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Updated Trends of Herpes Zoster Incidence among Veterans

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Master of Public Health

Applied Epidemiology

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Updated Trends of Herpes Zoster Incidence among Veterans

By

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MD

Pontificia Universidad Catolica Madre y Maestra

2011

Master of Public Health

Thesis Committee Chair: Jodie Guest, 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

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Abstract

Updated Trends of Herpes Zoster Incidence among Veterans

By Amelia Muniz Hernandez

Background. The estimated incidence of herpes zoster (HZ) in the U.S. in 2011 was 4.5 per 1000 across all age groups, and 10.5 per 1000 among persons aged >60 years. National data for 2006-2016 indicate incidences that are increasing among younger adults and plateauing among older adults. Among persons served by the Veterans Affairs Health System (VAHS), HZ incidence steadily increased from 3.1 per 1000 in the year 2000 to 5.2 per 1000 in the year 2007. However, unpublished data suggests that HZ incidence among veterans may have started to show a plateau phase in 2014. We undertook this study to update and assess the patterns in HZ incidence in the VA healthcare system between 2008 and 2018.

Methods. Data was obtained from the VA Managerial Cost Accounting System. The period of analysis included fiscal year 2008 through fiscal year 2018. We calculated the annual incidence of herpes zoster by dividing the total number of veterans with a herpes zoster diagnosis in a given fiscal year by the total number of veterans seen during that same fiscal year. We used Poisson regression to analyze the trend of herpes zoster incidence throughout the study period and we calculated the incidence rate ratio and the incidence rate difference comparing all consecutive 2-year combinations.

Results. The annual incidence of herpes zoster among veterans decreased from 5.69 per 1,000 veterans in fiscal year 2008 to 3.37 per 1,000 veterans in fiscal year 2018, which represents a 40.7% decrease in incidence ($p < 0.0001$).

Conclusion. This study provides updated information on the epidemiology of herpes zoster among veterans. For the first time in over a decade, the annual herpes zoster incidence rate among veterans is on a significantly decreasing trend. Our data did not contain information that could help us determine the reasons for the observed change in the trend of HZ incidence.

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Table of Contents

Contribution

All data analysis, figure and table development as well as literature review and writing of this thesis was done by the author, Amelia Muniz Hernandez.

Chapter 1: Literature Review

The varicella-zoster virus (VZV) is a double stranded DNA virus belonging to the herpesvirus family that causes varicella, also known as chickenpox, most commonly during childhood (Arvin, 1996). After this primary infection, VZV remains dormant in the sensory or cranial nerve dorsal root ganglia and can reactivate later in life to cause an intensely painful and often burning vesicular rash, usually following a unilateral dermatomal pattern, known as herpes zoster or shingles (Arvin, 1996).

A link between varicella and herpes zoster was first described in the late 1800s, but it was not until the 1960s that the theory of latency and reactivation of the same virus was established (Hope-Simpson, 1965; Kawai, Gebremeskel & Acosta 2014).

VZV establishes primary infection in the body after entering through the respiratory tract and reaching circulating T lymphocytes (Gershon et al., 2010). After a short incubation period, the virus then reaches the skin where disease manifests with the classical multi-staged fluid filled blisters of varicella that show up on the chest, back, face and extremities (Gershon et al., 2010; CDC, 2018). For most individuals, primary infection results in the acquisition of lifelong immunity from clinical varicella (Gershon & Silverstein, 2009).

Varicella is most often mild and uncomplicated when it occurs in children; however, it can be severe when occurring in healthy adults and can be life threatening among patients with a significantly compromised immune system (Arvin et al., 1996; CDC, 2019a).

It is thought that during the period of primary infection, the virus moves through neural pathways from the periphery of the body to the corresponding sensory or cranial nerve dorsal root ganglia where it establishes latency in T lymphocytes (Arvin et al., 1996; Gershon et al., 2010).

Later in life and in the presence of decreased cell-mediated immunity, which can happen as a result of normal ageing or because of a pathologic process causing immunosuppression, VZV is reactivated and again moves along neural pathways to establish new symptomatic disease in the skin cells (Arvin et al., 1996; Gershon et al., 2010). This time the disease manifests as stabbing and/or burning pain that is succeeded by a vesicular rash that classically follows the distribution of a dermatome; this symptomatology is termed herpes zoster or shingles (Arvin, 1996; Gershon et al., 2010). Shingles is most commonly seen occurring along the trigeminal nerve distribution, or along a cervical or thoracic sensory nerve distribution; it is most often observed unilaterally, although bilateral or multidermatomal distributions can also occur (Schmader, 2016).

Although rare, herpes zoster can be life threatening when it occurs in immunocompromised individuals, due to complications such as pneumonia and encephalitis (Arvin et al., 1996; Cohen, 2013; CDC, 2019b). Even when it is not life threatening however, shingles often causes significant morbidity and can have a consequential negative impact on quality of life among elderly individuals who are otherwise healthy, mainly due to a sequela termed postherpetic neuralgia (PHN) (Cohen, 2013; Gater et al., 2015; Johnson et al., 2018).

