Distribution Agreement

In presenting this thesis or dissertation as a partial fulfillment of the requirements for an advanced degree from Emory University, I hereby grant to Emory University and its agents the non-exclusive license to archive, make accessible, and display my thesis or dissertation in whole or in part in all forms of media, now or hereafter known, including display on the world wide web. I understand that I may select some access restrictions as part of the online submission of this thesis or dissertation. I retain all ownership rights to the copyright of the thesis or dissertation. I also retain the right to use in future works (such as articles or books) all or part of this thesis or dissertation.

Signature:

_____ _____

Matthew Pham Date

Trends in U.S. Community Hospitalizations Due to Herpes Zoster: 2001-2015

By

Matthew Pham
Master of Public Health

Epidemiology

_____

Saad B. Omer, MBBS, MPH, PhD
Committee Chair

Trends in U.S. Community Hospitalizations Due to Herpes Zoster: 2001-2015

By

Matthew Pham

B.S.
Emory University
2011

Thesis Committee Chair: Saad B. Omer, MBBS, MPH, PhD

An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Public Health
in Epidemiology
2018

Abstract

Trends in U.S. Community Hospitalizations Due to Herpes Zoster: 2001-2015

By Matthew Pham

Background In 2005, the U.S. Advisory Committee on Immunization Practices recommended a booster dose at 4-6 years in the varicella vaccine schedule. In 2006, 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 2001-2015 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 (2011-2015)-herpes zoster vaccine 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-herpes zoster vaccine era was -1.8 per 100,000 hospitalizations (5600 fewer hospitalizations in 2015 than expected). Key age group rate differences: 0-3 years (-0.3 per 100,000; 50 fewer), 4-14 years (-1.1 per 100,000; 500 fewer), 50-59 years (0.7 per 100,000; 300 more), 60-69 years (-2.3 per 100,000; 800 fewer), 70-79 years (-8.7 per 100,000; 1700 fewer), 80+ years (-24.6 per 100,000; 2950 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 2006 herpes zoster vaccine may have impacted declining herpes zoster hospitalization rates for adults age ≥ 60 years despite vaccination coverage < 31% by 2015.

Trends in U.S. Community Hospitalizations Due to Herpes Zoster: 2001-2015

By

Matthew Pham

B.S.
Emory University
2011

Thesis Committee Chair: Saad B. Omer, MBBS, MPH, PhD

A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Public Health
in Epidemiology
2018

Acknowledgements

I would like to thank Dr. Saad Omer and Dr. Robert Bednarczyk for their patience and guidance during the research process.

I would also like to thank Dr. Edmund Becker and Dr. Walter Orenstein for their insight and input.

Table of Contents

Literature Review

The Varicella Zoster Virus and Herpes Zoster

The varicella zoster virus (VZV) is an exclusively human herpesvirus that can cause two distinct clinical conditions: varicella, commonly known as chickenpox, and herpes zoster (HZ), commonly known as shingles. The virus can be transmitted through air or direct contact and enters the host through the upper-respiratory tract or the conjunctiva [1,2]. Primary VZV infection generally results in chickenpox, characterized by an itchy skin rash that spreads over the body. Following a chickenpox episode, VZV remains latent within the cranial or dorsal ganglion cells of the sensory nerves and can reactivate later in life, resulting in HZ[1].

The HZ prodromal stage is characterized by pain, burning, tingling, or numbness in the affected area several days to weeks before the appearance of a rash. Patients often report differing sensations including: deep aching or burning pain, prickling or tingling in response to physical stimuli (paresthesia), abnormal and usually painful sensation in response to physical stimuli (dyesthesia), exaggerated response to stimuli (hyperesthesia), pain from trivial stimuli (allodynia), escalating pain from repeated stimuli (windup pain), and electric shock-like pain[3,4]. Additionally, patients may experience flu-like symptoms such as fever, headache, chills, and nausea approximately 72 hours prior to the appearance of a rash. Because the prodromal symptoms are so similar to multiple conditions, it is very difficult to diagnose HZ during early infection [3-5].

During the active stage, HZ is characterized by a painful, unilaterally-focused rash in the dermatome corresponding to the area surrounding the affected nerve. The most commonly affected dermatomes are cranial, thoracic, lumbar and cervical, and approximately 20% of patients experience overlapping lesions in adjacent dermatomes [6]. Conversely, simultaneous lesions in multiple noncontiguous dermatomes is very rare. Following the initial eruption, new lesions may continue to appear for up to five days, and healing is usually complete within two to four weeks. Though, immunocompromised patients may experience longer or repeated HZ infections [1-3,5,6].

Two major complications of HZ are post-herpetic neuralgia (PHN) and herpes zoster ophthalmicus (HZO). PHN is generally defined as severe pain in and around the affected dermatome persisting for greater than one month up to multiple years following the disappearance of HZ blisters [5,7]. This debilitating condition is the result of injury to nerves in the affected area and altered central nervous system processing. There is uncertainty as to whether PHN should be defined as pain lasting more than 30, 60, 90 or 120 days after disappearance of HZ blisters [4,8]. Thus, due to the variability in definitions for PHN, it is difficult to draw conclusions from studies on risk for PHN. HZO, occurs when VZV reactivates in the ophthalmic branch of the trigeminal nerve. Though blindness resulting from HZO is rare, there is a significant risk of HZO-associated complications including damage to the optic nerve, retina, and CNS [9].

