Vaccination Against Zoster Remains Effective in Older Adults Who Later Undergo Chemotherapy

Hung Fu Tseng,1 Sara Tartof,1 Rafael Harpaz,2 Yi Luo,1 Lina S. Sy,1 Rulin C. Hetcher,1 and Steven J. Jacobsen1

1Department of Research and Evaluation, Kaiser Permanente Southern California, Pasadena; and 2Division of Viral Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia

(See the Editorial Commentary by Oxman and Schmader on pages 920–2.)

Background. Approximately 40% of adults develop invasive cancer during their lifetimes, many of whom require chemotherapy. Herpes zoster (HZ) is common and often severe in patients undergoing chemotherapy, yet there are no data regarding whether these patients retain specific protection against HZ if they had previously received zoster vaccine. We conducted a study to determine whether zoster vaccine was effective in patients who subsequently underwent chemotherapy.

Methods. The cohort study consisted of Kaiser Permanente Southern California members aged ≥60 years treated with chemotherapy. The exposure variable was receipt of zoster vaccine prior to initiation of chemotherapy. Incident HZ cases were identified using International Classification of Diseases, Ninth Revision diagnostic codes. HZ incidence rates were calculated; hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox proportional hazards regression models.

Results. There were 91 and 583 HZ cases in the vaccinated and unvaccinated cohorts, respectively, yielding an incidence rate of 12.87 (95% CI, 10.48–15.80) vs 22.05 (95% CI, 20.33–23.92) per 1000 person-years. Thirty-month cumulative incidence was 3.28% in the vaccinated group and 5.34% in the unvaccinated group (P < .05). The adjusted HR for HZ was 0.58 (95% CI, .46–.73) and showed no significant variation by age, sex, or race. HZ incidence rates remained increased in the small subgroup of persons receiving zoster vaccine within 60 days before chemotherapy, but this was the only group affected by indication bias. No vaccinated patients underwent hospitalization for HZ, compared with 6 unvaccinated patients.

Conclusions. Zoster vaccine continues to protect against HZ if recipients later undergo chemotherapy. Our findings provide an additional rationale for offering zoster vaccine to indicated adults while they are immunocompetent.

Keywords. chemotherapy; immunosuppression; vaccine effectiveness; zoster vaccine.

Herpes zoster (HZ) is a painful and often debilitating disease caused by reactivation of varicella zoster virus (VZV) that remains dormant after primary infection. HZ incidence increases substantially in adults as they age, but the other key risk factor for HZ is immunosuppression, whether due to human immunodeficiency virus (HIV) infection [1], treatment of autoimmune diseases [2–4], stem cell or solid organ transplant [5–7], hematologic malignancies, or chemotherapeutic treatment of solid tumors [8, 9]. Rates of HZ in patients undergoing chemotherapy for solid tumors, for instance, are almost 4 times the rate in healthy adults [8, 9]. In addition, immunosuppressed individuals are at greatest risk of the most severe ophthalmologic and neurologic complications of HZ, including visceral dissemination [10].

Zoster vaccine (Zostavax) has been shown to be safe and protective in immunocompetent elderly populations [11–13], but the vaccine is comprised of the live attenuated Oka strain of VZV and is thus contraindicated in immunocompromised persons due to a lack of data on vaccine safety and efficacy in these patients; the Shingles Prevention Study excluded patients who were immunosuppressed due to malignancy, HIV infection,
immunosuppressive or cytotoxic chemotherapy, or high-dose corticosteroid therapy. These patients were thought, on a theoretical basis, to be at higher risk for side effects and less likely to benefit from the vaccine [13].

Most persons with immunocompromising conditions acquire the conditions as adults. Therefore, there are opportunities to vaccinate these persons before they become immunocompromised. In one approach, by widely offering zoster vaccine to the recommended population of adults aged ≥60 years, a portion of the vaccinated adults will discover months or years later that they acquired a medical condition that is immunocompromising or that requires immunocompromising treatments. Alternatively, adults aged ≥60 years who remain unvaccinated may discover that they acquired a medical condition that requires immunocompromising treatments in coming weeks or months; the Advisory Committee on Immunization Practices (ACIP) recommends that these persons be offered zoster vaccine while their immunity is intact if it can be administered at least 14 days, and ideally 1 month, before initiation of immunosuppressive therapy [14].

However, the safety and effectiveness of these approaches have never been empirically tested in a study. It is plausible that VZV-specific immunity will be lost as more general immunosuppression occurs. In fact, live attenuated zoster vaccine can establish latency and itself reactivate to cause zoster [15]. This is rare in immunocompetent individuals, but it is possible that the vaccine virus might contribute to the risk of zoster and its complications once immunosuppression occurs.

As the expected number of elderly persons who will become immunocompromised due to treatments or diseases increases, it is important to evaluate the safety and effectiveness of zoster vaccination in patients who subsequently receive immunosuppressive treatments. In this study, we identified a cohort of individuals who received myelosuppressive chemotherapy at age 60 years and older and compared the incidence of HZ after chemotherapy between those who had been vaccinated with zoster vaccine before chemotherapy and those who had not.