Postherpetic neuralgia is a chronic pain syndrome characterized by episodes of spontaneous shooting, burning pain that occur along the dermatomal distribution where the

shingles rash had taken place (Arvin, 1996; Cohen, 2013; Gater et al., 2015). PHN can also present with allodynia (pain in response to a stimulus that is not expected to cause pain, such as light touch) and hyperalgesia (increased sensitivity to pain) (Gater et al., 2015). The pain caused by PHN can be so severe that it negatively impacts sleep and other activities of daily life, causing significant decrease in quality of life (Cohen, 2013; CDC, 2019b; Johnson et al., 2018). Unfortunately, this symptomatology may persist for several months or years, and can lead to other conditions usually associated with chronic pain syndromes, such as anxiety, depression, fatigue and anorexia (Cohen, 2013).

In addition to PHN, herpes zoster can also be associated with other significant neurologic, cardiovascular and ophthalmologic complications such as Bell's palsy, transverse myelitis, stroke, myocardial infarction, uveitis and necrosis of the retina (Cohen, 2013; Marra et al., 2017; Warren-Gash, 2018).

Herpes zoster is a common condition throughout the world, and it is considered a significant source of morbidity, especially among individuals aged 50 years old or older (Yawn et al., 2007; Pinchinat et al., 2013; Yawn & Gilden, 2013).

The risk of herpes zoster increases as an individual's VZV-specific cell-mediated immunity decreases; which can happen as a result of increasing age, or due to an illness or intervention that affects the immune system. Medical conditions such as certain cancers, human immunodeficiency virus/acquired immunodeficiency syndrome, bone marrow or solid organ transplantation and immunosuppressive medications can increase the risk for herpes zoster (CDC, 2019c).

Varicella vaccination has been shown to decrease the risk of herpes zoster among children and adolescents (Weinman et al., 2013; Civen et al., 2016). Among older adults, there are concerns that widespread childhood varicella vaccination may increase the risk of herpes zoster, as VZV-specific immunity weans in unvaccinated individuals because of the absence of exposure to the virus (Brisson et al., 2000). However, the evidence to support this hypothesis is scarce and controversial (Varela, Pinto & Scotta, 2019; CDC, 2019c).

In the overall population, the median incidence of herpes zoster, estimated from studies with populations from North and South America, Europe, Asia and Australia, is approximately 4.5 cases per 1,000 population (Yawn & Gilden, 2013; Kawai, Gebremeskel & Acosta, 2014). Across the different countries, herpes zoster incidence similarly increases sharply after age 50 and has been estimated to reach approximately 10 to 14 cases per 1,000 population among those aged 65 years old or older (Yawn et al., 2007; Pinchinat et al., 2013; Kawai, Gebremeskel & Acosta, 2014; Schmader, 2016). Herpes zoster can also present as a reoccurrence, although the incidence of recurrent episodes has not been well established (Yawn et al., 2011; Schmader, 2016; Kim et al., 2019).

In the United States, it is estimated that approximately one million new cases of herpes zoster occur each year, and the lifetime risk of developing herpes zoster is thought to be around 30% in the general population but may be as high as 50% among individuals aged 85 years old or older. (Yawn et al., 2007; Harpaz & Leung, 2019).

These current estimates represent a gradual increase in herpes zoster incidence over time. Between 1945 and 1959, a study using multi-institutional medical records from Minnesota, estimated that the overall incidence of herpes zoster in the United States

increased from 1.1 per 1,000 population in the period going from 1945 to 1949, to 1.5 per 1,000 population in the period going from 1955 to 1959 (Ragozzino et al., 1982). A later study that employed a retrospective population-based methodology with medical record data from Minnesota, estimated that the herpes zoster incidence among adults 22 years old and older increased from 3.2 per 1,000 population in 1996 to 1997, to 4.1 per 1,000 population in 2000 to 2001 (Yawn et al., 2007).

A study that used telephone survey data from the Behavioral Risk Factor Surveillance System (BRFSS) from Massachusetts, estimated that the overall herpes zoster incidence in the United States increased from 2.8 per 1,000 population in 1999 to 5.3 per 1,000 population in 2003 (Yih et al., 2005). In a similar time-period, a study using medical claims data from an administrative database (MarketScan) found that the overall incidence of herpes zoster increased from 1.7 per 1,000 population in 1993, to 4.4 per 1,000 population in 2006 (Leung et al., 2011).

In a retrospective study of Medicare claims from 1992 to 2010, the incidence of herpes zoster among adults aged 65 years old or older increased form 10 per 1,000 population in 1992, to 13.9 per 1,000 population in 2010 (Hales et al., 2013).

