



Trends in U.S. Community hospitalizations due to herpes zoster: 2001–2015



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ARTICLE INFO

Article history:

Received 27 August 2018

Received in revised form 11 December 2018

Accepted 17 December 2018

Available online 4 January 2019

Keywords:

Epidemiology

Herpes zoster

Varicella

Trends

Nationwide inpatient sample

Policy

Hospitalization

ABSTRACT

Background: In 2007, based on decisions by the U.S. Advisory Committee on Immunization Practices, the CDC recommended a booster dose at 4–6 years in the varicella vaccine schedule. In 2008, a herpes zoster vaccine was recommended for use in persons age ≥ 60 years. The purpose of this study was to examine trends in herpes zoster hospitalization rates and assess the impact of both policy recommendations using U.S. hospital discharge data.

Methods: Nationwide Inpatient Sample discharge data from 2001 to 2015 were used to identify primary or secondary herpes zoster diagnoses. Trends in annual total and age-specific herpes zoster hospitalization rates and average length of stay were examined. Average annual rates for the pre (2001–2005) and post (2012–2015)-zoster vaccine policy eras were compared. Absolute change in herpes zoster hospitalizations were calculated.

Results: The rate difference of U.S. herpes zoster hospitalizations in the post vs. pre-zoster vaccine policy era was -1.9 per 100,000 population (6,200 fewer hospitalizations in 2015 than expected). Key age group rate differences: 0–3 years (-0.4 per 100,000; 50 fewer), 4–6 years (-0.6 per 100,000; 50 fewer), 7–14 years (-1.3 per 100,000; 400 fewer), 50–59 years (0.7 per 100,000; 300 more), 60–69 years (-2.5 per 100,000; 900 fewer), 70–79 years (-10.2 per 100,000; 2,000 fewer), 80+ years (-29.9 per 100,000; 3,600 fewer).

Conclusions: Reduction of wild-type varicella due to the 2-dose varicella vaccination recommendation may have impacted declining herpes zoster hospitalization rates among children ≤ 14 years. The 2008 herpes zoster vaccine may have impacted declining herpes zoster hospitalization rates for adults age ≥ 60 years despite vaccination coverage $< 31\%$ by 2015.

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1. Introduction

Since the licensure of the varicella vaccine in 1995, the Advisory Committee on Immunization Practices (ACIP) has issued multiple recommendations which have the potential to dramatically alter the epidemiology of herpes zoster in the United States. In 2005, the ACIP updated its varicella vaccination recommendation to include a routine second dose for children aged 4–6 years, and in 2006, a single-dose live, attenuated vaccine for the prevention of herpes zoster was recommended for use in individuals ≥ 60 years (51.3% clinical efficacy) [1,2]. The 2-dose varicella and single-dose live, attenuated herpes zoster vaccine recommendations were

officially recommended by the Centers for Disease Control in 2007 and 2008 respectively. Approximately 99.5% of the US population aged ≥ 40 years has serologic evidence of previous varicella infection and are therefore at risk for developing herpes zoster [3,4]. Of these people, approximately 30% are estimated to develop herpes zoster at some point during their lifetime, resulting in an estimated 1 million cases in the U.S. each year [5].

Currently, there are limited published studies on the effects of the two-dose varicella and single-dose herpes zoster vaccine recommendations on herpes zoster incidence in the U.S. With implementation of these ACIP recommendations, herpes zoster incidence in the U.S. could potentially decrease in the long term. However, it is also hypothesized that a decrease in wild-type varicella among vaccinated children could potentially increase herpes zoster incidence among adults who would have fewer exogenous wild-type varicella exposures that may bolster immunity [3].

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Although public health surveillance is routinely conducted to monitor varicella incidence, herpes zoster is not a reportable condition and few states maintain active surveillance for the disease.