Treatment for HZ typically consists of oral antiviral therapy alongside pain management. Currently, three orally administered antiviral drugs are approved in the

United States for the treatment of HZ: Famiciclovir, Valacyclovir, and Acyclovir. These drugs reduce or halt viral replication within the sensory nerves which reduces pain duration, shortens the active stage of infection, accelerates lesion healing, and reduces the duration of viral shedding [4,5]. In immunocompromised patients or cases where HZ has disseminated to visceral organs or the central nervous system, intravenous acyclovir is recommended for treatment rather than oral antivirals [4-6,10]. Pain management strategies may differ between cases depending on the degree of pain experienced by the patient, and for most cases, over-the-counter pain medication may be sufficient for pain management. However, short-acting narcotic analgesics are commonly prescribed in more severe cases. Regardless, early, aggressive pain management may reduce the risk for PHN [4,5].

Varicella Vaccines (Varivax and ProQuad)

In 1975, Takahashi et al. isolated VZV from an immunocompetent 3 year old child experiencing an active varicella infection. The isolated virus was passaged 11 times in human embryo fibroblasts and 12 times in guinea pig embryo fibroblasts, resulting in the temperature-sensitive and host-dependant live-attenuated Oka strain of VZV [11]. On March 17, 1995, a vaccine for VZV (Varivax) was licensed in the United States by Merck and Co., Inc. for use in persons 12 months of age and older. The vaccine contains the live-attenuated Oka VZV strain at $\geq$ 1350 plaque-forming units (pfu) per dose (3.13 $\log_{10}$ pfu) and is administered subcutaneously [12].

In clinical trials, the single dose Varivax vaccine regimen effectively elicited both humoral and cell-mediated immune responses against VZV without viremia.

Seroconversion - defined by detectable VZV-specific antibodies >0.3 glycoprotein-enzyme-linked immunosorbent assay (gpELISA) units - occurred by 4-6 weeks post-immunization in approximately 97% of susceptible children aged 1-12 years [1], and VZV-specific T-Cell proliferation was maintained in 90% and 87% of children aged 2-12 years at 1 and 5 years post-vaccination, respectively [13]. Additionally, the degree of primary antibody response at 6 weeks post-immunization correlated with protection against disease. Among children with detectable antibody titers at 6 weeks post-immunization, children with titer < 5 gpELISA units were 3.5 times more likely to experience breakthrough varicella – defined as varicella disease that develops > 42 days post-immunization – than children with antibody titer $\geq$ 5 gpELISA units [14].

On September 6, 2005, a combination vaccine (ProQuad) containing vaccine components for measles, mumps, rubella, and varicella (MMRV) was licensed in the United States by Merck and Co., Inc. for use in children aged 12 months to 12 years. The MMRV vaccine contains equal titers of attenuated measles, mumps, and rubella viruses as the MMRII vaccine (which contains only measles, mumps, and rubella) with the addition of a higher minimum titer (3.99 $\log_{10}$ pfu) of Oka/Merck VZV [15]. Though clinical efficacy studies of the MMRV vaccine have not yet been performed, 91.2% of children aged 12-23 months who received one dose of MMRV achieved VZV-specific antibody titers of $\geq$ 5 gpELISA units by 6 weeks post-immunization [15]. Thus, the MMRV vaccine was licensed on the basis of noninferiority of immunogenicity rather than clinical efficacy when compared to administration of MMRII and Varivax concurrently [16].

After licensure of the Varivax vaccine in 1995, the Advisory Committee on Immunization Practices (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 VZV-specific antibody titers. In 1999, the ACIP updated its recommendations to include school and childcare facility entry requirements, use of the vaccine for outbreak control, and use of the vaccine in children with HIV [1]. Following these recommendations by the ACIP, vaccination coverage steadily increased across the United States ranging from 69%-96% by state in 2005 [16]. During this time period, incidence of varicella hospitalizations declined across all age groups, with the greatest decreases among those under age 19. While vaccine effectiveness of the one dose vaccine schedule ranged from 70%-90% [1,17-19].

Despite decreases in morbidity and mortality since the implementation of the universal childhood varicella vaccination program, varicella incidence remained constant or minimally decreased even in some areas with high vaccination coverage [1,20]. Thus, in 2005, the ACIP updated its varicella vaccine recommendations to include a scheduled booster dose for children aged 4-6 years, catch-up vaccination for all people who only received one dose, school entry vaccination requirements for all grade levels, and 2 vaccine doses for all people who do not have evidence of immunity [1]. At 6 weeks post-immunization, the proportion of children with antibody titers $\geq$ 5 gpELISA units was higher among children who received two doses of the varicella vaccine (99.6%) compared to children who only received one dose (85.7%). Additionally, the rate of

breakthrough varicella was 3.3 times lower among children who received a second dose compared to children who only received one dose [21].

Epidemiology of Herpes Zoster

The primary risk factor for HZ is previous infection with VZV. Approximately 99.5% of the US population aged ≥ 40 years has serologic evidence of a previous infection by VZV and are therefore at risk for reactivation of VZV and development of HZ [3,22]. Of these people, approximately 30% are estimated to develop HZ at some point during their lifetime, resulting in an estimated 1 million cases of HZ in the US each year [23]. Other major risk factors for HZ are immunosuppression and increasing age, with risk increasing sharply for adults aged ≥ 50 years. Patients within this age group also have a higher risk of developing PHN or other HZ-related complications, requiring hospitalization [3]. Though VZV infection rates do not differ by gender, female gender is potentially another risk factor for development of HZ as incidence of VZV reactivation is often higher among women than men [24,25]. This trend, however, is not consistent between cohorts [24-26].

The triggers for reactivation of VZV are not yet well understood. However, cell-mediated immunity (CMI) rather than antibody response may be integral in preventing VZV reactivation [3]. Anti-VZV antibody levels may not have a role in HZ prevention, but anamnestic anti-VZV antibody response correlates with protection [27]. The major component of CMI involved in HZ protection is memory CD4 T cell expression, measured by responder cell frequency assay and IFN-γ ELISPOT assay [28,29].

