Hospitalizations to Treat Herpes Zoster in Older Adults: Causes and Validated Rates

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Background. The availability of a vaccine for the prevention of herpes zoster has increased interest in methods to measure zoster disease burden. Hospitalizations assigned a zoster diagnosis code have been used as indicators of severe zoster in prior studies. However, a zoster diagnosis code may not be a specific indicator of severe zoster illness, because the code may be assigned to a hospitalization for another cause in a person with coincident zoster.

Methods. To assess the validity of a hospital diagnosis code of zoster as an indicator of hospitalizations that are attributable to zoster, we identified all hospitalizations with a zoster diagnosis code assigned in any position among members of a managed-care organization who were ≥50 years of age during 1992–2004. Of those, we selected a sample of 260 hospitalizations for chart review.

Results. Chart reviews were completed for 225 hospitalizations. Sixty-five (29%) were because of zoster or a complication of zoster treatment, and an additional 9 (4%) were because of postherpetic neuralgia or a complication of postherpetic neuralgia treatment. Although the overall age-adjusted rate of hospitalizations with a zoster diagnosis code was 42.5 hospitalizations per 100,000 population per year, the estimated rate of hospitalizations because of zoster, postherpetic neuralgia, or adverse effects of a medication used to treat zoster or postherpetic neuralgia was only 14.0 hospitalizations per 100,000 population per year.

Conclusions. Rates of hospitalizations associated with a zoster diagnosis code will substantially overestimate the burden of hospitalizations attributable to zoster in older adults.

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The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

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The availability of a vaccine for the prevention of herpes zoster [1] has led to increased interest in methods to measure and track zoster disease burden. In addition to substantial morbidity due to pain, zoster can cause severe complications, including disseminated disease and ophthalmic or CNS involvement, and can result in hospitalization for clinical management or intravenous antiviral therapy. A substantial portion of the medical care burden from zoster can be associated with these hospitalizations, so it is particularly important that data on hospitalizations be accurate.

Administrative databases have been used to characterize the epidemiology of zoster by identifying medical encounters, primarily in the outpatient setting, associated with a zoster diagnosis code [2–7]. In a previous study, we documented the fact that a zoster diagnosis code assigned to an outpatient visit was highly predictive (94%) of a validated episode of acute zoster in older adults in a managed-care setting [2]. However, although several studies have used administrative data to characterize rates of hospitalizations associated with zoster, the validity of these data has not been well defined. It is possible, for example, that a zoster diagnosis code may be assigned to hospitalizations for another cause for a person with coincident zoster. We describe a population-based assessment of older adults in which the characteristics of zoster-coded hospitalizations were defined by medical record review, to determine the validity of a zoster hospital discharge diagnosis code as an indicator of hospitalization attributable to zoster. In addition, we have determined the portion of cases occurring among persons eligible for zoster vaccine, and we have established a more accurate estimate of the population rate of hospitalizations for zoster.
METHODS

The study population included adults \( \geq 50 \) years of age who were enrolled in Group Health, an integrated health care system in western Washington State with \( \sim 350,000 \) members, during 1992–2004. Group Health members receive inpatient care primarily from community hospitals not affiliated with Group Health, but the admission and discharge summaries forwarded from those hospitals are routinely incorporated into the patient’s Group Health medical record and are available for review. For the study population, Group Health administrative data sources were used to identify overnight hospitalizations with a zoster International Classification of Diseases, 9th Revision, Clinical Modification discharge diagnosis code (053.x) assigned in any 1 of the 12 available positions.

During the study period, 484 study cohort members had 595 hospitalizations with a zoster diagnosis code. Of that group, 402 persons had a single hospitalization with a zoster code, and 82 had multiple hospitalizations. The percentage of persons with multiple zoster-coded hospitalizations increased with age, accounting for 12% of those 50–79 years of age, compared with 24% of those \( \geq 80 \) years of age (\( P < .001 \)).