To our knowledge, there are no reports on U.S. national trends in herpes zoster hospitalizations following the 2007/2008 ACIP recommendations on the varicella and herpes zoster vaccine schedules, and with the advent of a more clinically effective two-dose recombinant sub-unit herpes zoster vaccine (October 2017) [6], it is important to examine how herpes zoster epidemiology has changed with the implementation of these recommendations. Thus, we analyzed U.S. national data on herpes zoster hospitalizations to determine: (1) changes in the rate of herpes zoster hospitalization following the 2007/2008 ACIP recommendations and (2) changes in length of hospital stay associated with herpes zoster as a measure of disease severity.

2. Methods

2.1. Data sources

The Nationwide Inpatient Sample (NIS), maintained by the Agency for Healthcare Research and Quality, contains annual discharge data for a 20% sample of U.S. hospitals. The NIS is the largest publicly available all-payer inpatient care database in the U.S., containing approximately 8 million hospitalizations annually. The primary sampling units of the NIS are community hospitals, and sampling probabilities are proportional to the size of each cluster. The NIS sampling framework has expanded every year since its inception. Thus, stratification and weighting variables enable calculation of national estimates and trends while accounting for the complex sampling design and expanding sampling framework. We analyzed NIS data from 2001 to 2015 during which the sampling frame expanded from covering 81% to over 97% of the U.S. population within 46 states. Discharge diagnoses are coded with the use of the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) or ICD-10-CM with the first-listed diagnosis designated as the primary diagnosis.

2.2. Definition of hospitalization for herpes zoster

Herpes zoster-associated hospitalization was defined by a first or second discharge diagnosis indicated with specific ICD-9-CM or ICD-10-CM codes (Supplementary Table S1). Cases with a primary diagnosis of postherpetic trigeminal neuralgia or postherpetic polyneuropathy were not included (2.95% of all herpes zoster cases) because of their increased potential to represent long-term follow-up for prior herpes zoster episodes. Because the NIS contains only discharge data, hospital admission dates were determined from admission month, length of hospital stay, and year of discharge.

2.3. Data analysis

This study was approved by the Emory University IRB. Data analyses were performed using SAS 9.4 (Cary, NC USA) and Epi Info 7. NIS data from 2001 to 2015 were used to estimate the annual number of herpes zoster hospitalizations among ten age groups (0–3, 4–6, 7–14, 15–29, 30–39, 40–49, 50–59, 60–69, 70–79, and ≥ 80 years). Annual total and age-specific rates of herpes zoster hospitalization in the U.S. were determined by dividing the weighted counts of herpes zoster hospitalizations by the total U.S. populations as determined by the U.S. census bureau.

We calculated annual rates of herpes zoster hospitalization for all years during the study period and estimated average annual rates for two periods: 2001–2005 (pre-zoster vaccine policy) and

2012–2015 (post-zoster vaccine policy). The variance of the average annual rates for both periods was the sum of each year's variance divided by the number of years squared. The single-dose live-attenuated herpes zoster vaccine was licensed in the United States on May 25, 2006. However, due to manufacturing issues, there was a vaccine supply shortage lasting until around 2012 [7]. Therefore, we treated 2006–2011 as a transition period which was not included in grouped pre/post vaccine policy comparison analyses. Age-specific rate differences and absolute changes in herpes zoster hospitalizations between pre and post licensure periods were calculated to evaluate the early impact of the 2007/2008 ACIP varicella and herpes zoster policy recommendations. The variance of the rate difference was the sum of the variances in the pre/post average rates. Estimates for the overall rate difference and absolute change in hospitalizations were standardized to the U.S. population age distribution in 2015. Changes in the rates from the pre vs. post-zoster vaccine policy eras were examined by Mantel-Haenszel χ^2 test for trend.

3. Results

There were 400,651 herpes zoster hospitalizations from 2001 to 2015 which accounted for 0.07% of all U.S. hospitalizations during the study period. The proportion of herpes zoster hospitalizations among all hospitalizations within each age group were 0.07% among ages 7–14, 0.06% among ages 40–49, 0.07% among ages 50–59, 0.09% among ages 60–69, 0.12% among ages 70–79, 0.16% among ages 80+, and less than 0.05% among all other groups. Overall, the number of herpes zoster hospitalizations increased with increasing age.