Lastly, a follow up study to Leung et al. that extended their analysis of the MarketScan database through 2016, found that the incidence of herpes zoster among younger adults, aged 35 to 55 years old, has continued on a steadily increasing trend; however, among older adults, aged 55 years old and older, the previously observed increasing trend in the incidence of herpes zoster has shown deceleration and a possible plateau (Harpaz & Leung, 2019).

Despite the abundant literature documenting herpes zoster incidence over time, reasons that can satisfactorily explain the observed trends are not well understood and there seems to be an element of unpredictability surrounding herpes zoster incidence trends (CDC, 2019c; Harpaz & Leung, 2019). Furthermore, the recent variation in the incidence trend among different age groups suggests the need to continue to monitor the incidence of herpes zoster in the population.

Because herpes zoster incidence is substantially higher among adults aged 50 years old and older, persons served by the Veterans Affairs Health System (VAHS), historically an older age group, represent a population that can reflect herpes zoster trends in the ageing population of the United Sates.

Previously, one study used data from the Veterans Affairs Managerial Cost Accounting System, a national information management system containing data for VAHS inpatient and outpatient care, to establish the herpes zoster incidence among Veterans from 2000 to 2007 (Rimland & Moanna, 2010). This study found that the incidence of herpes zoster increased from 3.1 per 1,000 Veterans in 2000 to 5.2 per 1,000 Veterans in 2007.

Two other studies have looked at herpes zoster incidence among veterans. One of these studies focused on veterans living with HIV before and after the era of highly active antiretroviral therapy (HAART) and showed a significant decrease in herpes zoster incidence among veterans with HIV during HAART-era compared to pre-HAART era, from 6.3 per 100 to 1 per 100 (Moanna & Rimland, 2013). The other study compared the incidence of herpes zoster between veterans with HIV and veterans without HIV from fiscal year 2002 to fiscal year 2015; they reported a decrease in incidence, from 17.6 per

1,000 to 8.1 per 1,000, among veterans with HIV; and an increase in incidence, from 2.3 per 1,000 to 4.1 per 1,000, among veterans without HIV (Hawkins et al., 2018).

The current study is a follow up study to Rimland & Moanna that extends the analysis of herpes zoster incidence in the overall veteran population through 2018. This paper aims to document the trend of herpes zoster incidence among veterans in the VA healthcare system overall and by age group between 2008 and 2018.

Chapter 2: Journal Article

Updated Trends of Herpes Zoster Incidence among Veterans in the United States

Background

The varicella-zoster virus (VZV) is a double stranded DNA virus belonging to the herpesvirus family that causes varicella, also known as chickenpox, most commonly during childhood (Arvin, 1996). After this primary infection, VZV remains dormant in the sensory or cranial nerve dorsal root ganglia and can reactivate later in life to cause an intensely painful and often burning vesicular rash, usually following a unilateral dermatomal pattern, known as herpes zoster or shingles (Arvin, 1996).

Although rare, herpes zoster can be life threatening when it occurs in immunocompromised individuals, due to complications such as pneumonia and encephalitis (Arvin et al., 1996; Cohen, 2013; CDC, 2019b). Even when it is not life threatening however, shingles often causes significant morbidity and can have a consequential negative impact on quality of life among elderly individuals who are otherwise healthy, mainly due to postherpetic neuralgia (PHN), which can persist for several months or years, and can lead to other conditions usually associated with chronic pain syndromes, such as anxiety, depression, fatigue and anorexia (Cohen, 2013; Gater et al., 2015; Johnson et al., 2018).

In the United States, it is estimated that approximately one million new cases of herpes zoster occur each year, and the lifetime risk of developing herpes zoster is thought to be around 30% in the general population but may be as high as 50% among individuals aged 85 years old or older. (Yawn et al., 2007; Harpaz & Leung, 2019).

The incidence of herpes zoster in the United States has been on a steadily increasing trend over several decades, but recently the incidence among adults aged 55 years old and older, has started to plateau (Ragozzino et al., 1982; Yawn et al., 2007; Yih et al., 2005; Leung et al., 2011; Hales et al., 2013; Harpaz & Leung, 2019).

Among persons served by the Veterans Affairs Health System (VAHS), a group that can reflect herpes zoster trends among the ageing population of the United Sates, herpes zoster incidence steadily increased from 2000 to 2007 (Rimland & Moanna, 2010). This is a follow-up study to document the continued trend of herpes zoster incidence among Veterans from 2008 to 2018.

Methods

Data for this study was obtained from the VA Managerial Cost Accounting System, a national information management system containing information for VAHS inpatient and outpatient care.

The period of analysis included fiscal year 2008 (beginning in October of 2008) through fiscal year 2018 (ending September 2018).

We obtained the total number of unique veterans seen for an inpatient or outpatient encounter for a diagnosis of herpes zoster during each year of the analysis period. Social Security Number was used to filter out unique patients. Diagnosis of herpes zoster was identified using International Classification of Diseases, Ninth and Tenth Revisions (ICD-9, ICD-10) codes. We also obtained the total number of unique veterans seen for an inpatient or outpatient encounter in all VA facilities for each year of the study period to serve as denominator.

