

Trends in Hospitalizations With Primary Varicella and Herpes Zoster During the Prevaricella and Initial Postvaricella and Herpes Zoster Vaccine Eras, Connecticut, 1994–2012

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Background. The introductions of the varicella vaccine in 1995 and herpes zoster (HZ) vaccine in 2006 have an ongoing potential to modify the epidemiology of both diseases. Analysis of data on hospitalizations can be conducted to examine trends in the occurrence of severe disease over time and to assess the possible impact of vaccination on the incidence of hospitalization.

Methods. Statewide hospital discharge data 1994–2012 in Connecticut were used to identify individuals discharged with a diagnosis of varicella and the initial admissions of persons with a discharge diagnosis of HZ in the first or second diagnostic position. Trends in overall age-standardized and age group-specific hospitalization rates for preselected time intervals before and after the introduction of vaccines were examined using Poisson regression models or Mantel–Haenszel χ^2 tests.

Results. Beginning in 2001, 5 years after the introduction of varicella vaccine, HZ hospitalization rates decreased significantly in individuals <15 years at an average rate of 19.4% per year through 2012. Among individuals ≥ 60 years, HZ hospitalization rates increased by 5.1% per year from 2001 to 2006 but decreased by 4.2% per year from 2007 to 2012. Primary varicella hospitalization rates declined 82.9% from the prevaccine era (1994–1995) to the 1-dose era (2001–2005) ($P < .001$). Rates further decreased significantly in the 2-dose era (2010–2012) among 5 to 9 year olds (100% decrease).

Conclusions. Varicella vaccine seems to have had an impact on both varicella and HZ hospitalizations, and introduction of the HZ vaccine may be having an impact on HZ hospitalizations.

Keywords. herpes zoster vaccination; hospitalizations/statistics and numerical data; shingles/epidemiology; varicella/epidemiology; varicella vaccination.

Over the past 2 decades, the Advisory Committee on Immunization Practices (ACIP) issued several recommendations for vaccination against primary varicella

and herpes zoster (HZ). In the year after varicella vaccine licensure in 1995, it was recommended that children aged 12–18 months receive 1 dose, that susceptible children aged 19 months–12 years receive a catch-up dose, and that susceptible individuals ≥ 13 years receive 2 doses [1]. However, after an initial sharp decline, the incidence of varicella leveled, outbreaks continued in schools, and there were concerns about waning immunity. In response, the ACIP revised its recommendation in 2006 to include (1) 2-dose vaccination of children, with the first dose administered at 12–15 months and the second at 4–6 years, and (2) catch-up vaccination with a second dose for individuals who previously received 1 dose [2]. After the licensure of the HZ vaccine (Zostavax) in 2006, the ACIP recommended that individuals ≥ 60 years be vaccinated with a single dose [3].

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Before 1995, it was estimated that 86.0% of US children 6–11 years old and 93.2% of 12–19 year olds were infected with varicella [4] and that 10%–30% of varicella-infected individuals would eventually develop HZ [5]. Varicella epidemiology has already changed markedly after the introduction of varicella vaccine. The incidence of varicella decreased sharply after the 1-dose recommendation and decreased again after the 2-dose recommendation [6–8]. At the start of the vaccination program, it was expected that the average age at infection would increase due to prevention of early exposure, but there was concern that this could result in higher severe morbidity because complications are more common with older age [9].

Both varicella and HZ vaccines are expected to modify the incidence of HZ. A long-term reduction in the incidence of HZ is anticipated due to fewer people becoming infected with wild varicella virus. Furthermore, there should be a reduction in incidence among adults aged 60 or older who receive the HZ vaccine. At the same time, it has been hypothesized that HZ incidence could increase due to a decrease in immune “boosting” that results from exposure of previously infected adults to naturally circulating varicella virus [10].

Although public health surveillance is being conducted to monitor the impact of varicella vaccine on varicella incidence, few if any state health departments conduct ongoing surveillance for HZ [6, 8]. Hospital discharge datasets provide an opportunity to monitor trends and possible vaccine impact at the severe end of the disease spectrum.

The epidemiology of primary varicella and HZ requiring hospitalization in the 10 years prior to the vaccine has been characterized in Connecticut [11]. However, to our knowledge, there are no reports from any state of trends in HZ hospitalizations focused on the possible impacts of both varicella and HZ vaccines, and there are no reports of the additional impact of the 2-dose schedule on varicella hospitalizations.