The annual incidence rate of herpes zoster hospitalizations in the U.S. was 8.6 per 100,000 population during 2001 and decreased to 6.8 per 100,000 population during 2015 (Fig. 1A). The highest peak rates of herpes zoster hospitalization were among those aged 80+ years at approximately 115 per 100,000 population, followed by approximately 45 per 100,000 population for ages 70–79, approximately 17 per 100,000 population for ages 60–69, and approximately 9 per 100,000 population for ages 50–59. All other age groups had peak hospitalization rates lower than 6 per 100,000 population. Despite steady increases from 2001 to 2008, the overall rate of herpes zoster hospitalizations decreased significantly between 2001 and 2015. The largest decreases in herpes zoster hospitalization rates between 2001 and 2015 occurred among groups directly targeted by the 2007/2008 ACIP vaccine policy decisions (4–6 and 60+ years), the 0–3 years group, and the 7–14 years group while the 15–29, 40–49, and 50–59 years age groups increased in rate (Fig. 2A & B, Table 1).

The overall, age-adjusted average annual change in hospital rates from the pre vs. post herpes zoster vaccine period was 1.9 fewer hospitalizations per 100,000 population ($p < 0.001$), which translates to approximately 6,200 fewer herpes zoster hospitalizations in 2015 in the U.S. than would have been expected if the rates had remained unchanged from those in the pre-zoster vaccine policy period. Within the different age groups, the 80+ years group had a reduction of 29.9 per 100,000 population ($p < 0.001$) which translated into 3,600 fewer herpes zoster hospitalizations, the 70–79 years group had a reduction of 10.2 per 100,000 population ($p < 0.001$) or 2,000 fewer herpes zoster hospitalizations, the 60–69 years group had a reduction of 2.5 per 100,000 population ($p < 0.001$) or 800 fewer herpes zoster hospitalizations, the 30–39 years group had a reduction of 0.2 per 100,000 population ($p < 0.05$) or 100 fewer hospitalizations, the 7–14 years group had a reduction of 1.3 per 100,000 population ($p < 0.001$) or 400 fewer herpes zoster hospitalizations, the 4–6 years group had a reduction of 0.6 per 100,000 population ($p < 0.001$) or 50 fewer