In keeping with the methodology implemented by Rimland & Moanna, we included primary and secondary diagnoses of herpes zoster in order to increase the chance of finding cases of herpes zoster as an additional diagnosis during an inpatient or outpatient encounter for a different primary purpose (Rimland & Moanna, 2010).

In order to eliminate the possibility of counting multiple visits for one single episode of acute herpes zoster, we implemented the same methodology used by Rimland & Moanna; which consisted of counting only one encounter with a diagnosis of herpes zoster during a particular fiscal year. An additional encounter with a diagnosis of herpes zoster during a different fiscal year was counted as a separate herpes zoster episode (Rimland & Moanna, 2010).

For this study, data was generated by age group and by sex. Race data in the VA Managerial Cost Accounting System is incomplete and was not evaluated.

We calculated the annual incidence of herpes zoster by dividing the total number of veterans with a herpes zoster diagnosis in a given fiscal year by the total number of veterans seen during that same fiscal year. We used the same calculation to obtain annual incidence by age group and sex.

We used Poisson regression to analyze the trend of herpes zoster incidence throughout the study period and we calculated the incidence rate ratio comparing all consecutive 2-year combinations as well as the incidence rate difference comparing all consecutive 2-year combinations.

The methodology of using ICD codes to correctly identify patients with an acute herpes zoster diagnosis in the VA Managerial Cost Accounting System database has been

previously validated by Rimland & Moanna by individual manual review of electronic medical records for patients with a diagnosis of herpes zoster at the Atlanta VA Medical Center for a six year period (Rimland & Moanna, 2010). They found a positive predictive value of 0.56 for correct identification through this method (Rimland & Moanna, 2010).

This study was approved by the Emory University Institutional Review Board and the Atlanta VA Research and Development Committee.

Results

The total number of veterans seen at VA facilities around the nation was, on average, 6,270,891 per year, from fiscal year 2008 to fiscal year 2018. Female veterans were between 9.3% and 11.8% of the total population each year. Veterans aged 60 years old and older represented approximately 60% of the total population each year (between 60.1% and 61.9%).

The total number of herpes zoster diagnoses decreased from 31,885 in fiscal year 2008 to 23,424 in fiscal year 2018 (Figure 1). Poisson analysis of the trend in proportion revealed a statistically significant decreasing trend in the proportion of herpes zoster diagnoses over the years in the study period ($p = 0.0052$).

At the beginning of the study period, in fiscal year 2008, the herpes zoster incidence rate was 5.69 (95% CI 5.63 – 5.75) per 1,000 veterans. At the end of the study period, in fiscal year 2018, the incidence rate was 3.37 (95% CI 3.33 – 3.42) per 1,000 veterans. This reveals an overall decreasing trend in the herpes zoster incidence during the study period and translates into a 40.7% decrease in incidence ($p < 0.0001$) (Figure 2).

When looking at the incidence rate ratio and the incidence rate difference comparing all 2-year combinations, we note that between fiscal year 2008 and 2013, the incidence of herpes zoster was on the rise, with the largest increase happening between fiscal years 2011 and 2012 (12.79% increase in incidence rate ($p<0.0001$)). Starting on fiscal year 2014, the incidence of herpes zoster started to decrease and the largest decrease for a single 2-year comparison was seen between fiscal year 2015 and fiscal year 2016, when there was a 39.97% decrease in incidence rate ($p <0.0001$). After fiscal year 2016 the incidence remained mostly steady (Table 1).

Similar trends were seen for both male and female veterans (data not presented).

Breakdown by age groups revealed overall similar patterns across veterans in age groups from 40-49 to 90 and above that became more pronounced with increasing age. The age groups with the most drastic differences in overall herpes zoster incidence throughout the study period were 60 to 69, 70 to 79, 80 to 89 and 90 and above, with percent decreases in incidence between fiscal year 2008 and 2018 of 36.02% ($p<0.0001$), 44.18% ($p<0.0001$), 46.09% ($p<0.0001$) and 47.15% ($p<0.0001$), respectively. Veterans in age groups younger than 40 years old showed no significant change in the herpes zoster incidence throughout the study period (Table 2).

Discussion

This study of a large population of veterans provides updated and important information regarding the epidemiology of herpes zoster among veterans in the United States. Our data suggests that for the first time in over a decade, the incidence of herpes zoster is declining in the overall veteran population. The annual incidence rate of herpes

zoster in our study decreased from 5.69 per 1,000 veterans in fiscal year 2008 to 3.37 per 1,000 veterans in fiscal year 2018. This decreasing trend was seen for male and female veterans starting at age 40 years, and was more pronounced with increasing age, as is expected due to the higher burden of herpes zoster among older individuals.