The study cohort of 484 persons was further restricted to the 411 persons with an identified Group Health clinic chart base for whom medical records were available. Of those 411, a sample of 260 persons was selected for record review. This sample included all 40 persons aged 50–59 years and a randomly selected 220 of the 371 persons aged \( \geq 60 \) years. Only first hospitalizations associated with a zoster diagnosis code during the study period were eligible for review.

Trained abstractors reviewed hospitalization records to determine the cause of the hospitalization. Abstractors recorded whether the records indicated that zoster, postherpetic neuralgia (PHN), or complications of medications used to treat zoster or PHN was the cause of the hospitalization. For hospitalizations not due to these 3 factors, abstractors indicated the probable reason for the zoster code. These included coincident zoster or PHN that was present at hospital admission but that was not the reason for admission, zoster that developed after hospital admission, notation of a history of zoster or PHN in the absence of current disease, or other reasons (e.g., miscoding of herpes simplex). Abstractors also recorded information about the presence of concomitant illnesses, including immunocompromising conditions, and about the use of oral or intravenous antiviral agents during the hospitalization. In instances when antivirals were given both orally and intravenously during hospitalization, we defined the mode of administration as intravenous.

It is possible that primary or secondary zoster discharge codes better predict hospitalizations attributable to zoster or related complications than do zoster discharge codes assigned at a later position. Because severe zoster is often treated with intravenous acyclovir, use of intravenous acyclovir may also be a marker for hospitalizations attributable to zoster. Three indicators—zoster as primary code, zoster as primary or secondary code, and administration of intravenous acyclovir—were evaluated for their ability to predict 2 outcomes [8]. The first outcome was hospitalization attributable to zoster, PHN, or adverse effects of medications given for treatment of those conditions, and the second outcome was the subset of those hospitalizations specifically attributable to zoster illness.

Rates of zoster in the Group Health population of persons \( \geq 50 \) years of age for each of the study years are reported as crude and as age-standardized rates. Age standardization was performed by direct standardization to the United States 2000 census population. The mean values of length of hospital stay were compared, using Student’s \( t \) test, between persons hospitalized because of zoster and those hospitalized with zoster that was incidental to the reason for hospital admission.

RESULTS

Validation of hospitalizations with a zoster diagnosis code.

Of the 260 hospitalizations identified for review, 35 (13%) could not be reviewed because of insufficient information about the hospitalization in the Group Health medical record. Of the 225 completed reviews, the hospitalization was attributable to zoster or a complication of zoster treatment for 65 (29%), and the hospitalization was attributable to PHN or a complication of PHN treatment for 9 (4%) (figure 1). Thus, zoster, PHN, or a related complication was the cause of the hospitalization for only 74 (33%) of 225 hospitalizations assigned a zoster diagnosis code. This proportion did not vary statistically significantly by sex or decade of age.

Of the remaining 151 hospitalizations not attributable to zoster, PHN, or treatment complications, in most cases (117 hospitalizations [77%]), zoster or PHN was noted during the hospitalization but was not the reason for the hospitalization. For 65 (56%) of these 117 hospitalizations, zoster was present at hospital admission but was incidental to the reason for admission. For those persons, the causes of hospital admission were consistent with typical reasons for hospitalization in older adults and included indications such as pneumonia, stroke, fall, chest pain, altered mental status, and gastrointestinal bleeding. For another 40 hospitalizations (34%), PHN symptoms were noted at hospital admission, but this condition was incidental to the hospitalization and was not the reason for admission. Lastly, 12 patients (10%) had zoster with onset after hospital admission.

In 24 (71%) of the 34 hospitalizations during which zoster or PHN was not identified, the patient was noted to have a history of zoster or PHN, which appeared to be the reason for...
the assignment of the zoster diagnosis code. A diagnosis of herpes simplex infection, which appeared to have been mis-coded as zoster, was noted for only 3 (1%) of the hospitalizations reviewed.

