Increasing Incidence of Herpes Zoster among Veterans

David Rimland1,2 and Abeer Moanna1,2

1Atlanta Veterans Affairs Medical Center, Decatur, and 2Emory University School of Medicine, Atlanta, Georgia

Background. The incidence of herpes zoster in the United States has been estimated to be ≥1 million cases annually, with a higher rate in adults older than 60 years. The morbidity of the disease, including postherpetic neuralgia, imposes significant effects on quality of life. We analyzed reports of herpes zoster in the Veterans Affairs (VA) population because these patients are older and could provide a reflection of disease trends in the aging US population. These data will provide a baseline for future analyses of the incidence of herpes zoster after the introduction of the herpes zoster vaccine in late 2007.

Methods. To evaluate the trend in the annual incidence of herpes zoster for fiscal year 2000 (beginning October 1999) through fiscal year 2007 (through September 2007), we derived incidence rates using the Veterans Health Administration Decision Support System reports of herpes zoster by International Classification of Diseases, Ninth Revision codes from 2000 through 2007 and the corresponding denominator data for all veterans in care. These rates were validated by review of medical records of patients with diagnoses of herpes zoster at the Atlanta VA Medical Center.

Results. The annual incidence of herpes zoster increased from 3.10 episodes per 1000 veterans in 2000 to 5.22 in 2007 ($R^2 = 0.9743; P < .001$). This increasing rate was seen in both men and women but only in groups older than 40 years.

Conclusion. The increasing incidence of herpes zoster in our veteran population and its effect on the quality of life of the veterans validate the need for improved rates of vaccination in this population.

METHODS

The Veterans Health Administration Decision Support System (DSS) is a national automated management information system to integrate data from clinical and financial systems for both inpatient and outpatient care. The Veterans Health Administration began implement-
tation of DSS in 1994. Full implementation was completed in 1999, and DSS is now used throughout the VA health care system. Both hospital discharge and outpatient data sets became available in fiscal year 1999.

The period for the analysis included fiscal year 2000 (beginning October 1999) through fiscal year 2007 (through September 2007). Patient encounters and unique patient encounters (as determined by Social Security numbers) were extracted for the International Classification of Diseases, Ninth Revision (ICD-9) codes for herpes zoster (053 and subsets) except as noted herein. To eliminate duplicate visits for the same episode of acute herpes zoster, we chose to count only unique patients with a herpes zoster code seen each year. A subsequent episode of herpes zoster in a different year would be counted. We purposely did not search for the ICD-9 code for PHN (053.12) and postherpes polyneuropathy (053.13). Both inpatient and outpatient data were included. Primary and secondary diagnoses of herpes zoster were included; this expands the chances of finding cases of herpes zoster as the primary purpose of the visit or any additional diagnosis during an inpatient or outpatient encounter. Data were generated by age group (by decades) and sex. Race data in the national databases are incomplete and were not evaluated.

The annual rates of herpes zoster were calculated by dividing the number of unique patients with herpes zoster by the total number of veterans seen that year. The same method was used to calculate the rate by age groups. The χ² test for trend was calculated for the total and age-specific rates for the entire period.

To validate the ICD-9 diagnoses used in the national data, we reviewed all electronic medical records for patients given a diagnosis of herpes zoster at the Atlanta VA Medical Center during the same periods (calendar years 2001–2007). Because these were electronic, 100% of records were available for review by 1 person (D.R.), a board-certified infectious disease specialist with 32 years of clinical experience. Records were carefully evaluated for documentation of a diagnosis of acute herpes zoster, using the typical description of a painful unilateral rash, often with a vesicular component. Underlying immunocompromising diagnoses were specifically sought, including HIV disease, active malignant neoplasm, or chemotherapy for malignant neoplasm. We did not include patients who were receiving steroids or tumor necrosis factor (TNF) inhibitors as immunocompromised for this analysis. For patients who did not have a specific diagnosis of acute herpes zoster, other diagnoses were categorized as PHN, remote episode of herpes zoster, no medical record documentation, or other specific dermatologic disorders, such as herpes simplex, syphilis, and contact dermatitis. With these administrative data, there is no way to calculate sensitivity or specificity. However, we were able to calculate a positive predictive value for the ICD-9 diagnoses, defined as the number of patients with ICD-9 diagnosis and herpes zoster present divided by the number of patients with ICD-9 diagnosis present plus the number of patients with ICD-9 diagnosis and herpes zoster not present. This study was approved by the Emory University Institutional Review Board and the Atlanta VA Research and Development Committee.