During the active stage of HZ infection, VZV shed from zoster lesions can cause varicella in susceptible people [30-32]. However, it is unknown whether exogenous VZV can trigger reactivation of latent VZV to cause HZ. In fact, exogenous VZV may potentially boost CMI and reduce risk of HZ [33]. Thus, prior to licensure of the VZV vaccine, a major concern regarding the VZV vaccine was that decreasing exogenous VZV due to VZV vaccination would lead to an increase in HZ incidence. However, no change in HZ trends was observed after implementation of the universal varicella vaccination program despite significant decreases in VZV infection incidence [34,35].

Herpes Zoster Vaccine (Zostavax)

On May 25, 2006, a live-attenuated vaccine (Zostavax) for the prevention of HZ was licensed in the United States by Merck and Co., Inc. for use in adults aged 60 and older. The subcutaneously administered vaccine contains the same Oka/Merck VZV strain as the VZV vaccine but at a higher concentration of 19,400 pfu (4.29 $\log_{10}$), approximately 14-times the potency [3]. In pre-licensure clinical trials, HZ incidence was reduced by 51.3% and PHN incidence was reduced by 66.5% among patients aged >60 years who were immunized with the HZ vaccine compared to those who did not receive the vaccine [8]. Among patients who were immunized with the HZ vaccine, increased CMI responses over baseline persisted for 3-6 years post-vaccination with peaks observed at 1-3 weeks [36,37].

In clinical trials, the HZ vaccine was well tolerated and safe in older immunocompetent adults. During the first 42 days post-vaccination, the number of observed serious adverse events were similar (1.4%) between HZ vaccine and placebo groups [8]. In the safety substudy, the rate of serious adverse events during the first 42 days post-vaccination were higher among vaccine recipients (1.9%) than among placebo recipients (1.3%) [8]. However, no temporal or clinical patterns of adverse events were observed across the study population to suggest a causal relationship to immunization with HZ vaccine, and none of the differences between vaccine and placebo regarding serious adverse events at or below the level of body system affected were statistically significant. Additionally, the mortality rate between vaccine and placebo groups did not significantly differ during a 3.39 year follow-up [38].

Despite the safety and efficacy of the HZ vaccine, vaccination coverage among the target population following licensure remained low likely due to multiple perceived barriers [39]. By 2008, only 7% of adults aged $\geq$ 60 had received the HZ vaccine [40], and vaccination coverage only slightly increased to 15.8% by 2011 [41]. At approximately $200, the HZ vaccine is currently the most expensive vaccine for older adults. The cost for the vaccine may be prohibitive to many patients particularly because many private insurers require patients to pay out-of-pocket before applying for reimbursement. Additionally, the HZ vaccine is currently reimbursed through the complex and cumbersome Medicare Part D process unlike other vaccines which are automatically and fully reimbursed under Medicare Part B. Additional perceived barriers to HZ vaccination

included: 1) stringent freezer-storage requirements 2) vaccine manufacturer shortage issues and 3) lack of patient education of HZ [39,42]

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 booster 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 $\geq$ 60 years (51.3% clinical efficacy)[1,20]. Approximately 99.5% of the US population aged $\geq$ 40 years has serologic evidence of previous varicella infection and are therefore at risk for developing herpes zoster [3,22]. 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 [23].

Currently, the early effects of the two-dose varicella and single-dose herpes zoster vaccine recommendations on herpes zoster incidence in the U.S. are not yet well known. With implementation of these ACIP recommendations, herpes zoster incidence in the U.S. is expected to 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]. 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 2005/2006 ACIP recommendations on the varicella and herpes zoster vaccine schedules, and with the advent of amore clinically effective two-dose recombinant sub-unit herpes zoster vaccine (October 2017)[43], 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 2005/2006 ACIP recommendations and 2) changes in length of hospital stay associated with herpes zoster.

Methods

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 2001-2015 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.

Definition of hospitalization for Herpes Zoster

Herpes zoster-associated hospitalization was defined by a primary or secondary 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.

Data Analysis

This study was approved by the Emory University IRB. Data analyses were performed using SAS 9.4 (Cary, NC USA). NIS data from 2001- 2015 were used to estimate the annual number of herpes zoster hospitalizations among eight age groups (0-3, 4-14, 15-29, 30-39, 40-49, 50-59, 60-69, 70-79, and $\geq$ 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-herpes zoster vaccine) and 2011-2015 (post-herpes zoster vaccine). 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[44]. Therefore, we treated 2006-2010 as a transition period which was not included in grouped pre/post licensure 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 2005/2006 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.

Results

There were 400,505 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 0.06% among ages 4-14, 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, older age groups had more hospitalizations than

younger age groups. Females consistently had a significantly higher proportion of the herpes zoster hospitalization burden, but this proportion did not change significantly throughout the study period.

The annual incidence rate of herpes zoster hospitalizations in the U.S. was 8.6 per 100,000 hospitalizations during 2001 and decreased to 6.8 per 100,000 hospitalizations during 2015 (Figure 1A). The highest peak rates of herpes zoster hospitalization were among those aged 80+ years at approximately 115 per 100,000 hospitalizations, followed by approximately 40 per 100,000 hospitalizations for ages 70-79, approximately 20 per 100,000 hospitalizations for ages 60-69, and approximately 10 per 100,000 hospitalizations for ages 50-59. All other age groups had peak hospitalization rates lower than 10 per 100,000 hospitalizations. 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 2005/2006 ACIP vaccine policy decisions (4-14 and 60+ years) and the 0-3 years group while the 50-59 years age group was the only group to have an increase in rate (Figure 2A & 2B, Table 1).