Data on hospitalizations in Connecticut were reviewed to (1) establish the epidemiology of varicella and HZ disease requiring hospitalization in the postvaccine eras and (2) assess the possible impact of vaccination recommendations on the incidence of hospitalizations with either disease.

METHODS

Data Sources

The Connecticut Department of Public Health Office of Health Care Access Acute Care Hospital Inpatient Discharge Database was used to identify hospitalizations due to primary varicella or HZ. The database contains discharge information on all persons hospitalized at any one of the 30 acute care hospitals in Connecticut.

Study Definitions

The discharge database was examined for the period January 1, 1994 through December 31, 2012. Cases were defined as any

individual admitted during this period who had a discharge code of 052.xx for primary varicella (in any one of the 10 diagnostic positions) or a discharge code of 053.xx for HZ (in either the first or second diagnostic position). All diagnostic positions were chosen for primary varicella so as to be inclusive of the small number of hospitalizations. HZ was limited to diagnoses in the first 2 positions to capture incident cases and not persons with HZ incidental to the primary reason for hospitalization. Patient records containing codes for both primary varicella and HZ were excluded from the analysis. For patients admitted multiple times to the same hospital, only the first hospitalization was included.

Trends in the epidemiology of primary varicella were examined from the prevaccine period to the 1-dose era to the 2-dose era. The prevaccine era was 1994–1995, before the licensure of varicella vaccine. The 1-dose era was 2001–2005, the period in Connecticut before the 2-dose recommendation when the incidence of varicella was low and stable [12]. The 2-dose era was 2010–2012, which allowed time for the 2-dose recommendation to be largely implemented and some impact to have occurred [13]. For impact of varicella vaccine on HZ in <60 year olds, 2 time periods were examined: 1994–2000, baseline period, and 2001–2012, the postvaricella vaccine period when high vaccination rates had been achieved. For possible impact of HZ vaccine, the prevaccine period was 2001–2006, the period with low and stable varicella circulation before the licensure of the HZ vaccine, and the postvaccine period was 2007–2012.

Demographic Data

Patient data available through the database included a unique patient identification, admission year, age, the principle diagnostic code and up to 9 secondary discharge diagnostic codes, and length of stay (LOS). The same method using discharge diagnosis codes was used to classify patients with underlying conditions as in an earlier Connecticut study [11], with the addition of several codes: 996.80-89, complications of organ transplant; V08, a new code for human immunodeficiency virus (HIV); V42.0-1 and V42.3-9, organ/tissue replaced by transplant; and V58.65, long term (current) use of steroids.

Statistical Analysis

Overall age-adjusted and age-specific hospitalization rates were calculated for each year using intercensal denominator data obtained from the US Census Bureau (years 1994–2011) and the annual Connecticut Department of Public Health population estimates (2012). Age-adjusted rates were standardized to the US 2000 standard million population. Age groups for HZ were 0–14, 15–29, 30–39, 40–49, 50–59, and ≥ 60 years. For several analyses including age-adjustment, the >60 group was divided into smaller age groups. For varicella, they were <1 year, 1–4, 5–9, 10–14, 15–19, 20–29, 30–39, 40–49, and ≥ 50 years.

For HZ, Poisson regression models were used to evaluate annual trends in age-specific hospitalization rates for those

Table 1. Reported Numbers of Herpes Zoster Hospitalizations and Rates, 1994–2000, 2001–2006, and 2007–2012

	1994–2000		2001–2006		2007–2012	
	No.	Hospitalization Rate per 100 000 Person-Years	No.	Hospitalization Rate per 100 000 Person-Years	No.	Hospitalization Rate per 100 000 Person-Years
Overall ^a	1482	5.9	1461	6.2	1748	6.7
Age group						
0–14	57	1.2	38	0.9	8	0.2
15–29	57	1.3	51	1.3	59	1.4
30–39	138	3.5	93	3.1	56	2.2
40–49	150	4.2	127	3.7	122	3.7
50–59	147	5.8	169	6.2	227	7.3
≥60	933	22.2	983	26.1	1276	30.2
60–79	551	16.7	498	17.4	585	18.0
≥80	382	42.7	485	54.0	691	71.3

^a Age-adjusted to US 2000 Standard Million population.