RESULTS

National data. The total number of unique veterans seen increased from 3,905,085 in 2000 to 5,518,848 in 2007. The total number of encounters with a herpes zoster code increased from 24,269 to 47,658 during this same period. The number of unique herpes zoster episodes increased from 14,452 in 2000 to 28,710 in 2007 because we chose to count only unique patients with a herpes zoster code seen each year. The annual incidence of zoster (calculated as unique episodes) increased from 3.10 episodes per 1000 veterans in 2000 to 5.22 in 2007 ($R^2 = 0.9743; P < .001$) (Figure 1). This increasing rate was seen in both men and women (Figure 2) but only in groups older than 40 years ($P = .013$ for ages 40–49 years and $P < .001$ for all decades after 50 years of age) (Figure 3).

Atlanta validation data. During the same period of the study (2000–2007), we documented 2503 encounters for herpes zoster diagnoses by 1506 unique patients at the Atlanta VA Medical Center. After careful review of the electronic medical records, only 843 (56.0%) of 1506 represented an acute episode of herpes zoster. This corresponds to a positive predictive value of 0.56. The resolution of other diagnoses included 240 (15.9%) with a remote episode of herpes zoster, 205 (13.6%) with PHN, 109 (7.2%) with no medical record documentation of a diagnosis of herpes zoster, 68 (4.5%) with recurrent herpes simplex virus, and 31 (2.0%) with a variety of other diagnoses. No major changes were found in the distribution of these final diagnoses over time (Table 1). The incidence of documented acute herpes zoster increased from 1.52 episodes per 1000 veterans in 2001 to 2.67 in 2007 ($P = .007$). Of the 843 patients with acute herpes zoster, 107 (12.7%) were infected with HIV, and only 53 (6.3%) had other serious immunosuppressive con-
ditions (active malignant neoplasm or chemotherapy for malignant neoplasm). We also performed a sensitivity analysis with the Atlanta data excluding cases with HIV disease, malignant neoplasm, and chemotherapy. The increasing trend over time was still documented ($P = .003$).

**DISCUSSION**

Our data in a large veteran population show a striking increase in the incidence of herpes zoster during the 7-year period studied. The annual incidence increased from 3.10 episodes per 1000 veterans in 2000 to 5.22 in 2007. The increasing rate was seen in both men and women but only in groups older than 40 years. These rates have consistently increased from 2000 to 2007 in these older populations. In addition, our data confirm that the incidence of zoster increases with age. The rate has been previously noted to be 1.2–4.8 cases per 1000 persons in immunocompetent adults of all ages but increases to 7.2–11.8 cases per 1000 persons for immunocompetent adults older than 60 years [2].

The increasing rate of herpes zoster in veterans older than 40 years during the study period is probably multifactorial. The implementation of varicella vaccination in the United States since 1995 could be a contributing factor. Exposure to varicella in adults with latent varicella zoster virus infection may be protective against herpes zoster by boosting cell-mediated immunity to the virus [10, 11]. A mathematical model based on surveillance data and literature review predicted a significant increase in herpes zoster cases and morbidity due to herpes zoster after mass varicella vaccination for the first 30–50 years [10, 12], assuming that exposure to varicella induces protective immunity against herpes zoster for 20 years. Limited data have supported this proposed increased incidence. A telephone-based survey in Massachusetts found an increase in the age-standardized estimates of herpes zoster incidence from 2.77 to 5.25 cases per 1000
Increasing Herpes Zoster Incidence in Veterans