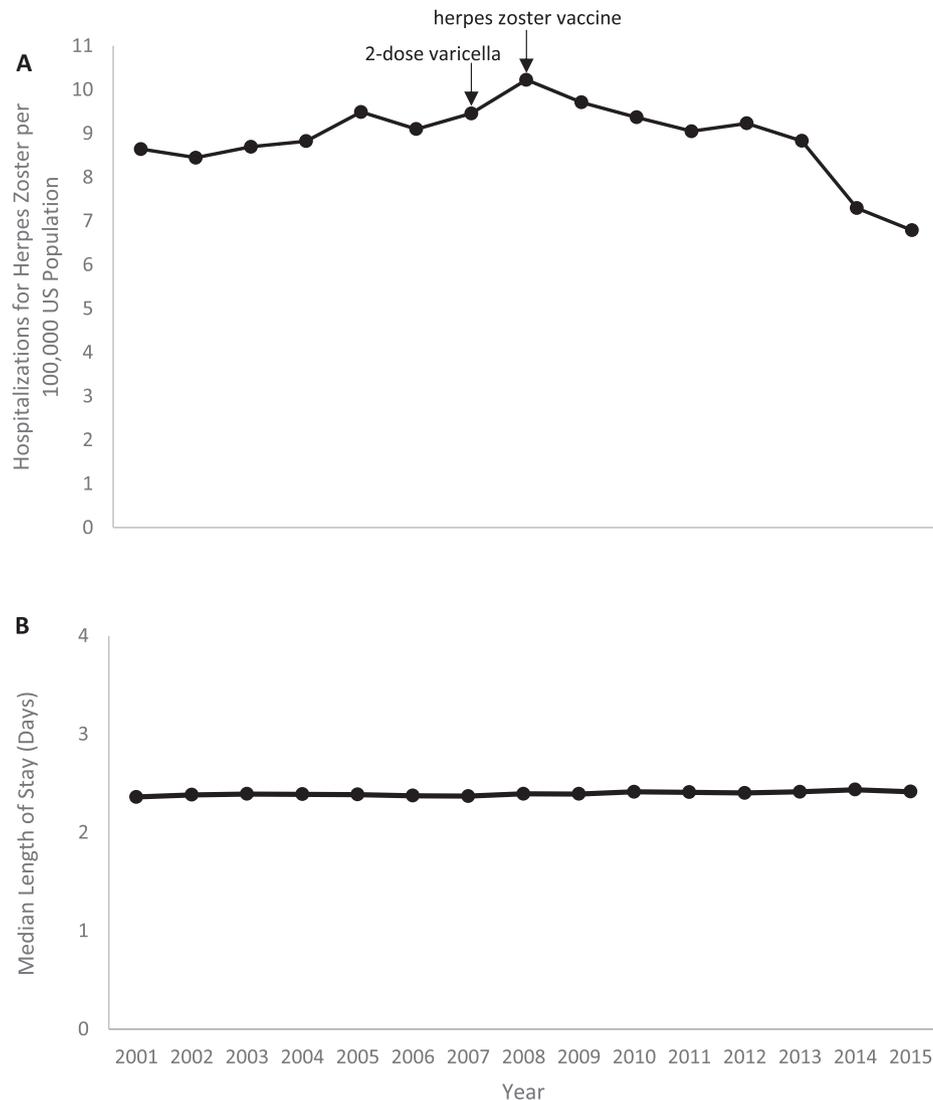


Fig. 1. Annual Hospitalization Rate and Median Length of Hospital Stay for Herpes Zoster in the U.S. from 2001 to 2015. Panel A shows annual hospitalizations for herpes zoster. Panel B shows median length of hospital stay for herpes zoster. * Arrow indicates the year of varicella or herpes zoster vaccine policy events.

herpes zoster hospitalizations, and the 0–3 years group had a reduction of 0.4 per 100,000 population ($p < 0.001$) or 50 fewer herpes zoster hospitalizations. The 50–59 years group had an increase of 0.7 per 100,000 population ($p < 0.001$) or 300 more herpes zoster hospitalizations, the 40–49 years group had an increase of 0.2 per 100,000 population ($p < 0.05$) or 50 more herpes zoster hospitalizations, and the 15–29 years group had an increase of 0.2 per 100,000 population ($p < 0.001$) or 100 more herpes zoster hospitalizations (Table 1).

We performed multiple analyses to assess the robustness of our findings. There were approximately 1,200,000 discharges excluded due to a herpes zoster diagnosis in the third or later diagnosis position. However, the observed trends did not change when these discharges were included in analysis. Additionally, in order to determine if changes in herpes zoster hospitalization rate could be determined by overall changes in all cause hospitalization, we adjusted herpes zoster hospitalization frequency by percent change in all cause hospitalization from 2001. When the herpes zoster hospitalization frequencies were adjusted, the overall trends did not disappear (Supplementary Fig. 1). Finally, there was no change in the overall median length of stay for herpes zoster hospitalizations from 2001 to 2015 (Fig. 1B). Generally, older age

groups had higher median lengths of stay than younger age groups, ranging from 1.6 days for ages 0–3 to 3.8 days for ages 80+ (Fig. 2C & Supplementary Table S2).