<60 years from 2001 through 2012, and for those ≥60 years from 2001 through 2006 and from 2007 through 2012. The Mantel–Haenszel χ^2 test for trend was used to evaluate changes in the proportion of HZ cases with underlying conditions in selected age groups within the above time periods. For primary varicella, changes in rates from 1994–1995 to 2001–2005 to 2010–2012 were examined by the Mantel–Haenszel χ^2 test for trend. The Mantel–Haenszel χ^2 test was also used to evaluate changes in the proportion of cases by underlying conditions.

All statistical analyses were done with SAS 9.3 or Epi Info 7. This study was approved by the Yale University School of Medicine and Connecticut Department of Public Health human investigation committees.

RESULTS

Herpes Zoster

Overall Hospitalization Rates

Over the 19-year study period, there were 14 089 hospital discharges for HZ. After excluding those with concurrent varicella and HZ diagnoses ($n = 72$), multiple admissions of the same person ($n = 2348$), and with tertiary or higher diagnostic codes ($n = 6976$), there were 4693 unique persons with HZ-related discharges. The overall average age-adjusted hospitalization rates across time periods steadily increased from the first to last of the 3 time periods (Table 1). Within 1994–2000, rates did not change significantly over time (Figure 1; [Supplementary](#)

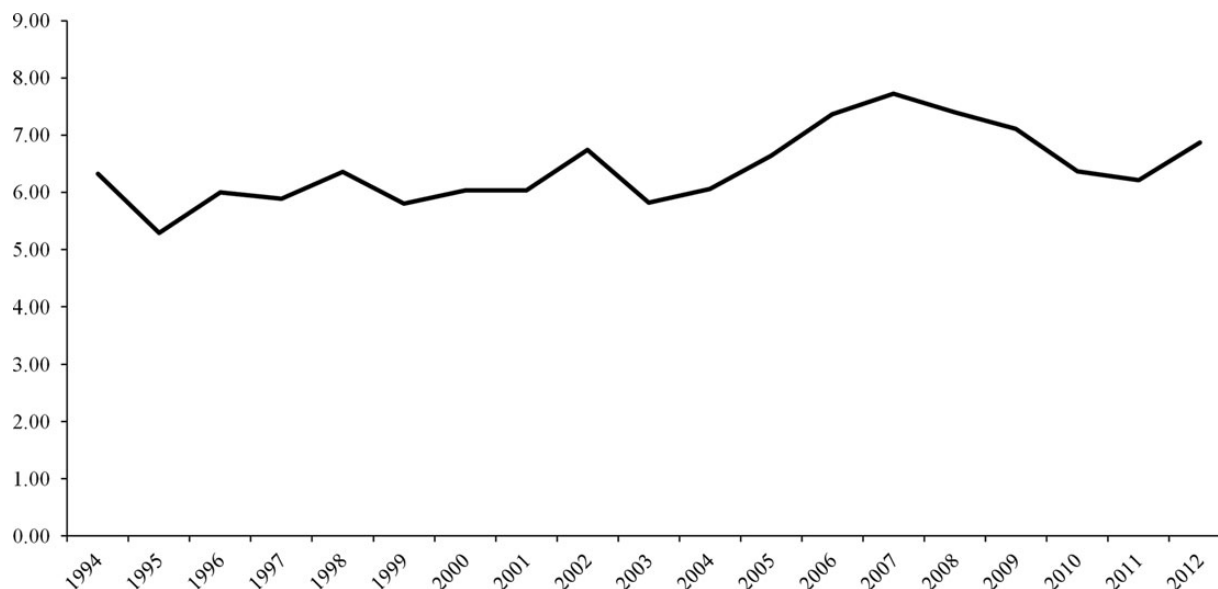


Figure 1. Age-standardized herpes zoster hospitalization rate per 100 000 population, 1994–2012.

Table 1). For the time period 2001–2006, there was a significant ($P < .05$) 4.4% per year average increase. Although the average rate for 2007–2012 was higher than 2001–2006, there was a significant decreasing trend averaging 2.2% per year despite an increase from 2011 to 2012 (Figure 1).

Age-Specific Hospitalization Rates

During 1994–2000, annual rates did not change significantly within any age group, except for a marginally significant decrease in the 40–49 age group ($P = .046$) (Supplementary Table 1).

