among 1- to 2-year-old vaccinees than those infected with wild-type VZV. In contrast, the HZ incidence rates among unvaccinated children in the 3–9 and 10–17 age groups more likely reflect the rates among children with a history of varicella and were significantly higher than HZ rates among vaccinated children of the

same age. VZV infection before 1 year of age is a known risk factor for childhood HZ attributed to immaturity of the host's immune response [20, 23]. As the first dose of varicella vaccine is recommended at 12–15 months of age, there is potential for vaccine strain VZV reactivation in early childhood.

In our study and previous studies of unvaccinated children, a low proportion of children reported severe HZ [1, 18]. We found that this proportion did not differ by vaccination status. Several clinical features tended to be milder in vaccinated children; however, we did not find that the clinical presentation of HZ, including pain, was modified significantly by varicella vaccination or VZV type. This contrasts with a previous report that vaccinated children aged <10 years were less likely to report pain from HZ than unvaccinated children (45% vs 77%) or reported less intense pain [4]. However, interpretation of symptoms and severity is complicated by differences in age at time of the HZ episode and by age-dependent abilities to self-report symptoms.

Consistent with a previous report [4], we found that HZ rash among vaccinated children occurred more commonly in the dermatomes corresponding to the sites where the varicella vaccine was given (cervical and lumbar). The high concentration of vaccine virus infecting the nerves at the vaccination site may predispose to a lower threshold at that site for reactivation. Study subjects with wild-type HZ experienced rash predominantly in the thoracic dermatomes, consistent with reports from the pre-VZV-vaccine era [18]. Presence of latent vaccine-strain VZV in distant and bilateral dorsal root ganglia has been described, suggesting that in addition to axonal transport of VZV, postvaccination viremia may also occur [24].

We identified 2 virus isolates that, based on limited sequence analysis, could have resulted from recombination between vaccine-strain and wild-type VZV. Determining the complete genome sequence of these viruses was not possible. This intriguing possibility of recombination requires further investigation.

Our study has several limitations. Because this was a practice-based study, we may have missed milder HZ cases in patients for whom medical care was not sought or who were misdiagnosed. However, we likely had better-than-usual ascertainment in this insured population that theoretically had few barriers to seeking and receiving care. Acyclovir treatment could have confounded illness course observations. Although we collected data for 4.5 years, we studied a limited number of vaccinated subjects. Data on history of varicella were not available for the population incidence rate calculations. Prior knowledge of the patients' varicella vaccination status may have influenced HZ diagnosis by the PCP.

This population-based study provides more evidence that childhood varicella vaccination reduces HZ risk. HZ incidence due to vaccine-strain VZV was lower than that due to wild-type VZV. The potential for vaccine-strain VZV reactivation at younger ages and clinical characteristics of HZ among 1- and 2-dose varicella vaccine recipients remain important areas for research. Ongoing monitoring of HZ incidence will be critical for understanding the varicella vaccination program's impact on HZ epidemiology.

Notes

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