Of the 74 hospitalizations attributable to zoster, PHN, or adverse effects of medical treatment (figure 1), 61 (82%) involved persons ≥60 years of age. Thirteen (21%) of these 61 patients were immunocompromised, as defined by the presence of hematologic or metastatic cancer, receipt of chemotherapy within the previous 3 months, chronic corticosteroid use, or receipt of other immunosuppressive medications. Thus, 79% of hospitalizations (48 of 61) attributable to zoster or PHN in persons ≥60 years of age involved persons eligible for zoster vaccination.

**Description of the hospitalizations for acute zoster or PHN.**

Of the 65 persons hospitalized because of zoster, 56 were admitted to the hospital because of the illness itself, and 9 were admitted because of adverse effects of medications used to treat the zoster episode. Among the 56 patients who were admitted to the hospital for the zoster illness, the most common reasons for admission were suspected or confirmed severe complications of zoster, including ophthalmic zoster (2 patients), dissemination (5), CNS involvement (6), and weakness, dehydration, confusion, or hyponatremia attributed to the zoster episode (12). Ten patients were admitted to the hospital for evaluation of a pain syndrome that was later attributed to zoster, including abdominal pain, shoulder pain, or headache, and 3 patients were admitted for neurologic symptoms that were later attributed to zoster (e.g., facial droop, upper extremity weakness, and vertigo). Six patients were admitted to the hospital for control of zoster-related pain, 6 patients were admitted for treatment of suspected facial cellulitis associated with zoster, and 2 patients were admitted for zoster-related urinary retention.

Of the 9 patients admitted to the hospital for complications of zoster treatment, 4 had nausea, vomiting, or constipation due to narcotics; 2 had suspected CNS toxicity from acyclovir; and 3 had nausea and vomiting attributed to oral acyclovir, with 1 person experiencing an esophageal rupture that required surgical repair.

There was no difference in the mean length of stay for the 65 persons admitted to the hospital because of acute zoster (mean length of stay, 4.0 days; 95% CI, 3.1–4.9 days), compared with that for the 65 persons with acute zoster that was incidental to hospitalization (mean length of stay, 3.9 days; 95% CI, 3.0–4.8 days). The percentage of persons with an outpatient diagnosis code of zoster (053.x) recorded within 30 days before the hospitalization also did not differ between those 2 groups and included 52% of those admitted to the hospital because of zoster (34 patients) and 51% of those with incidental zoster (33 patients).

Of the 9 persons admitted to the hospital because of PHN, 1 was admitted for pain control, 2 were admitted for evaluation of abdominal pain that was later attributed to PHN, including abdominal pain, shoulder pain, or headache, and 3 were admitted for neurologic symptoms that were later attributed to zoster (e.g., facial droop, upper extremity weakness, and vertigo). Six patients were admitted to the hospital for control of zoster-related pain, 6 patients were admitted for treatment of suspected facial cellulitis associated with zoster, and 2 patients were admitted for zoster-related urinary retention.

Of the 9 patients admitted to the hospital for complications of PHN treatment, 4 had nausea, vomiting, or constipation due to narcotics; 2 had suspected CNS toxicity from acyclovir; and 3 had nausea and vomiting attributed to oral acyclovir, with 1 person experiencing an esophageal rupture that required surgical repair.
tributable to aspirin and treatment with nonsteroidal anti-inflammatory drugs (1).

**Predictors of hospitalization for zoster.** Zoster was the primary (for 44 hospitalizations) or secondary (72) discharge diagnosis code for 116 (52%) of the 225 hospitalizations reviewed. For the 44 hospitalizations with zoster as the primary code, acute zoster (for 42 hospitalizations) or PHN (2) was present at hospital admission and represented the reason for hospital admission for 38 (86%) of these hospitalizations. Thus, the positive predictive value of a zoster primary discharge diagnosis code for predicting hospitalization attributable to zoster or PHN (or adverse effect of medications given for treatment) is 86%. For 34 (77%) of these 44 hospitalizations, zoster illness represented the specific reason for hospital admission.