During 2001–2012, only 2 age groups experienced a significant decrease in the annual hospitalization rate, with rates decreasing by 19.4% each year among 0–14 year olds and by 6.1% among 30–39 year olds (Figure 2; Supplementary Table 2a). The 19.4% annual decrease in 0–14 year olds was of the same magnitude for both those with an underlying condition (–19.8%) and those with no underlying conditions (–19.2%) (Supplementary Table 2b). When cases with an HIV diagnosis were

excluded, the measured drop in HZ incidence in 30–39 year olds disappeared.

For individuals ≥ 60 , there was a 5.1% increase in the hospitalization rate each year from 2001 to 2006 ($P = .03$) switching to a 4.2% annual decrease from 2007 to 2012 ($P < .01$) (Figure 2; Supplementary Tables 3 and 4). When an age-stratified analysis was performed using 5-year age groups to examine whether a specific age group was driving each trend, there was no difference between the rates at which each age group increased (Supplementary Table 3). However, for the 2007–2012 decrease, those 60–79 years had a more pronounced decrease (5.8% per year, $P = .013$) than those ≥ 80 (1.8% per year, $P = .42$) (Supplementary Table 4).

We performed several analyses to assess the robustness of our findings. None of these trends were changed when the excluded 6000+ persons with discharge HZ diagnoses in the 3rd or later positions were included, nor if we limited cases to persons with a primary discharge diagnosis of HZ. We also considered that admission criteria might have changed. If less severe cases were being admitted, we would expect there to be more short-term hospitalization. There were no changes in median LOS (4 days) during 2001–2012 in those 0–14 years or during 2001–2006 or 2007–2012 in those ≥ 60 years.

Underlying Conditions

Overall, the proportion of cases with an underlying condition decreased from 29.8% in the prevaccine era to 23.3% in 2001–2006 to 19.7% in 2007–2012 ($P < .001$) (Table 2).

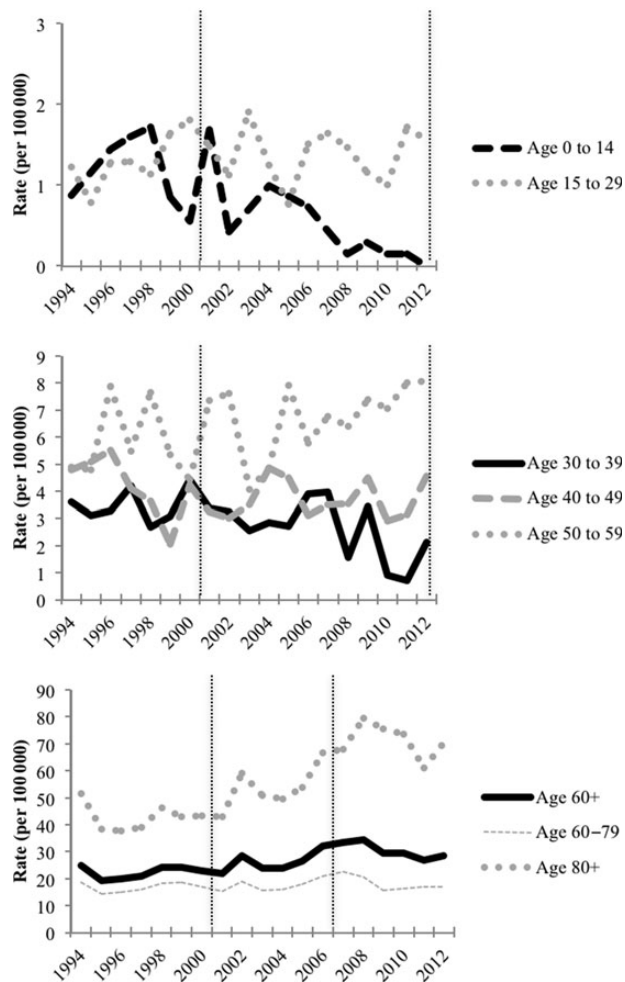


Figure 2. Herpes zoster hospitalization rate (per 100 000 population), by age group, 1994–2012.