Table 1. Herpes Zoster Validation Data, Atlanta Veterans Affairs Medical Center

<table>
<thead>
<tr>
<th>Category</th>
<th>2001</th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total encounters, no.</td>
<td>198</td>
<td>218</td>
<td>263</td>
<td>245</td>
<td>500</td>
<td>495</td>
<td>584</td>
<td>2503</td>
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<tr>
<td>Total unique patient encounters, no.</td>
<td>154</td>
<td>154</td>
<td>187</td>
<td>170</td>
<td>275</td>
<td>263</td>
<td>303</td>
<td>1506</td>
</tr>
<tr>
<td>Cases of acute herpes zoster, no.</td>
<td>72</td>
<td>103</td>
<td>115</td>
<td>105</td>
<td>147</td>
<td>139</td>
<td>162</td>
<td>843</td>
</tr>
<tr>
<td>Unique acute herpes zoster patient encounters, %</td>
<td>46.8</td>
<td>66.9</td>
<td>61.5</td>
<td>61.8</td>
<td>53.4</td>
<td>52.8</td>
<td>53.5</td>
<td>56.0</td>
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<tr>
<td>Underlying disease, no.</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>HIV</td>
<td>6</td>
<td>16</td>
<td>21</td>
<td>15</td>
<td>16</td>
<td>20</td>
<td>13</td>
<td>107</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>6</td>
<td>5</td>
<td>4</td>
<td>7</td>
<td>14</td>
<td>14</td>
<td>53</td>
</tr>
<tr>
<td>Misdiagnoses, no.</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Postherpetic neuralgia</td>
<td>22</td>
<td>14</td>
<td>20</td>
<td>17</td>
<td>39</td>
<td>41</td>
<td>52</td>
<td>206</td>
</tr>
<tr>
<td>Remote episode</td>
<td>13</td>
<td>11</td>
<td>27</td>
<td>25</td>
<td>52</td>
<td>62</td>
<td>50</td>
<td>240</td>
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<tr>
<td>No medical record documentation</td>
<td>34</td>
<td>16</td>
<td>15</td>
<td>16</td>
<td>12</td>
<td>9</td>
<td>7</td>
<td>109</td>
</tr>
<tr>
<td>HSV</td>
<td>8</td>
<td>6</td>
<td>10</td>
<td>5</td>
<td>16</td>
<td>11</td>
<td>12</td>
<td>68</td>
</tr>
<tr>
<td>Other</td>
<td>5</td>
<td>4</td>
<td>0</td>
<td>2</td>
<td>9</td>
<td>1</td>
<td>10</td>
<td>31</td>
</tr>
<tr>
<td>Herpes zoster vaccine, no.</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
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<td>...</td>
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</tbody>
</table>

**NOTE.** HIV, human immunodeficiency virus; HSV, herpes simplex virus.

persons from 1999 to 2003, whereas the incidence of varicella decreased [13]. In addition, a recent national study of herpes zoster–associated hospitalizations demonstrated a significant increase after the introduction of varicella vaccine in the United States [14]. This latter approach may overestimate true rates, however [15]. In contrast, a large health maintenance organization (HMO) study in Seattle, Washington, in 1992–2002 found no increase in the age-specific incidence rates of herpes zoster associated with decreasing incidence of varicella [16]. Another HMO study in Oregon and Washington during 1997–2002 found an increase in herpes zoster incidence only in children aged 10–17 years; this increase was thought to be related to the increased administration of oral steroids to this specific group [3]. Our study evaluated the incidence of herpes zoster 5–11 years after the introduction of the varicella vaccine, unlike the HMO studies that looked at herpes zoster incidence only up to 7 years after vaccine introduction.

The use of varicella vaccine is probably not the only cause for this increased incidence because a number of studies have demonstrated a similar increase in age-related incidence in the absence of a varicella vaccine program [17–19]. In a population-based study in Rochester, Minnesota, an increase in herpes zoster incidence was observed during the 1945–1959 study period [17]. Another study in Spain found an increasing annual incidence of herpes zoster for the period 1997–2004 before the introduction of the varicella vaccination [18]. Similarly, a population-based study from Alberta, Canada, demonstrated an increase in the incidence rate of herpes zoster for the period 1986–2002 before the introduction of varicella vaccination [19]. All in all, whether varicella vaccination leads to an increased incidence in herpes zoster cases is still unclear, both in general and in our study in particular.

Increasing moderate immunosuppression secondary to diseases or immunosuppressive agents could play a role in the increasing rates of zoster at the VA. In one study of patients with rheumatoid arthritis at VA medical centers, patients who were receiving TNF inhibitors were at the greatest risk of developing herpes zoster [20]. Another study in non-VA patients found that patients with rheumatoid arthritis have a higher incidence of herpes zoster, especially those patients taking steroids or disease-modifying antirheumatic drugs [21]. Use of TNF inhibitor monoclonal antibodies was found to increase the incidence of herpes zoster in patients with rheumatoid arthritis by 82% [22]. We do not have data on rheumatoid arthritis or the use of TNF inhibitors in our study, but this should represent a small amount of our population.