To our knowledge, this study provides the most updated information on herpes zoster incidence among the overall veteran population. The only other study of the incidence of herpes zoster that we found in this population, that includes a similar time-period (data up to fiscal year 2015), reported data stratified by HIV status; the authors of that study reported a large decrease in HZ incidence between fiscal years 2002 and 2015 among veterans living with HIV (17.6 to 8.1/1000); and a mild increase in incidence during the same period among veterans without HIV (2.3 to 4.1/1000) (Hawkins et al., 2018). Our data did not contain information on HIV status and therefore we cannot directly compare our findings with this study.

In the general population, the incidence of herpes zoster has been reported to be increasing, however, one of the most recent analyses of administrative data has shown a deceleration and possible plateau among individuals aged 55 years old and older as of 2016 (Harpaz & Leung, 2019). No study of the general population has reported a clear decrease in the herpes zoster incidence similar to our findings. Furthermore, our findings contradict those of studies that project an expected increase of over 200% in the incidence of herpes zoster among adults aged 65 years old and older between 2015 and 2030, based on the trend of increasing ageing population (Varghese et al., 2017).

The etiology behind the observed decrease in herpes zoster incidence among our population is likely multifactorial, but difficult to ascertain based on our data which

contained no individual-level variables. We could consider as a possible reason for this decrease the introduction in the United States of two vaccines against herpes zoster. A live-attenuated vaccine that was available from 2006 until 2020 reduced the risk of developing herpes zoster by approximately 50% in individuals aged 60 years old and older, but efficacy decreased with age (Oxman et al., 2005; Hurley et al, 2018). A recombinant vaccine has been available since 2017; this vaccine has between 96.6% and 97.9% efficacy at preventing herpes zoster among adults aged 50 years old and older (Lal et al., 2015; Hurley et al., 2018). Vaccination rates have been shown to be acceptable in the general population in the United States but very low among veterans (Lu et al., 2017; Hawkins et al., 2018). It is therefore unlikely that vaccination is the cause of the decrease in herpes zoster incidence in our study.

Other possible reasons for the change in trend in the incidence of herpes zoster in our population could include significant improvements in the management of immunocompromising conditions and common comorbid conditions that are known to increase the risk of herpes zoster, as well as the long-term effect of childhood varicella vaccination programs. However, the lack of detail in our data did not allow for evaluation of these factors.

This study is subject to several limitations. First, as mentioned above, our data consisted only of count data without any individual-level information, therefore because we cannot accurately describe the clinical and demographic variables of our population, we cannot determine the generalizability of our results. Second, the use of ICD codes to identify acute episodes of herpes zoster has been shown to have a positive predictive value of only 0.56 (Rimland & Moanna, 2010). This may have led to an incorrect estimation of

the true herpes zoster incidence in our population but should not affect the estimated trend in incidence. Third, we may have missed cases of herpes zoster among veterans that obtained medical care outside of the VA healthcare system. We are not aware of any recent studies estimating the percent of veterans that obtain medical care outside of VA facilities, but we have no reason to believe that this percent may have changed in recent years, which could falsely decrease the incidence of herpes zoster in our population. Fourth, our results show very similar trends in herpes zoster incidence across all age-groups; since herpes zoster incidence is very significantly determined by age, this raises suspicion for an issue with the quality of our data. However, we are not aware of any systemic changes in the VA healthcare system that would affect the diagnosis of herpes zoster or the ICD codes used to identify herpes zoster.

In conclusion, this study updates the trends of herpes zoster incidence among veterans and shows that for the first time in over a decade the incidence of herpes zoster among veterans is decreasing. Further studies of veteran cohorts with individual-level data are needed to determine the causes behind this trend.

Chapter 3: Conclusions

Herpes Zoster is a common condition among older adults, a demographic that comprises most of the veteran population in the United States. This disease and its complications pose a significant burden on patients, the healthcare system and caregivers (Gater et al., 2015).

The incidence of herpes zoster has been on an increasing trend among the veteran population as well as in the overall population of the United States for decades, however this trend may be starting to reverse. Our study of a large population of veterans found that the annual incidence rate of herpes zoster decreased from 5.69 per 1,000 veterans in fiscal year 2008 to 3.37 per 1,000 veterans in fiscal year 2018. This decreasing trend was seen for male and female veterans starting at age 40 years and was more pronounced with increasing age. To our knowledge, this is the most updated information on herpes zoster incidence currently available among the veteran population.

One of the most recent analyses of herpes zoster incidence in the general population in the Unites States showed a deceleration of the previously observed trend of increasing incidence and a possible plateau among individuals aged 55 years old and older as of 2016 (Harpaz & Leung, 2019). However, no study of the general population has reported a clear decrease in herpes zoster incidence similar to our findings.

Among veterans, only one previous study includes data from a similar time-period to ours (data up to fiscal year 2015); this study reported data stratified by HIV status and found a large decrease in HZ incidence among veterans living with HIV and a mild increase in incidence during the same period among veterans without HIV (Hawkins et al., 2018).