Table 2. Percentage of Hospitalized Herpes Zoster Cases With an Underlying Condition Including and Excluding Human Immunodeficiency Virus (HIV)

Age	1994–1995	2001–2006	2007–2012	P Value*
Including HIV				
Overall	29.8	23.3	19.7	<.001
Age group				
0–14	42.9	31.6	37.5	.686
15–29	76.9	37.3	32.2	.014
30–39	69.2	59.1	42.9	.009
40–49	60.4	51.2	34.4	<.001
50–59	21.9	33.1	33.5	.354
60+	16.4	13.5	14.1	.609
Excluding HIV				
Overall	20.1	17.5	16.2	.073
Age group				
0–14	38.5	27.8	28.6	.564
15–29	50.0	27.3	20.0	.129
30–39	33.3	34.5	25.6	.424
40–49	32.1	27.9	18.4	.071
50–59	19.4	26.6	25.6	.700
60+	16.4	13.4	14.0	.587

* Mantel-Haenszel χ^2 test for trend.

Table 3. Reported Numbers of Primary Varicella Hospitalizations and Rates, 1994–1995, 2001–2005, and 2010–2012

Age	1994–1995		2001–2005		2010–2012		Rate Difference ^a	
	No. (%)	Hospitalization Rate per 100 000 Person-Years	No. (%)	Hospitalization Rate per 100 000 Person-Years	No. (%)	Hospitalization Rate per 100 000 Person-Years	2001–2005 vs 1994–1995	2010–2012 vs 2001–2005
Overall ^b	324	4.8	145	0.8	79	0.7	–4.0***	–0.1
Age group								
<1	30 (9.3)	33.7	9 (6.2)	4.3	4 (5.1)	3.6	–29.4***	–0.7
1–4	78 (24.1)	20.5	12 (8.3)	1.4	4 (5.1)	0.8	–19.1***	–0.5
5–9	55 (17.0)	11.6	11 (7.6)	0.9	0 (0.0)	0.0	–10.7***	–0.9*
10–14	7 (2.2)	1.6	4 (2.8)	0.3	2 (2.5)	0.3	–1.3**	0.0
15–19	12 (3.7)	3.0	12 (8.3)	1.0	5 (6.3)	0.7	–2.0**	–0.4
20–29	60 (18.5)	6.7	13 (9.0)	0.7	8 (10.1)	0.6	–6.1***	–0.1
30–39	49 (15.1)	4.2	24 (16.6)	1.0	13 (16.5)	1.0	–3.3***	0.1
40–49	14 (4.3)	1.4	20 (13.8)	0.7	13 (16.5)	0.8	–0.7*	0.1
≥50	19 (5.9)	1.0	40 (27.6)	0.7	30 (38.0)	0.8	–0.3	0.1

^a Mantel–Haenszel χ^2 test for trend.

^b Age-adjusted to US 2000 Standard Million population.

* $P < .05$.

** $P < .01$.

*** $P < .001$.

When the time periods 2001–2006 and 2007–2012 were examined for changes in the annual proportion of cases with an underlying condition among those ≥ 60 years, no significant trends were observed (Supplementary Tables 5 and 6).

Primary Varicella

Overall Hospitalization Rate

Over the 19-year study period, there were 1181 hospital discharges for primary varicella. After excluding those with concurrent varicella and HZ diagnoses ($n = 72$) and multiple admissions of the same person ($n = 35$), there were 1074 unique persons with primary varicella-related discharges. There was an annual average of 4.9 hospitalizations/100 000 person-years in the prevaccine era, 0.8 hospitalizations/100 000 person-years in the 1-dose era, and 0.7 hospitalizations/100 000 person-years in the 2-dose era (Table 3). Hospitalization rates declined 82.9% from the prevaccine to the 1-dose era ($P < .001$). The additional 11.9% decrease from the 1-dose to the 2-dose era was not statistically significant.

Age-Specific Hospitalization Rates

Hospitalization rates declined significantly within each age group except those ≥ 50 years from the prevaccine to the 1-dose era, with the largest declines ($\sim 90\%$ each) seen among the 3 youngest age groups (Table 3). Only the 5–9 year age group experienced a significant (100%, $P = .013$) decline from the 1-dose to the 2-dose era.

Proportion of Cases by Age

In the prevaccine era, individuals < 10 years made up 50% of the hospitalizations. By 2001–2005, they made up

$\sim 20\%$ and by 2010–2012 they made up $\sim 10\%$, with none in children aged 5–9 (Table 3).