Although the prevalence of HIV disease among herpes zoster cases in the Atlanta population was 12%, it is unlikely that the national increase of herpes zoster rates in our study is due to HIV infection. Recent data provide no evidence for increasing rates of HIV infection in the VA nationally [23]. Only 23,750 patients with HIV disease were seen in the VA nationally in 2007 [23]. This represents only 0.4% of the VA population in care. Moreover, a recent study at the Atlanta VA Medical Center found a decreasing incidence of herpes zoster in patients with HIV infection in 1987–2007 (D.R., unpublished data).

Zoster vaccine (Zostavax), developed by Merck, was recently approved by the Food and Drug Administration for the prevention of herpes zoster in adults aged 60 years and older [24]. The supporting evidence for approval included one major efficacy trial conducted in US veterans aged 60 years or older [1]. In this trial, zoster vaccine reduced the burden of illness (incidence, severity, and herpes zoster–associated pain) by 61.1%, the incidence of PHN by 66.5%, and the incidence of herpes zoster by 51.3% (from 11.1 to 5.4 per 1000 patient-years). The recent guidelines of the Advisory Committee on
Immunization Practices recommend giving 1 dose of the herpes zoster vaccine to all adults who are aged 60 years or older [25]. The implication for the use of this vaccine in the veteran population is large, considering the older age of this population and the cost of the vaccine. Cost-effectiveness is related to duration of protection, but it appears that administering the vaccine to adults older than 60 years is likely to be cost-effective [26–28]. The VA guidelines recommend giving the herpes zoster vaccine to patients aged 60 years or older who have no contraindications to receiving it [29]. This will potentially decrease the incidence of herpes zoster and PHN and improve quality of life in those patients. Unfortunately, the uptake of the herpes zoster vaccine has been poor to date. In 2007, herpes zoster vaccine use nationally among adults older than 60 years was only 1.9% [30]. Of the 30,000 patients eligible at the Atlanta VA Medical Center during a 2-year period, only 277 veterans and 308 veterans received the herpes zoster vaccine in fiscal years 2008 and 2009, respectively, with a rate of ∼2%.

The strengths of our study include the large number of patients evaluated, the availability of electronic medical records, and large administrative databases. All these factors allowed calculation of herpes zoster rates, demonstrating the increasing rates in the older population. Our validation study in the Atlanta patients demonstrated that ICD-9 codes are often erroneous, but the increasing rate of true acute herpes zoster cases in the Atlanta cohort supports our findings. Similar data for more recent periods are not available. We are not aware of any systemic changes within the VA that would make herpes zoster a more reportable diagnosis. Specifically, there were no guidelines or information letters distributed to increase clinician awareness. In addition, we are not aware of any changes that occurred in coding for herpes zoster.

The main limitation in our study is the absence of national data available on the incidence of herpes zoster among veterans in care before 2000. This does not allow us to examine the incidence of herpes zoster before and after the introduction of the varicella vaccine in 1995. In addition, our study may have missed a number of cases of herpes zoster in veterans whose conditions were diagnosed and who were treated at non-VA facilities; these numbers are hard to estimate, however. Veterans aged 65 years and older are eligible for Medicare and may seek medical care in the private sector. A retrospective study in 1999 estimated that, of 1.47 million veterans, 18% used the VA, 36% used Medicare, and 46% used both the VA and Medicare for outpatient treatments [31]. In the same study, 36% of veterans used the VA for inpatient treatments, whereas 69% used Medicare only [31]. Whether these estimates apply to recent VA use is unknown. In addition, there are no data to evaluate the use of non-VA sources for acute diseases such as herpes zoster. Finally, our study may be limited by the fact that we did not analyze patients receiving steroids or TNF inhibitors, but the number of these patients should be small.

This study shows a striking increase in the incidence of herpes zoster in a population of veterans between 2000 and 2007. The availability of the VA administrative databases will allow us to track the trends in herpes zoster incidence in this population with expanding use of zoster vaccine. This will help address the potential causes for increasing rates in this population. The increasing incidence of herpes zoster in our population and its effect on the quality of life of the veterans validate the need for improved rates of vaccination in this population.

Acknowledgments
We thank Nancy Lapointe (Director of Clinical User Support, Department of Veterans Affairs, Bedford, Massachusetts) for the national data. Potential conflicts of interest. D.R. and A.M.: no conflicts.

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