Of the 74 hospitalizations that were validated by medical record review to be attributable to zoster, PHN, or medication effects, 38 (51%) had zoster listed as the primary code. In general, the primary diagnosis code assigned to the other 36 hospitalizations reflected the complication or symptoms that led to hospital admission. For example, a primary code indicating hyponatremia or volume depletion was assigned to 12 of those 36 hospitalizations, 6 had a primary code indicating gastrointestinal disease, and 4 had a primary code for neurologic symptoms or disease, such as encephalitis or delirium.

We abstracted information on administration of antiviral treatment during hospitalization. Administration of antiviral agents was noted for 92 (41%) of the 225 hospitalizations reviewed. Antiviral treatment was administered only to persons with zoster during the hospitalization, either present at hospital admission (82 [63%] of 130) or with onset during the hospitalization (10 [8%] of 12). Of the 130 persons affected with zoster at hospital admission, those with hospitalization attributable to zoster were more likely to be given intravenous treatment than were those with incidental zoster (34% vs. 5%), but both groups were equally likely to receive oral treatment (41% vs. 46%). Of the 13 persons admitted because of suspected disseminated zoster, ophthalmic zoster, or CNS zoster, all received antiviral treatment, and 11 (85%) received intravenous treatment. For 20 (17%) of the 116 hospitalizations with zoster as a primary or secondary code, administration of intravenous acyclovir was noted during chart review.

Table 1 reports the performance of the use of zoster diagnosis codes and recorded intravenous acyclovir treatment for correct identification of zoster hospitalizations. In general, the sensitivity and positive predictive value tended to be higher for patients aged 50–69 years than for those aged ≥70 years. For example, the positive predictive value for zoster recorded as the primary code for the outcome of zoster or PHN (or adverse effect of medications given for zoster or PHN treatment) was 94% in the younger group and 81% in the older group (P = .04), and the sensitivity of that criterion was 72% in the younger group and 42% in the older group (P = .03).

**Rates of hospitalization for zoster.** Table 2 reports rates of hospitalization associated with a zoster diagnosis code, in any position, in the study population of Group Health members ≥50 years of age during 1992–2004. Annual rates had a range of 28.7 hospitalizations per 100,000 person-years (1999) to 52.1 hospitalizations per 100,000 person-years (1992), but there were no trends over time. Although the overall age-adjusted rate of hospitalizations with a zoster diagnosis code was 42.5 hospitalizations per 100,000 population per year, the estimated rate of hospitalizations attributable to zoster, PHN, or adverse effects of a medication used to treat zoster or PHN was only 14.0 hospitalizations per 100,000 population per year.

**DISCUSSION**

Hospitalizations associated with a zoster diagnosis code have been used as indicators of the burden of severe zoster infection.

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**Table 1. Performance of algorithms used to validate herpes zoster (HZ) hospitalizations.**

<table>
<thead>
<tr>
<th>Outcome and criterion</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>PVP, %</th>
<th>NPV, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>HZ or PHN (or adverse effects of medications given for treatment) as the reason for hospital admission (n = 74)</td>
<td>51</td>
<td>96</td>
<td>86</td>
<td>80</td>
</tr>
<tr>
<td>HZ primary code</td>
<td>66</td>
<td>56</td>
<td>42</td>
<td>77</td>
</tr>
<tr>
<td>HZ primary or secondary code</td>
<td>23</td>
<td>100</td>
<td>100</td>
<td>72</td>
</tr>
<tr>
<td>HZ primary or secondary code and IV acyclovir treatment</td>
<td>23</td>
<td>98</td>
<td>85</td>
<td>72</td>
</tr>
<tr>
<td>HZ illness as the reason for hospital admission (n = 56)</td>
<td>61</td>
<td>94</td>
<td>77</td>
<td>88</td>
</tr>
<tr>
<td>HZ primary code</td>
<td>75</td>
<td>56</td>
<td>36</td>
<td>88</td>
</tr>
<tr>
<td>HZ primary or secondary code</td>
<td>30</td>
<td>100</td>
<td>100</td>
<td>81</td>
</tr>
<tr>
<td>HZ primary or secondary code and IV acyclovir treatment</td>
<td>30</td>
<td>98</td>
<td>85</td>
<td>81</td>
</tr>
</tbody>
</table>