4. Discussion

In 1995, the ACIP recommended routine varicella vaccination of children aged 12–18 months with catch-up vaccinations recommended for children aged 19 months to 12 years who do not have detectable varicella-specific antibody titers [8]. This varicella vaccination program led to substantial declines in morbidity and mortality. By 2000, cases in active varicella surveillance sites had declined by 71–84% [9]. Varicella hospitalization rates during 1993–2001 declined by 75% [10]. And from 1990 to 2001, the average age-adjusted mortality rate due to varicella dropped by 59% with age-specific mortality rate reductions as high as 92% [11]. However, despite these decreases in morbidity and mortality, incidence of breakthrough varicella among vaccinated children and outbreaks of varicella continued to occur even in areas with high vaccination coverage [1,2]. Thus, in 2005, the ACIP updated its varicella vaccine recommendations to include a scheduled second dose for children aged 4–6 years, catch-up vaccination for all people

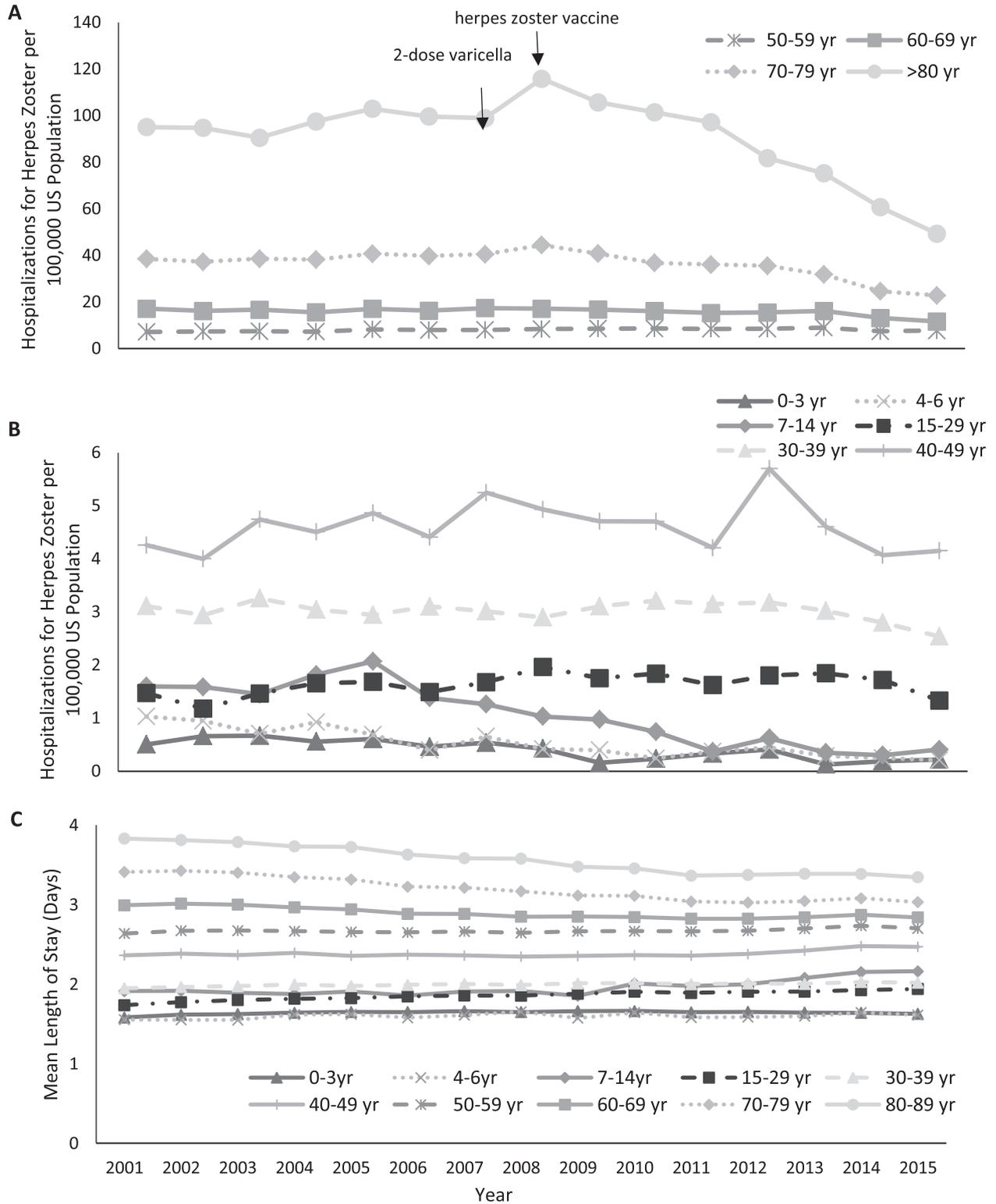


Fig. 2. Average Annual Hospitalizations and Median Length of Hospital Stay for herpes zoster in the U.S. by Age Group, from 2001 to 2015. Panel A shows annual hospitalizations for herpes zoster in the 50–59, 60–69, 70–79, >80 age groups. Panel B shows annual hospitalizations for herpes zoster in the 0–14, 15–29, 30–39, and 40–49 age groups. Panel C shows median length of hospital stay for herpes zoster across all age groups. * Arrow indicates the year of varicella or herpes zoster vaccine policy events.

who only received one dose, and school entry vaccination requirements for all grade levels [1]. In a post-licensure clinical trial comparing the efficacy of the one and two-dose varicella regimens over a 10 year period, the estimated vaccine efficacy for the one dose regimen was significantly lower than the two dose regimen ($p < 0.001$) at 94.4% versus 98.3% [12].