The etiology behind the trends in herpes zoster incidence is likely multifactorial. Previous studies have tied the increase in herpes zoster incidence to the uptake in varicella vaccination among children, based on the theory of exogenous boosting (Hope-Simpson, 1965; Arvin, 1996). This theory suggests that when adults that are carrying dormant varicella zoster virus come into contact with children with varicella, there is boosting of natural immunity against VZV, which in turn inhibits reactivation of the virus (Hope-Simpson, 1965; Arvin, 1996). An increase in varicella vaccination among children would decrease the opportunity for this exogenous boosting and would, therefore, lead to a temporary increase in herpes zoster incidence that mathematical models have predicted would last for approximately 30 years after the initiation of widespread varicella vaccination programs (Schuette & Hethcote, 1999; Ogunjimi, Van Damme & Beutels, 2013). However, this theory is not supported by other studies that have found that the increasing trend in herpes zoster incidence started prior to widespread varicella vaccination in the United States and has shown no significant changes since then (Leung et al., 2011; Hales et al., 2013).

In our study, the incidence of herpes zoster among veterans started a decreasing trend in fiscal year 2013. These findings are not consistent with the predicted timeline based on the theory of exogenous boosting which would lead us to expect a continued increasing trend in herpes zoster incidence until approximately the year 2026. Furthermore, our data showed a sharp decrease in HZ incidence between fiscal years 2015 and 2016; this is again not consistent with the exogenous boosting theory, that would predict a gradual decrease in incidence as the proportion of individuals vaccinated against varicella, and

therefore with less risk for HZ, increases in a gradual manner (Schuette & Hethcote, 1999; Ogunjimi, Van Damme & Beutels, 2013).

Aside of the exogenous boosting theory, an expected effect of widespread childhood varicella vaccination programs that can affect herpes zoster incidence is the decrease in the proportion of adults carrying dormant wild type VZV, which should lead to a reduction in herpes zoster incidence since fewer adults would be a risk for it. However, studies performed since the implementation of childhood varicella vaccination have shown no clear evidence supporting this effect at a population-level (Leung et al., 2011; Hales et al., 2013). Our data did not include varicella vaccination status; therefore, we cannot assess this hypothesis in our study; but once again, the sharp decrease in HZ incidence observed in our data in a short period of time cannot be explained by this phenomenon.

Changes in the trend of herpes zoster incidence in the United States could also be expected based on the introduction of two vaccines against the disease. In 2006, a live vaccine against herpes zoster was approved by the FDA; this vaccine decreased the risk of developing herpes zoster by approximately 50% among vaccinated adults aged 60 and older, but efficacy decreased significantly with increasing age (Hurley et al., 2018). This vaccine is no longer recommended and has become unavailable in the United States (CDC, 2019c). In 2017, a recombinant vaccine became available which is more than 90% effective at reducing the risk of developing herpes zoster in adults aged 50 years and older (Lal et al., 2015; CDC, 2019c).

Recent estimates of national vaccination coverage against herpes zoster showed that among adults aged 60 years old and older, vaccination increased from approximately 7% in 2008 to almost 35% in 2018, which is above the 30% target set forth by the Healthy

People 2020 initiative (CDC, 2020). Among veterans however, the rates of vaccination against herpes zoster have been lower than in the general population, ranging from approximately 2% to 20% according to two separate reports using data corresponding to 2008 and 2015 (Rimland & Moanna, 2010; Hawkins et al., 2018).

Among the general population, the increase in vaccination coverage has not translated into a significant decrease in herpes zoster incidence at a population-level as of yet, as evidenced by the most recently available data on national HZ incidence rates (Harpaz & Leung, 2019). For this reason, it would be unjustified to assume that the decrease in incidence seen in our data could be attributed solely to increased vaccination among veterans.

As mentioned previously, the risk of developing herpes zoster has been associated to several different factors, from increasing age to medical conditions such as cancer or HIV that can affect the immune system's normal functioning. While there has been significant improvement in the successful management of HIV/AIDS, other conditions that can increase the risk of herpes zoster have become more prevalent, therefore it is unlikely that herpes zoster incidence could have decreased in our population due to decrease of risk factors other than HIV/AIDS.

In conclusion, our study of a large population of veterans provides an update on the trend of herpes zoster incidence among veterans and suggests that for the first time in over a decade the incidence of herpes zoster in this population is decreasing. However, based on our data, we cannot provide conclusive reasons for the observed change in the trend of HZ incidence.

Due to the significant burden that herpes zoster represents for the healthcare system as well as patients and their families, we believe it is justified and recommended that further studies of veteran cohorts with individual-level data be undertaken to elucidate the possible causes behind the decrease in HZ incidence.