Underlying Conditions

The overall prevalence of having at least 1 underlying condition was 30.5% and did not change during the 3 time periods (Supplementary Table 7).

DISCUSSION

We found that hospitalizations with varicella and with HZ declined in recent years, with the decline related in time to the introduction and widespread use of varicella vaccine. In addition, we found varicella hospitalizations further declined after 2006 in the target vaccination age group after the switch from the 1-dose to the 2-dose varicella vaccine recommendation. We also found that HZ rates declined after the introduction of HZ vaccine. These findings suggest that ongoing surveillance for HZ will be important and that more aggressive use of the HZ vaccine could be beneficial.

We detected a significant decrease in the HZ hospitalization rate in 2 age groups (0–14 and 30–39) from 2001 to 2012. There are at least 2 possible explanations for these findings: (1) a vaccine-induced reduction in the number of persons with latent wild varicella infection, and (2) a reduction in the prevalence of underlying conditions that are associated with a higher risk of HZ. The reduction in varicella incidence since the introduction of the vaccine is likely to be the major cause of the lowered HZ hospitalization rates in 0–14 year olds. Children with and

without underlying conditions experienced a marked decline in the hospitalization rate from 2001 to 2012. However, both age groups had significant decreases in the proportion of cases with an underlying condition that was partially explained by a decrease in the proportion with HIV. It is possible that the decline in HIV perinatal transmission since the 1990s and increasing use of highly active antiretroviral therapy may explain some of the decrease among 0–14 year olds and most of the decrease in 30–39 year olds [14].

This study adds to and extends 2 earlier studies that found reduced rates of HZ among age groups who were mostly infected with the vaccine strain rather than wild strains of varicella vaccine. A population-based HZ incidence study in California found a 55% reduction in HZ in children <10 years old from 2000 to 2006 [15]. A study of HZ hospitalizations using the Nationwide Inpatient Sample from 1993–2004 found that HZ rates “trended down” from 2001 to 2004 in children <10 years [16]. It seems that highly vaccinated cohorts will experience a much lower rate of HZ than cohorts who were infected with wild varicella virus [17]. Nonetheless, continued monitoring of HZ incidence trends in highly vaccinated age groups and study of cohorts of vaccinated children experiencing breakthrough varicella are needed to determine the long-term risk of HZ.

In contrast to the trend observed in 0–14 year olds, we detected a significant increase in the overall HZ hospitalization rate from 2001 to 2006, driven almost entirely by increases in the ≥ 60 age group from 2001 to 2006, followed by a decrease in this age group from 2007 to 2012. This increase could not be explained by an increase in the proportion of cases with underlying conditions or a reduction in the threshold for admitting persons with HZ to the hospital as measured by LOS. Most studies in the United States looking at HZ trends since the introduction of varicella vaccine have found increases in HZ incidence or hospitalizations [15, 16, 18–21]. Although increases in the elderly have been prominent, others have found increases in younger age groups as well, something we were unable to confirm [15, 16, 18–20]. In addition, although we and another hospitalization study [16] were only able to document clear increases since 2001, the 2 other studies examining timing, both using insurance claims data, found increases beginning before varicella vaccine was introduced [18, 21]. The other studies did not examine trends before the widespread use of varicella vaccine [15, 19, 20]. Although the potential for waning immunity from lack of boosting by varicella exposure has been offered as at least a partial possible explanation for the recent increases in HZ [16, 19, 20], others have noted secular trends toward an increase independently of varicella vaccination [15, 18]. Furthermore, it is implausible that waning immunity due to lack of exposure to varicella would mainly affect the elderly, most of whom have much less contact with children with chickenpox than younger adults [22].

Our study is the first to separate out the time period since the introduction of HZ vaccine and examine HZ trends within it.

The decrease in HZ hospitalization rates from 2007 to 2012 could not be explained by a reduction in the proportion of cases with an underlying condition and is consistent with increasing vaccine impact. The only study of HZ incidence that includes this time period did not specifically examine trends since 2007, but figures included in it show a similar decrease after a previously increasing trend in incidence [21]. Nonetheless, HZ vaccine impact can only explain a fraction of the reduction. Assuming that the increasing incidence during 2001–2006 in those ≥ 60 would have continued at the same 5.1% per year rate, there was a net reduction of 46.5% from 2007 to 2012. National HZ vaccine coverage data indicate that vaccine uptake among the ≥ 60 age group by 2012 was only 20.1% [23]. Other hypotheses for the observed decrease include decreasing prevalence of underlying conditions (eg, use of immunosuppressive therapy) and higher thresholds for hospital admission to treat HZ. Additional studies are needed to determine whether this recent trend toward a decrease (1) is being seen elsewhere, (2) is sustained, and (3) follows continuing increases in HZ vaccine utilization. Studies are also needed to explore reasons for the increases in HZ admissions from 2001 to 2006 and to explore alternative hypotheses for the reduction in HZ admissions since then.