**NOTE.** IV, intravenous; NPV, negative predictive value; PVP, positive predictive value.
Table 2. Rate of overnight hospitalizations associated with a zoster diagnosis code among adults aged ≥50 years in the Group Health source population, by age group and year, 1992–2004.

<table>
<thead>
<tr>
<th>Age group or hospitalization year</th>
<th>No. of hospitalizations</th>
<th>Person-years</th>
<th>Crude hospitalization rate per 100,000 population</th>
<th>Age, adjusted* rate per 100,000</th>
<th>Hospitals validated to be due to zoster, PHN, or adverse effect of medication used to treat zoster or PHN, %</th>
<th>Estimated rate of hospitalizations validated to be zoster related, per 100,000 population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50–59</td>
<td>49</td>
<td>636,178</td>
<td>9.1</td>
<td>6.2</td>
<td>7.7</td>
<td>NA</td>
</tr>
<tr>
<td>60–69</td>
<td>72</td>
<td>372,893</td>
<td>19.1</td>
<td>19.5</td>
<td>19.3</td>
<td>NA</td>
</tr>
<tr>
<td>70–79</td>
<td>207</td>
<td>305,118</td>
<td>65.6</td>
<td>70.9</td>
<td>67.8</td>
<td>NA</td>
</tr>
<tr>
<td>≥80</td>
<td>267</td>
<td>159,858</td>
<td>176.7</td>
<td>149.5</td>
<td>167.0</td>
<td>NA</td>
</tr>
<tr>
<td>≥50</td>
<td>595</td>
<td>1,474,047</td>
<td>45.2</td>
<td>43.5</td>
<td>44.0</td>
<td>33</td>
</tr>
<tr>
<td>Year</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>1992</td>
<td>49</td>
<td>94,048</td>
<td>60.0</td>
<td>42.5</td>
<td>52.1</td>
<td>58.1</td>
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<tr>
<td>1993</td>
<td>45</td>
<td>96,672</td>
<td>54.5</td>
<td>36.8</td>
<td>46.6</td>
<td>48.6</td>
</tr>
<tr>
<td>1994</td>
<td>42</td>
<td>98,142</td>
<td>51.9</td>
<td>31.7</td>
<td>42.8</td>
<td>45.4</td>
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<tr>
<td>1995</td>
<td>45</td>
<td>100,347</td>
<td>45.5</td>
<td>44.1</td>
<td>44.8</td>
<td>46.8</td>
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<tr>
<td>1996</td>
<td>41</td>
<td>104,020</td>
<td>34.2</td>
<td>44.5</td>
<td>39.4</td>
<td>40.8</td>
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<tr>
<td>1997</td>
<td>37</td>
<td>108,788</td>
<td>42.1</td>
<td>24.3</td>
<td>34.0</td>
<td>34.6</td>
</tr>
<tr>
<td>1998</td>
<td>41</td>
<td>114,466</td>
<td>33.8</td>
<td>38.3</td>
<td>35.8</td>
<td>36.9</td>
</tr>
<tr>
<td>1999</td>
<td>34</td>
<td>118,283</td>
<td>29.5</td>
<td>27.9</td>
<td>28.7</td>
<td>30.2</td>
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<tr>
<td>2000</td>
<td>56</td>
<td>120,561</td>
<td>57.8</td>
<td>32.9</td>
<td>46.5</td>
<td>48.7</td>
</tr>
<tr>
<td>2001</td>
<td>57</td>
<td>125,213</td>
<td>58.4</td>
<td>30.0</td>
<td>45.5</td>
<td>48.3</td>
</tr>
<tr>
<td>2002</td>
<td>46</td>
<td>129,693</td>
<td>36.6</td>
<td>34.1</td>
<td>35.5</td>
<td>38.1</td>
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<tr>
<td>2003</td>
<td>49</td>
<td>131,387</td>
<td>41.6</td>
<td>32.1</td>
<td>37.3</td>
<td>40.2</td>
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<tr>
<td>2004</td>
<td>53</td>
<td>132,427</td>
<td>45.3</td>
<td>33.6</td>
<td>40.0</td>
<td>42.0</td>
</tr>
</tbody>
</table>