In 2006, a single-dose live, attenuated vaccine for the prevention of herpes zoster was licensed by the Food and Drug Administration and soon after recommended by the ACIP for use in individuals ≥ 60 years [3]. Among the targeted age group, clinical vaccine efficacy of the live-attenuated herpes zoster vaccine ranged from 39.6% [13] to 51.3% [14]. Later, in 2017, a two-dose

Table 1
Differences in rates of hospitalization for herpes zoster before (2001–2005) and after (2012–2015) the 2007/2008 varicella and herpes zoster vaccine policy recommendations.

Age	U.S. population, 2015 Millions	Differences in hospitalization rates per 100,000 population, 2001–2005 vs. 2012–2015 ^A No. (95% CI)	Percent change in hospitalizations, 2001–2005 vs 2012–2015	Estimated Absolute change in hospitalizations in 2015
			% (95% CI)	No. (95% CI)
0–3	15.9	−0.4** (−0.6, −0.1)	−60.2 (−95.9, −24.5)	−50 (−91.6, −23.3)
4–6	12.1	−0.6** (−0.9, −0.3)	−65.4 (−100.1, −30.7)	−50 (−100, −50)
7–14	33.1	−1.3** (−1.6, −0.9)	−75.3 (−96.3, −54.3)	−400 (−550, 300)
15–29	66.2	0.2** (0.0, 0.4)	12.0 (−7.5, 31.5)	100 (−50, 300)
30–39	41.9	−0.2* (−0.7, 0.3)	−5.9 (−21.3, 9.5)	−100 (−250, 100)
40–49	41.0	0.2* (−0.4, 0.8)	3.6 (−10.0, 17.2)	50 (−200, 300)
50–59	44.1	0.7** (−0.2, 1.5)	8.7 (−2.4, 19.8)	300 (−100, 650)
60–69	35.1	−2.5** (−3.9, −1.1)	−15.1 (−23.3, −6.9)	−900 (−1350, −400)
70–79	19.6	−10.2** (−12.9, −7.5)	−26.4 (−33.4, −19.3)	−2000 (−2550, −1450)
80+	12.1	−29.9** (−36.3, −23.6)	−31.1 (−37.7, −24.6)	−3600 (−4350, −2850)
All age groups ^B	321.1	−1.9** (−3.5, −0.4)	−18.7 (−33.6, −3.9)	−6200 (−11150, −1300)

^A Mantel-Haenszel χ^2 test for trend.

^B Standardized estimates to the age-group distribution of the 2015 U.S. population.

* $p < 0.05$.

** $p < 0.001$.

recombinant sub-unit herpes zoster vaccine with higher clinical efficacy (>90%) was licensed for use in individuals ≥ 50 years [15]. Thus, the ACIP decided to recommend the use of the new sub-unit vaccine in adults aged ≥ 50 years while the live, attenuated vaccine can be used in adults aged ≥ 60 years.