We found a significant decrease in primary varicella hospitalization rates in the 1-dose vaccine era compared with the prevaccine era across all age groups, and we found a significant change among those 5–9 from the 1-dose to the 2-dose era. Only 1 other study has examined the impact of 2-dose vaccination on hospitalization rates, and that study found a >40% overall decrease in varicella-related hospitalizations from the 1-dose era (2002–2005) to the 2-dose era (2006–2010), a decrease from 18 to 10 cases, none of whom were vaccinated [6]. Similar to our study, most hospitalizations were in those ≥ 20 years. The much smaller initial decrease in varicella hospitalizations after the implementation of the 2-dose recommendation compared with the 1-dose recommendation likely reflects the currently low levels of varicella circulation. When varicella vaccine was initially introduced, substantial herd immunity resulted with benefits of reduced incidence of hospitalizations and deaths in all age groups [24]. Added herd immunity after the 2-dose recommendation seems to be mainly in those of school-age with reduced number of school outbreaks and reduced incidence mainly in children thus far [6, 25].

The analysis of this study has a number of limitations. First, the ICD-9 coding that was used for case ascertainment was not validated. Thus, it was not possible to distinguish between hospitalizations due to primary varicella or HZ infection incidental to the primary reason for hospitalization versus hospitalizations where primary varicella or HZ infection was the primary reason for hospitalization. This could lead to an overestimate of the hospitalization rates for each disease [26]. For HZ, we attempted to minimize this bias by using only the first or second diagnostic

position to identify cases, counting only the initial admission to a given hospital and focusing our analysis on trends rather than absolute rates. Second, our data examine hospitalizations only, and inferences should not be made to trends in outpatient HZ or varicella zoster virus. Hospitalizations represent only a small percentage (<3%) of each infection. Third, we were unable to fully measure all underlying conditions that might increase the risk of HZ hospitalization and their trends, particularly the use of various newer forms of immunosuppressive therapy. Slight modifications in the rate at which HZ cases are admitted, whether from changes in the prevalence of underlying conditions or changes in access to healthcare, could contribute to and even be responsible for the trends seen. Fourth, no information on patient vaccination history was obtained, so it is not possible to directly attribute changes in hospitalization rates to each of the vaccines. Finally, the timing of this evaluation of possible decreases in HZ hospitalizations in older age groups as a result of HZ vaccine and in younger age groups as a result of decreased infection prevalence with wild varicella virus is too soon to see their full possible effects. National HZ vaccination coverage during the study period was low, and the first birth cohorts to have mostly experienced varicella vaccination instead of chickenpox are children born in the late 1990s, ie, <20 years ago. Larger decreases in HZ hospitalization should occur with increased HZ vaccination rates and as the 1990s' birth cohorts age and new highly vaccinated birth cohorts are added.

CONCLUSIONS

In summary, this study reports on changes in the epidemiology of primary varicella and HZ disease requiring hospitalization. Findings from this study add to the body of evidence documenting high vaccine impact on primary varicella and a recent increase in HZ morbidity among the oldest age groups. This study also provides evidence of varicella vaccine impact on HZ hospitalizations among individuals under the age of 15 years, as well as suggestive evidence of HZ vaccine impact on hospitalizations in individuals aged ≥ 60 years. These findings support current recommendations for use of both vaccines and suggest that higher coverage with HZ vaccine will have a measurable impact on the number of hospitalizations for HZ. Long-term monitoring is needed to assess whether the recent reductions in HZ hospitalizations continue over time. Periodic analysis of hospital discharge data can complement other monitoring methods to accomplish this purpose.

Supplementary Material

Supplementary material is available online at *Open Forum Infectious Diseases* (<http://OpenForumInfectiousDiseases.oxfordjournals.org/>).

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