There was no change in the overall median length of stay for herpes zoster hospitalizations from 2001 to 2015 (Figure 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+(Figure 2C & Supplementary Table S2).

The overall, age-adjusted average annual change in hospital rates from the pre vs. post herpes zoster vaccine period was 1.8 fewer hospitalizations per 100,000, which translates to approximately 5,600 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-herpes zoster vaccine period. Within the different age groups, the 80+ years group had a reduction of 24.6 per 100,000 hospitalizations which translated into 2950 fewer herpes zoster hospitalizations, the 70-79 years group had a reduction of 24.6 per 100,000 hospitalizations or 1700 fewer herpes zoster hospitalizations, the 60-69 years group had a reduction of 2.3 per 100,000 hospitalizations or 800 fewer herpes zoster hospitalizations, the 4-14 years group had a reduction of -1.1 per 100,000 hospitalizations or 500 fewer herpes zoster hospitalizations, and the 0-3 years group had a reduction of -0.3 per 100,000 or 50 fewer herpes zoster hospitalizations. The 50-59 years group was the only group to have an increase in annual hospital rates compared to the pre-herpes zoster vaccine period with an increase of 0.7 per 100,000 hospitalizations or 300 more herpes zoster hospitalizations than would be expected in 2015 (Table 1).

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 [1]. However, despite early decreases in morbidity and mortality, varicella incidence remained constant or minimally decreased even in some areas with high vaccination coverage [1,20]. Thus, in 2005, the ACIP updated its varicella vaccine recommendations to include a scheduled

booster dose for children aged 4-6 years, catch-up vaccination for all people who only received one dose, and school entry vaccination requirements for all grade levels [1]. 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 $\geq$ 60 years (51.3% clinical efficacy) [3]. Later, in 2017, a two-dose recombinant sub-unit herpes zoster vaccine with higher clinical efficacy (> 90%) was licensed for use in individuals $\geq$ 50 years, and the ACIP decided to expand the recommended age of herpes zoster vaccination to $\geq$ 50 years[45].

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 2005/2006 ACIP varicella and herpes zoster vaccine policy recommendations (4-14 and 60+ years) as well as the 0-3 years group 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 2005 and 2006, the herpes zoster hospitalization rate continued to increase 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. [35]. Another potential explanation for early increases in herpes zoster hospitalization incidence is that herpes zoster 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 [41,46]. However, despite low vaccination coverage, we observed a steady decrease in herpes zoster hospitalization rate from 2009-2015, and a similar trend was also observed from 2007-2012 in a Connecticut study of herpes zoster hospitalizations [47]. Thus, 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 herpes zoster vaccine to include adults aged 50-59 years [48]. 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 [49]. 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 continued herpes zoster vaccine supply shortages[48]. Thus, age groups which were at higher risk were prioritized to receive herpes zoster vaccination. The findings in our study support the ACIP decision to keep existing recommendations as the majority of herpes zoster hospitalizations were among the $\geq$ 60 years group.

During the study period, the 50-59 years group was the only group to have 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 expand the recommended age range for herpes zoster vaccination to $\geq$ 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.

We observed a significant decline in herpes zoster hospitalization between pre and post herpes zoster vaccine/2-dose varicella vaccine eras in the 4-14 years group and a slight decrease among the 0-3 years group. 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 1993-2004, Patel et al observed herpes zoster hospitalization rates declined significantly among children aged 0-9 years following introduction of the varicella vaccine[50]. More recently, Humes et al observed a significant decrease in herpes zoster hospitalizations among children aged 0-14 years in Connecticut hospitals from 2001-2012[47]. 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%[51]. Around this same time period (2005-2009), herpes zoster incidence among vaccinated children < 18 years was 79% lower than in unvaccinated children[52]. Thus, these declines in herpes zoster hospitalization incidence are most likely due to a combination of active

boosting from 2-dose varicella vaccination and fewer exposures due to 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, resulting in overestimation of herpes zoster hospitalization rate. To minimize this bias, 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. Additionally, we 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. Second, 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.

Conclusion

To our knowledge, this is the first study to compare U.S. national trends in herpes zoster hospitalization rates before and after the 2005/2006 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 $\geq$ 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 $\geq$ 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.

Public Health Implications

The purpose of this study was to examine US national trends in HZ-associated hospitalization centered around the ACIP's recommendations for HZ vaccination in adults aged $\geq$ 60 years and an increase in routine VZV vaccinations from one to two

doses. To our knowledge, this is the first study to compare US national trends in HZ hospitalization rates before and after these ACIP recommendations. The HZ hospitalization trends observed in this study complement trends observed in another study of HZ hospitalization trends in Connecticut during the same time period [46]. Thus, analysis of discharge data from the Nationwide Inpatient Sample is an effective method for monitoring trends in HZ-hospitalization incidence.

Findings from this study contribute to the growing body of evidence of the VZV vaccine's significant impact on HZ-associated hospitalizations among children ages 0-14 years. Additionally, while HZ vaccination coverage remained low throughout the study period, HZ-associated hospitalization incidence among the HZ target group declined significantly in the post-HZ vaccine era compared to the pre-HZ vaccine era. Therefore, as we cannot determine the direct effects of HZ vaccination on HZ incidence in this study, continued surveillance will be necessary to determine if the downward trend continues especially as the new 2-dose recombinant subunit HZ vaccine is implemented in the US.