Tables and Figures

Figure 1

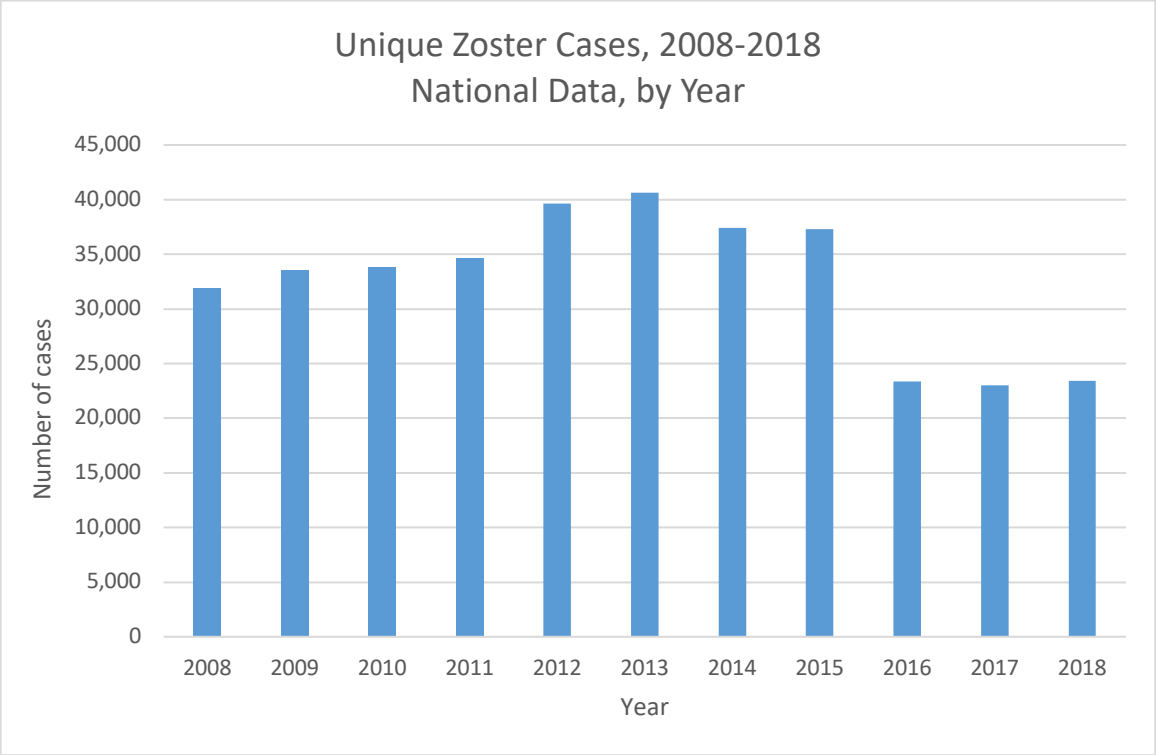

Figure 2

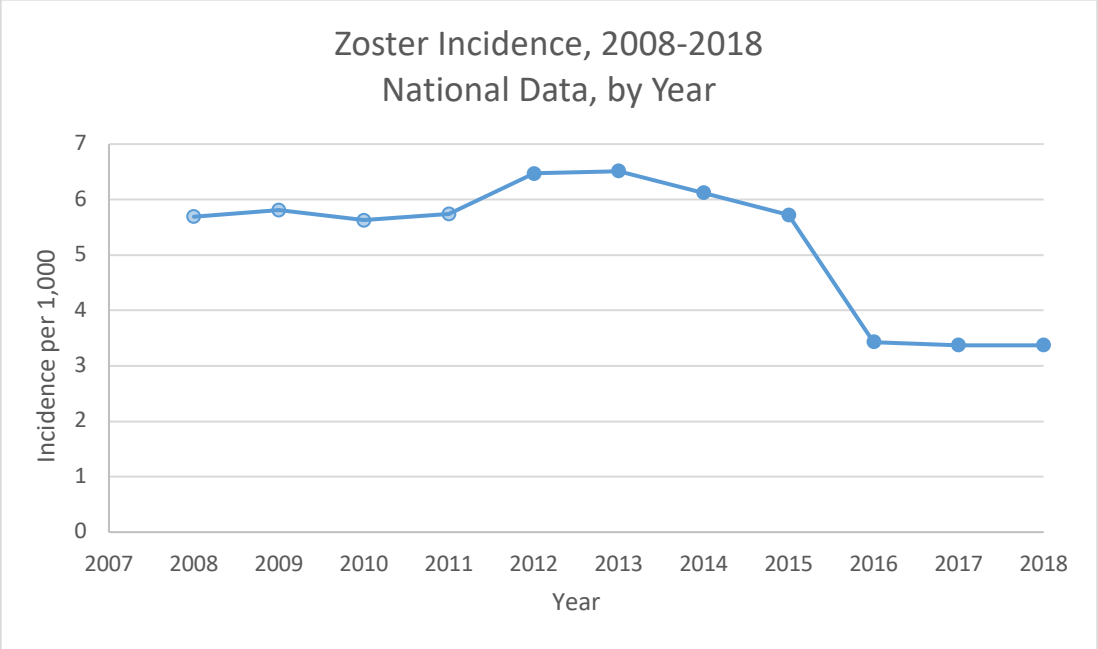

Figure 3

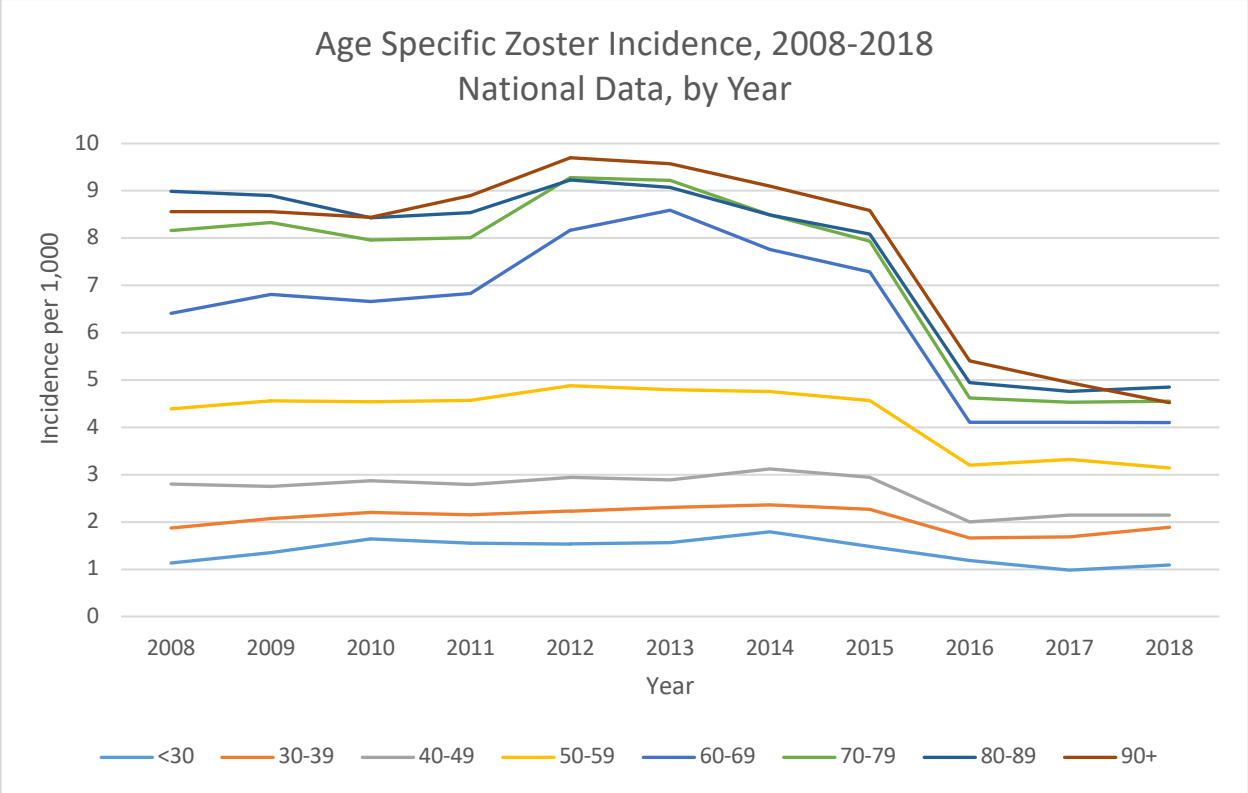

Table 1.

Incidence rate comparisons between all consecutive 2-year combinations

Years compared	**% difference**	**p-value**
2009 vs 2008	2.15% increase	0.0064
2010 vs 2009	3.12% decrease	<0.0001
2011 vs 2010	1.84% increase	0.0172
2012 vs 2011	12.79% increase	<0.0001
2013 vs 2012	0.61% increase	0.3901
2014 vs 2013	5.89% decrease	<0.0001
2015 vs 2014	6.62% decrease	<0.0001
2016 vs 2015	39.97% decrease	<0.0001
2017 vs 2016	1.96% decrease	0.0334
2018 vs 2017	2.3% increase	0.8019

Table 2.

Age-specific incidence rate comparisons between beginning and end of study-period

Age-group/Years compared	**% difference**	**p-value**
Less than 30 2018 vs 2008	2.81% decrease	0.7171
30-39 2018 vs 2008	1.03% increase	0.8431
40-49 2018 vs 2008	23.28% decrease	<0.0001
50-59 2018 vs 2008	28.43% decrease	<0.0001
60-69 2018 vs 2008	36.02% decrease	<0.0001
70-79 2018 vs 2008	44.18% decrease	<0.0001
80-89 2018 vs 2008	46.09% decrease	<0.0001
90 and older 2018 vs 2008	47.15% decrease	<0.0001

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