**NOTE.** NA, not applicable; PHN, postherpetic neuralgia.

* Adjusted by direct standardization to the United States 2000 census population.

in epidemiologic and economic assessments [6, 9–15]. In the present study, we found that only 33% of hospitalizations associated with a zoster discharge diagnosis code in any position were attributable to zoster, PHN, or a related complication. For the remaining 67%, the zoster diagnosis code was usually assigned because of concomitant zoster or PHN illness that was incidental to the reason for hospital admission or because there was a notation of a history of zoster or PHN. Thus, use of the rate of hospitalization associated with a zoster diagnosis code assigned in any position will result in a substantial overestimation of the rate of hospitalization attributable to zoster or related complications among older adults.

In contrast, the hospitalizations with zoster as the primary discharge diagnosis code (accounting for 19% of all hospitalizations), 86% were attributable to zoster, PHN, or an adverse effect of medication for those conditions. However, zoster was the primary diagnosis code for only 51% of all zoster-coded hospitalizations that were validated by medical record review to be attributable to zoster, PHN, or medication effects. Thus, a definition based on a primary discharge diagnosis code will fail to capture many zoster-related hospitalizations. The inclusion of hospitalizations with zoster as a secondary diagnosis code did not substantively improve sensitivity in defining hospitalizations attributable to zoster and greatly reduced the specificity and positive predictive value. Our results suggest that medical record review is required to identify those hospitalizations that were truly attributable to zoster or a related complication and to obtain accurate estimates of medical care or costs attributable to zoster.

Twenty percent of hospitalizations attributable to zoster or PHN (15 of 74) were attributable to adverse effects of medications used to treat zoster (9) or PHN (6). Although these events were relatively uncommon, their occurrence underscores the need for careful monitoring when administering medications that have the potential for significant systemic effects for older adults.

Our study suggests that hospitalizations may not provide accurate information regarding secular trends in the incidence of zoster, even when methods are validated and the hospitalizations are truly attributable to zoster. We found that 21% of hospitalizations attributable to zoster occurred among persons who were immunocompromised. The risk of severe zoster is quite elevated in such patients [16, 17]. In addition, health care providers may elect to hospitalize such patients when they experienced early, uncomplicated zoster, to monitor them for development of severe complications. Temporal trends or local patterns in the prevalence of immunosuppression could, therefore, have a dominating influence on the incidence of zoster.
hospitalization, which would mask the effects of any secular trends in zoster incidence among the general population. Trends in zoster incidence are of greatest importance among the immunocompetent population, because this is the group for whom the zoster vaccine is indicated.

This study had certain limitations. It was conducted in 1 geographic area and therefore may not be completely generalizable to other populations, although the cases did include persons hospitalized at a number of community hospitals in the region. In addition, we conducted chart reviews only for hospitalizations assigned a zoster diagnosis code and therefore did not identify hospitalizations for zoster illness that may have been associated with other codes.

In this study, we found no evidence of an increase over time in the rate of hospitalization associated with a zoster diagnosis code, which is consistent with our previous assessment of rates of outpatient and inpatient medical encounters associated with a zoster diagnosis code in the Group Health population during 1992–2002 [2]. Of those persons aged ≥60 years whose hospitalizations were attributable to zoster or PHN, most (72%) were immunocompetent persons and therefore represent hospitalizations that are potentially preventable by zoster vaccination.

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References