Tables & Figures

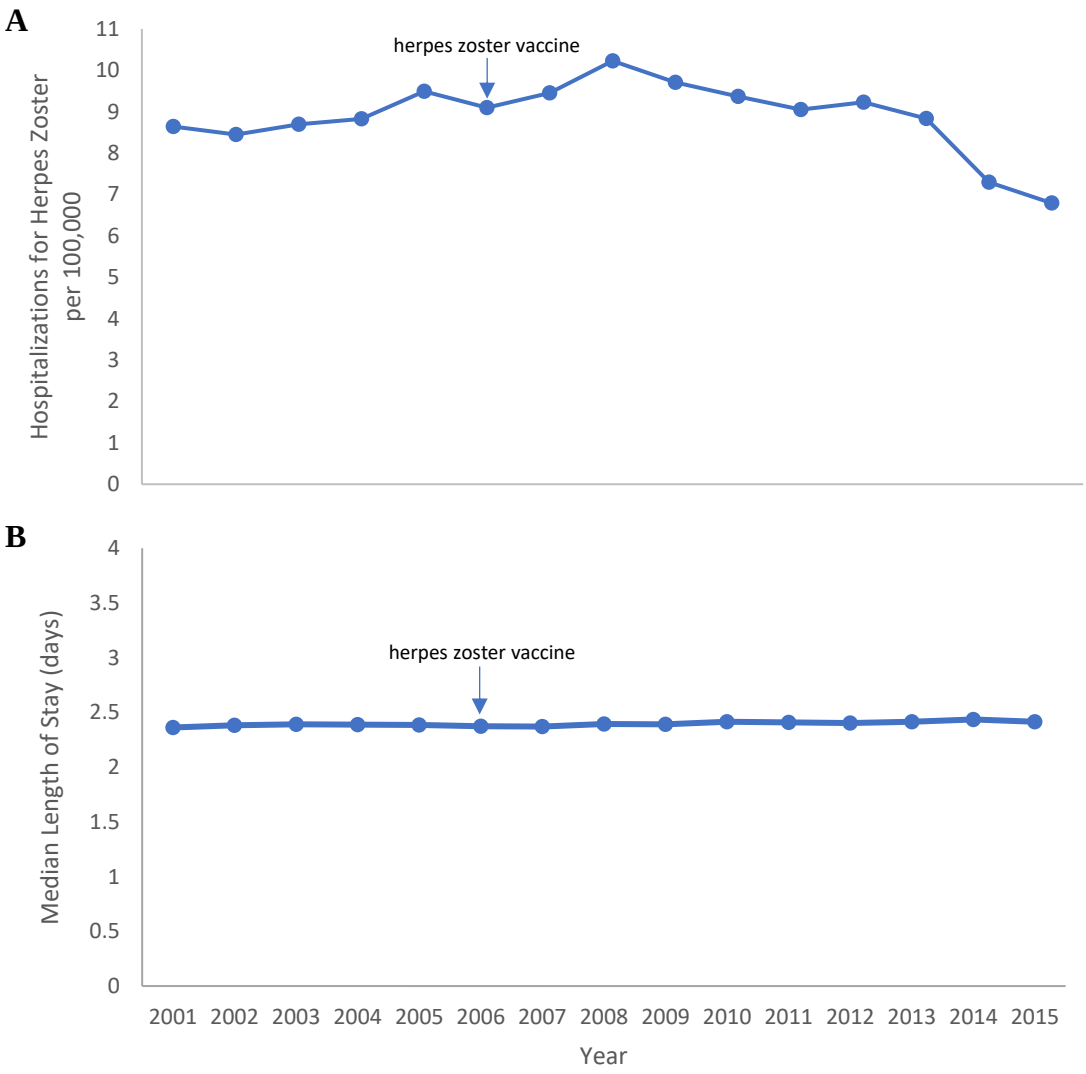

Figure 1. Annual Hospitalizations and Median Length of Hospital Stay for Herpes Zoster in the U.S. from 2001-2015

Panel A shows annual hospitalizations for herpes zoster.

Panel B shows median length of hospital stay for herpes zoster.