Over the course of the study period, overall herpes zoster hospitalization incidence increased steadily from 2001 to 2008 then declined steadily from 2009 to 2015, and thus overall herpes zoster hospitalization incidence in the post-herpes zoster vaccine era declined significantly when compared to the pre-herpes zoster vaccine era. Changes in overall annual herpes zoster hospitalizations were primarily driven by the 80+ years age group which contained the majority of yearly cases. By 2015, age groups that were targeted by the 2007/2008 ACIP varicella and herpes zoster vaccine policy recommendations (4–6 and 60+ years) as well as the 0–3 and 7–14 years groups had significant declines in herpes zoster hospitalization rate, while all other groups either increased or did not change significantly.

Though the ACIP recommendations were made in 2007 and 2008, the herpes zoster hospitalization rate continued to increase steadily through 2008. A possible explanation for these increases is that the target population received fewer exogenous varicella exposures as more children received the varicella vaccine rather than wild-type infection. However, herpes zoster incidence had been increasing at a similar steady rate prior to licensure of the varicella vaccine in the U.S. [16]. Similar trends of steadily increasing herpes zoster incidence before and after implementation of childhood varicella vaccination programs have been observed in other countries with childhood varicella vaccination programs [17–19].

We observed a steady decline in herpes zoster hospitalization rate from 2009 to 2015. A similar trend was also observed from

2007 to 2012 in a Connecticut study of herpes zoster hospitalizations [20]. In our study, the greatest declines in herpes zoster hospitalization incidences occurred among the 70–79 and ≥ 80 years groups (26.4% and 31.1%). However, in a study of herpes zoster vaccination coverage from 2007 to 2013 among adults aged ≥ 60 years, Zhang et al. observed that adults aged ≥ 65 years were less likely to receive the herpes zoster vaccine than those aged 60–64 years (23.9% vs 14.5%) [21]. Additionally, vaccination coverage has historically been low – only reaching as high as 30.6% in the target group by 2015 – primarily due to low manufacturer vaccine supply [22,23]. Thus, it is unlikely that the declines we observed were entirely due to herpes zoster vaccination and additional studies are needed to determine if this decreasing herpes zoster incidence trend continues as herpes zoster vaccination coverage increases in the U.S.

In March 2011, the Food and Drug Administration expanded the approved age of adult vaccinations with the live, attenuated herpes zoster vaccine to include adults aged 50–59 years [24]. In a clinical trial, vaccinated adults in this age group had a 69.8% reduced risk of developing herpes zoster compared to non-vaccinated adults [25]. However, despite positive clinical trial data, the ACIP decided not to expand the recommended herpes zoster vaccination age accordingly. This was due in part to evidence of waning vaccine efficacy after 5 years post-immunization [13]. Given that efficacy decreased with time, the vaccine policy would be more impactful if those at higher risk (aged ≥ 60) were targeted. Additionally, continued vaccine supply shortages meant that vaccination recommendations should prioritize those at higher risk [24]. In our study, the risk of herpes zoster hospitalization was associated with increasing age and the majority of hospitalizations were among the ≥ 60 years group. Therefore, our data support the 2011 ACIP decision to limit the age of recommended recipients of live-

attenuated herpes zoster vaccination especially given supply shortages.

During the study period, the 50–59 years group had a significant increase in estimated absolute change in herpes zoster hospitalization by 2015 (Table 1). With the advent of the new 2-dose recombinant sub-unit herpes zoster vaccine and the 2017 ACIP decision to include in the recommended age range for recombinant sub-unit herpes zoster vaccination those aged ≥ 50 years, herpes zoster incidence for the 50–59 years group is expected to decrease. Thus, continued surveillance is necessary to determine the effects of herpes zoster vaccination on this age group.