* Arrow indicates the year of herpes zoster vaccine licensure

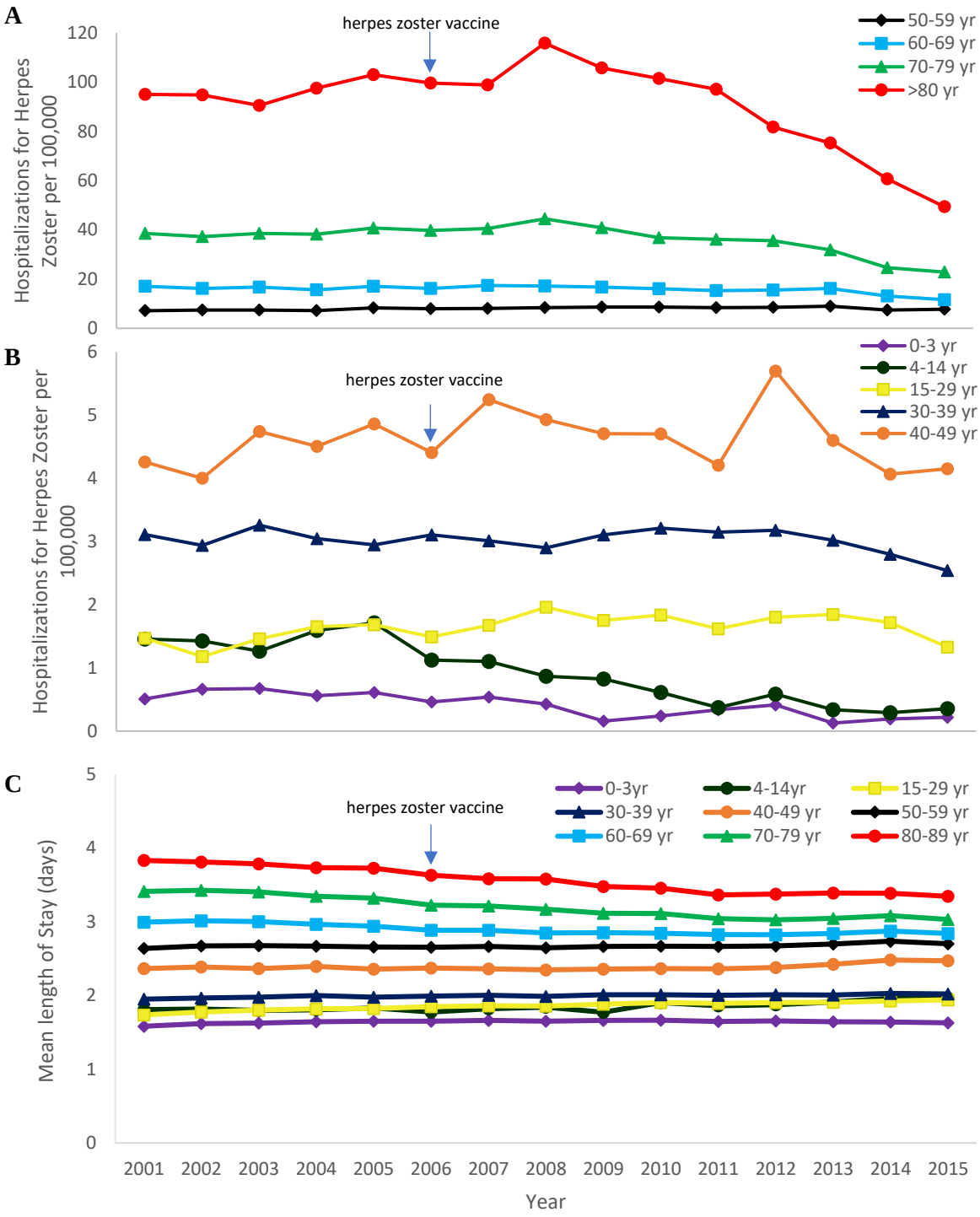

Figure 2. Average Annual Hospitalizations and Median Length of Hospital Stay for Herpes Zoster in the U.S. by Age Group, from 2001-2015

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 herpes zoster vaccine licensure

Table 1. Differences in Rates of Hospitalization for Herpes Zoster Before (2001-2005) and After (2011-2015) the Introduction of the Herpes Zoster Vaccine

Age	U.S. Population, 2015 *millions*	Differences in Hospitalization Rates per 100,000 Population, Pre-herpes zoster Vaccine vs. Post-herpes zoster Vaccine *no. (95% CI)*	Percent Change in Hospitalizations, Pre-herpes zoster Vaccine vs. Post-herpes zoster Vaccine *% (95% CI)*	Estimated Absolute Change in Hospitalizations, 2015 *no. (95% CI)*
0-3	15.9	-0.3 (-0.5, -0.2)	-57.2 (-83.5, -30.9)	-50 (-50, -100)
4-14	45.2	-1.1 (-1.4, -0.8)	-74.0 (-92.6, -55.4)	-500 (-600, -350)
15-29	66.2	0.2 (0.0, 0.4)	11.3 (-1.7, 24.3)	100 (0, 250)
30-39	41.9	-0.1 (-0.4, 0.2)	-4.2 (-14.7, 6.3)	-50 (-200, 100)
40-49	41.0	0.1 (-0.3, 0.5)	1.6 (-7.3, 10.6)	50 (-150, 200)
50-59	44.1	0.7 (0.1, 1.3)	9.5 (2.0, 16.9)	300 (50, 550)
60-69	35.1	-2.3 (-3.2, -1.3)	-13.6 (-19.5, -7.8)	-800 (-1150, -450)
70-79	19.6	-8.7 (-10.8, -6.7)	-22.6 (-28.0, -17.3)	-1700 (-2100, -1300)
80+	12.1	-24.6 (-29.7, -19.4)	-25.5 (-30.9, -20.1)	-2950 (-3600, -2350)
All age groups	320.9	-1.8 (-3.0, -0.5)	-17.0 (-28.7, -5.2)	-5600 (-9500, -1750)

* The values of the all age groups category are standardized estimates to the age-group distribution of the 2015 U.S. population

Supplementary Appendix

Table S1. ICD-9-CM and ICD-10-CM Codes used for Inclusion and Exclusion Criteria

ICD-9-CM		
	Inclusion	053.0-053.11, 053.14-053.9
	exclusion	053.12-053.13
ICD-10-CM		
	Inclusion	B02.0, B02.1, B02.21, B02.22, B02.29, B02.30-B02.39, B02.7-B02.9.
	Exclusion	B02.22-B02.23

Table S2. Average Annual Hospitalizations and Median Length of Hospital Stay for Herpes Zoster in the U.S., Pre-Herpes Zoster Vaccine (2001-2005) vs. Post-Herpes Zoster Vaccine (2011-2015)

	Age Group								
	0-3 yr	**4-14 yr**	**15-29 yr**	**30-39 yr**	**40-49 yr**	**50-59 yr**	**60-69 yr**	**70-79 yr**	**>80 yr**
Average annual hospitalizations — no./100,000 (95% CI)									
Pre-Herpes Zoster Vaccine	0.6 (0.5, 0.7)	1.5 (1.2, 1.8)	1.5 (1.3, 1.7)	3.1 (2.8, 3.3)	4.5 (4.1, 4.8)	7.5 (7.0, 8.0)	16.5 (15.7, 17.3)	38.6 (36.8, 40.4)	96.2 (91.5, 100.9)
Post-Herpes Zoster Vaccine	0.3 (0.2, 0.3)	0.4 (0.3, 0.5)	1.7 (1.6, 1.8)	2.9 (2.8, 3.1)	4.5 (4.3, 4.8)	8.2 (7.9, 8.5)	14.3 (13.7, 14.8)	29.9 (28.9, 30.9)	71.7 (69.5, 73.8)
Length of hospital stay (days)									
Pre-Herpes Zoster Vaccine									
Median	1.6	1.8	1.8	2.0	2.4	2.7	3.0	3.4	3.8
IQR	(1.1, 2.5)	(0.8, 3.7)	(1.1, 2.9)	(1.2, 3.4)	(1.1, 4.5)	(1.2, 5.1)	(1.4, 5.8)	(1.6, 6.3)	(2.0, 6.7)
Post-Herpes Zoster Vaccine									
Median	1.6	1.9	1.9	2.0	2.4	2.7	2.8	3.0	3.4
IQR	(1.1, 2.5)	(0.9, 3.9)	(1.2, 3.0)	(1.2, 3.3)	(1.2, 4.6)	(1.4, 5.1)	(1.5, 5.5)	(1.6, 5.8)	(1.9, 5.9)

References

1. Marin M, Guris D, Chaves SS, Schmid S, Seward JF. Prevention of varicella: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recommendations and reports : Morbidity and mortality weekly report Recommendations and reports 2007;56:1-40.
2. Wood MJ. History of Varicella Zoster Virus. Herpes : the journal of the IHMF 2000;7:60-5.
3. Harpaz R, Ortega-Sanchez IR, Seward JF. Prevention of herpes zoster: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recommendations and reports : Morbidity and mortality weekly report Recommendations and reports 2008;57:1-30; quiz CE2-4.
4. Johnson RW. Consequences and Management of Pain in Herpes Zoster. The Journal of Infectious Diseases 2002;186:S83-S90.
5. Sampathkumar P, Drage LA, Martin DP. Herpes zoster (shingles) and postherpetic neuralgia. Mayo Clinic proceedings 2009;84:274-80.
6. Wilson JF. HErpes zoster. Annals of Internal Medicine 2011;154:ITC3-1.
7. Hales CM, Harpaz R, Joesoef MR, Bialek SR. Examination of links between herpes zoster incidence and childhood varicella vaccination. Ann Intern Med 2013;159:739-45.
8. Oxman MN, Levin MJ, Johnson GR, et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. The New England journal of medicine 2005;352:2271-84.
9. Liesegang TJ. Herpes Zoster Ophthalmicus. Ophthalmology;115:S3-S12.
10. Pergam S, Limaye A. Varicella Zoster Virus (VZV). American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons 2009;9:S108-15.
11. Takahashi M, Okuno Y, Otsuka T, Osame J, Takamizawa A. Development of a live attenuated varicella vaccine. Biken journal 1975;18:25-33.
12. Recommended childhood immunization schedule--United States, January-June 1996. MMWR Morbidity and mortality weekly report 1996;44:940-3.
13. Zerboni L, Nader S, Aoki K, Arvin AM. Analysis of the persistence of humoral and cellular immunity in children and adults immunized with varicella vaccine. J Infect Dis 1998;177:1701-4.
14. Li S, Chan IS, Matthews H, et al. Inverse relationship between six week postvaccination varicella antibody response to vaccine and likelihood of long term breakthrough infection. The Pediatric infectious disease journal 2002;21:337-42.
15. Marin M, Broder KR, Temte JL, Snider DE, Seward JF. Use of combination measles, mumps, rubella, and varicella vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recommendations and reports : Morbidity and mortality weekly report Recommendations and reports 2010;59:1-12.
16. Kuter BJ, Brown ML, Hartzel J, et al. Safety and immunogenicity of a combination measles, mumps, rubella and varicella vaccine (ProQuad). Human vaccines 2006;2:205-14.
17. Izurieta HS, Strebel PM, Blake PA. Postlicensure effectiveness of varicella vaccine during an outbreak in a child care center. Jama 1997;278:1495-9.
18. Seward JF, Marin M, Vazquez M. Varicella vaccine effectiveness in the US vaccination program: a review. J Infect Dis 2008;197 Suppl 2:S82-9.