The live, attenuated virus in the varicella vaccine has the potential to become latent and can reactivate later as herpes zoster. However, the risk of this occurrence has been observed to be significantly lower than with wild type varicella virus [26,27]. In our study, we observed a significant decline in herpes zoster hospitalization between pre and post 2-dose varicella vaccine eras in the 0–3, 4–6, and 7–14 years groups. This provides further support for the idea that risk of herpes zoster is lower among those who received varicella vaccination vs. wild-type infection. Previous studies on herpes zoster incidence in the years following varicella vaccine licensure (1995) have similar observations of decreased herpes zoster incidence in the same population. In a study utilizing the NIS to examine herpes zoster hospitalizations in the U.S. from 1993 to 2004, Patel et al observed herpes zoster hospitalization rates declined significantly among children aged 0–9 years following introduction of the varicella vaccine [28]. More recently, Humes et al observed a significant decrease in herpes zoster hospitalizations among children aged 0–14 years in Connecticut hospitals from 2001 to 2012 [20]. During the single-dose varicella vaccine era (2000–2005), varicella incidence declined by 43.3%, and in the early phase of the 2-dose varicella vaccine era (2006–2010), varicella incidence declined by a further 71.6% [29]. Around this same time period (2005–2009), herpes zoster incidence among vaccinated children <18 years was 79% lower than in unvaccinated children [30]. Thus, it is likely that these declines in herpes zoster hospitalization incidence are due to a combination of active boosting from 2-dose varicella vaccination and the significant reduction of people with latent wild-type varicella infection. Ongoing surveillance will be needed as the cohort of people who are vaccinated against varicella increases over time.

In this study, length of stay was used as a proxy measure for determining disease severity as well as admission threshold. For all age groups, the average length of stay did not change significantly over the course of the study period. Thus, disease severity likely did not differ over the course of the study period. Additionally, because length of stay did not change, changes in herpes zoster hospitalization incidence within this study were not likely to be explained by differing admission thresholds over time.

This study had a few limitations because of its methodology and study population. First, because ICD-9 and ICD-10 codes were used to determine reason for hospitalization, it was possible to include nosocomial herpes zoster cases along with incident cases in analyses. Additionally, because of the sampling design of the NIS database, we were unable to determine and deduplicate potential serial admissions for individual patients. Both issues could result in overestimation of the herpes zoster hospitalization rate. To minimize these biases, we only included cases in which herpes zoster was listed in the primary or secondary diagnoses position as these were more likely to be incident cases. We also excluded all primary cases of postherpetic trigeminal neuralgia and postherpetic polyneuropathy because of their increased potential to represent long-term follow-up for a prior herpes zoster episode. Finally, the method for inclusion and exclusion was the same across all years of data. Therefore, any overestimation that may have occurred would have likely been consistent throughout the study period.

Another limitation of the study was that most herpes zoster cases in the U.S. are treated as outpatient, and hospital admission for herpes zoster is generally only considered for more severe cases. Thus, we considered length of stay as a proxy measure to determine changes in disease severity over time as well as to monitor any possible changes in hospital admission threshold. Additionally, inferences should only be made of inpatient herpes zoster.

5. Conclusion

To our knowledge, this is the first study to compare U.S. national trends in herpes zoster hospitalization rates before and after the 2007/2008 varicella and herpes zoster ACIP recommendations. We observed a significant decline in herpes zoster hospitalizations among the herpes zoster vaccine target group following licensure of the herpes zoster vaccine in 2006 as well as significant declines in herpes zoster hospitalizations among individuals aged 0–14 years following implementation of the 2-dose varicella vaccine schedule. These findings support ACIP recommendations for the use of the herpes zoster vaccine for prevention of herpes zoster in persons aged ≥ 60 years and the 2-dose varicella vaccine schedule. The recent licensure of a new 2-dose recombinant sub-unit herpes zoster vaccine and expansion of the recommended age of herpes zoster vaccination to ≥ 50 years should have significant impact in the U.S. on vaccination coverage and herpes zoster hospitalizations over time, and continued surveillance will be necessary to measure this impact.

Conflict of interest

We have no conflicts of interest to declare.

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.vaccine.2018.12.034>.

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