19. Haddad MB, Hill MB, Pavia AT, et al. Vaccine effectiveness during a varicella outbreak among schoolchildren: Utah, 2002-2003. Pediatrics 2005;115:1488-93.
20. Lopez AS, Guris D, Zimmerman L, et al. One dose of varicella vaccine does not prevent school outbreaks: is it time for a second dose? Pediatrics 2006;117:e1070-7.
21. Kuter B, Matthews H, Shinefield H, et al. Ten year follow-up of healthy children who received one or two injections of varicella vaccine. The Pediatric infectious disease journal 2004;23:132-7.
22. Kilgore PE, Kruszon-Moran D, Seward JF, et al. Varicella in Americans from NHANES III: implications for control through routine immunization. Journal of medical virology 2003;70 Suppl 1:S111-8.
23. Tseng HF, Smith N, Harpaz R, Bialek SR, Sy LS, Jacobsen SJ. Herpes zoster vaccine in older adults and the risk of subsequent herpes zoster disease. Jama 2011;305:160-6.
24. Fleming DM, Cross KW, Cobb WA, Chapman RS. Gender difference in the incidence of shingles. Epidemiology and infection 2004;132:1-5.
25. Opstelten W, Van Essen GA, Schellevis F, Verheij TJ, Moons KG. Gender as an independent risk factor for herpes zoster: a population-based prospective study. Annals of epidemiology 2006;16:692-5.
26. Donahue JG, Choo PW, Manson JE, Platt R. The incidence of herpes zoster. Archives of internal medicine 1995;155:1605-9.
27. Burke BL, Steele RW, Beard OW, Wood JS, Cain TD, Marmer DJ. Immune responses to varicella-zoster in the aged. Archives of internal medicine 1982;142:291-3.
28. Levin MJ, Smith JG, Kaufhold RM, et al. Decline in varicella-zoster virus (VZV)-specific cell-mediated immunity with increasing age and boosting with a high-dose VZV vaccine. J Infect Dis 2003;188:1336-44.
29. Levin MJ, Oxman MN, Zhang JH, et al. Varicella-zoster virus-specific immune responses in elderly recipients of a herpes zoster vaccine. J Infect Dis 2008;197:825-35.
30. Josephson A, Gombert ME. Airborne transmission of nosocomial varicella from localized zoster. J Infect Dis 1988;158:238-41.
31. Wreghitt TG, Whipp J, Redpath C, Hollingworth W. An Analysis of Infection Control of Varicella-Zoster Virus Infections in Addenbrooke's Hospital Cambridge over a 5-Year Period, 1987-92. Epidemiology and infection 1996;117:165-71.
32. Lopez AS, Burnett-Hartman A, Nambiar R, et al. Transmission of a newly characterized strain of varicella-zoster virus from a patient with herpes zoster in a long-term-care facility, West Virginia, 2004. J Infect Dis 2008;197:646-53.
33. Ogunjimi B, Van Damme P, Beutels P. Herpes Zoster Risk Reduction through Exposure to Chickenpox Patients: A Systematic Multidisciplinary Review. PLoS ONE 2013;8:e66485.
34. Jumaan AO, Yu O, Jackson LA, Bohlke K, Galil K, Seward JF. Incidence of herpes zoster, before and after varicella-vaccination-associated decreases in the incidence of varicella, 1992-2002. J Infect Dis 2005;191:2002-7.
35. Liesegang TJ. Varicella zoster viral disease. Mayo Clinic proceedings 1999;74:983-98.
36. Sperber SJ, Smith BV, Hayden FG. Serologic response and reactogenicity to booster immunization of healthy seropositive adults with live or inactivated varicella vaccine. Antiviral research 1992;17:213-22.
37. Levin MJ, Barber D, Goldblatt E, et al. Use of a live attenuated varicella vaccine to boost varicella-specific immune responses in seropositive people 55 years of age and older: duration of booster effect. J Infect Dis 1998;178 Suppl 1:S109-12.
38. Simberkoff MS, Arbeit RD, Johnson GR, et al. Safety of herpes zoster vaccine in the shingles prevention study: A randomized trial. Annals of Internal Medicine 2010;152:545-54.

39. Lu PJ, Euler GL, Jumaan AO, Harpaz R. Herpes zoster vaccination among adults aged 60 years or older in the United States, 2007: uptake of the first new vaccine to target seniors. Vaccine 2009;27:882-7.
40. Vaccination coverage estimates from the National Health Interview Survey: United States, 2008. 2008. (Accessed 18 January, 2017, at https://www.cdc.gov/nchs/data/hestat/vaccine_coverage/vaccine_coverage.htm.)
41. Noninfluenza vaccination coverage among adults - United States, 2011. MMWR Morbidity and mortality weekly report 2013;62:66-72.
42. Hurley LP, Lindley MC, Harpaz R, et al. Barriers to the use of herpes zoster vaccine. Ann Intern Med 2010;152:555-60.
43. Dooling KL, Guo A, Patel M, et al. Recommendations of the Advisory Committee on Immunization Practices for use of herpes zoster vaccines. American Journal of Transplantation 2018;18:756-62.
44. Gerberding J, Yawn BP. Discussing the zoster vaccine: an interview with Julie Gerberding, president of Merck vaccines. Population health management 2012;15:382-4.
45. Dooling KL. Recommendations of the Advisory Committee on Immunization Practices for Use of Herpes Zoster Vaccines. MMWR Morbidity and mortality weekly report 2018;67.
46. Williams WW. Surveillance of vaccination coverage among adult populations—United States, 2015. MMWR Surveillance Summaries 2017;66.
47. Humes EA, Weinberger DM, Kudish KS, Hadler JL. Trends in Hospitalizations With Primary Varicella and Herpes Zoster During the Prevaricella and Initial Postvaricella and Herpes Zoster Vaccine Eras, Connecticut, 1994–2012. Open Forum Infectious Diseases 2015;2:ofv001-ofv.
48. Hales CM, Harpaz R, Ortega-Sanchez I, Bialek SR. Update on recommendations for use of herpes zoster vaccine. MMWR Morbidity and mortality weekly report 2014;63:729-31.
49. Schmader KE, Levin MJ, Gnann JW, Jr., et al. Efficacy, safety, and tolerability of herpes zoster vaccine in persons aged 50-59 years. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2012;54:922-8.
50. Patel MS, Gebremariam A, Davis MM. Herpes zoster-related hospitalizations and expenditures before and after introduction of the varicella vaccine in the United States. Infection control and hospital epidemiology 2008;29:1157-63.
51. Control CfD, Prevention. Evolution of varicella surveillance--selected states, 2000-2010. MMWR Morbidity and mortality weekly report 2012;61:609.
52. Weinmann S, Chun C, Schmid DS, et al. Incidence and clinical characteristics of herpes zoster among children in the varicella vaccine era, 2005-2009. J Infect Dis 2013;208:1859-68.