**METHODS**

**Setting**

The study was conducted among members of Kaiser Permanente Southern California (KPSC), an integrated healthcare system that provides comprehensive prepaid health services for its 3.6 million members. Members are racially diverse and include the entire sociodemographic spectrum, and >99% are community-dwelling. The demographic makeup of the KPSC membership closely mirrors the Southern California population [16]. Compared with the United States population, the KPSC membership has twice as many individuals of Asian descent and 3 times as many Hispanics. Data regarding demographics, services, and diagnoses were tracked in KPSC electronic health records from the outpatient, emergency department, and hospital settings. Pharmacy and vaccination utilization is linked through patients’ unique medical record numbers. Vaccinations received outside of the health plan with appropriate documentation are recorded.

KPSC is a prepaid healthcare system. The vaccine was provided to KPSC members at no charge, which was an incentive for members to receive immunizations within the system. Also, there is a very strong motivation for members to use services internally. In addition, for outside providers to be reimbursed by the health plan for covered emergent or contract care, claims must be submitted with documentation of the episode of care. Thus, the capture of care delivered to the members by electronic administrative data is reasonably assumed to be very comprehensive.

The protocol was reviewed and approved by the KPSC Institutional Review Board. The requirement for informed consent was waived.

**Cohort**

The cohort consisted of KPSC members aged ≥60 years on 1 January 2007 who received chemotherapy with myelosuppressive agents (Supplementary Appendix Table 1) between 1 January 2007 and 31 December 2012. Cohort members were limited to those with continuous membership and drug benefits for the 6 months before chemotherapy treatment. In addition, cohort membership was restricted to those with no history of receiving any of these myelosuppressive agents and no diagnosis of zoster within the 6 months prior to chemotherapy. HIV-infected individuals, patients with hematopoietic cancers, individuals receiving zoster vaccine prior to 1 January 2007, and individuals developing HZ within 30 days following vaccination were excluded from the cohort.

**Exposure**

The exposure variable was receipt of zoster vaccine after 1 January 2007 and prior to the initiation of chemotherapy. Subjects who received zoster vaccine after initiation of chemotherapy were not included.

**Follow-up Period**

The period of follow-up started from the date of chemotherapy and ended at 30 months of follow-up or the date of HZ occurrence, termination of KPSC membership, or 31 December 2012, whichever was earliest.

**Incidence of HZ**

Incidence of HZ during the follow-up period was identified electronically by the first occurrence of an International Classification of Diseases, Ninth Revision (ICD-9) diagnosis code of 053.xx assigned in the inpatient, outpatient, and emergency department settings. Medical records for patients identified from inpatient settings were reviewed to determine if the hospitalization was due to HZ. If HZ developed during a hospital stay for
another condition, it was considered as an incident HZ but not HZ requiring hospitalization.

Covariates
Cohort members were categorized to assess factors associated with vaccination and risk of HZ, including age, sex, race, healthcare utilization, and use of antiviral medications (acyclovir, famciclovir, or valacyclovir) during the follow-up period. Healthcare utilization was defined as the number of hospitalizations or outpatient or emergency department visits in the 6 months prior to the follow-up period.

Statistical Analysis
The distribution of baseline characteristics was compared between the vaccinated and unvaccinated populations, including age, sex, race, healthcare utilization prior to chemotherapy, and use of antiviral medications during follow-up. The time from vaccination to chemotherapy was also calculated for the vaccinated group. The 30-month cumulative incidence of HZ after chemotherapy was estimated by Kaplan-Meier method, and the difference between the vaccinated and the unvaccinated population was tested by the log-rank test. Incidence rate of HZ was estimated by dividing the number of HZ cases by the total number of person-years of follow-up. The 95% confidence intervals (CIs) were estimated assuming that occurrence of HZ follows a Poisson distribution. Hazard ratios (HRs) and 95% CIs of HZ comparing the vaccinated and the unvaccinated cohort were estimated using Cox proportional hazards regression models with chemotherapy (on, off) treated as a time-dependent variable, and with adjustment for potential confounding factors, including age (years); sex (male, female); race (white, black, Asian/Pacific Islander, Hispanic, other/multiple/unknown); number of outpatient visits (0, 1–4, 5–10, ≥11), emergency department visits (0, 1, ≥2), and hospitalizations (0, 1, ≥2) in the 6 months prior to chemotherapy; and use of antiviral medications during follow-up time (yes, no). Time on chemotherapy was calculated from the initiation of treatment to 30 days after the end of a cycle [17]. Use of antiviral medications was included in the models because patients might receive them to treat other viral infections (ie, herpes simplex) or for prophylaxis [18]. Hazard ratios were also presented for age, sex, and race categories. Our sample size was sufficient to detect a relative risk of HZ incidence between the vaccinated and unvaccinated cohorts as low as 0.75 during the study interval, with power of >80% and type I error rate of 0.05. We set the significance at 0.05 based on a 2-sided test. We used SAS Enterprise Guide 4.2 (SAS Institute, Cary, North Carolina) for all analyses.

RESULTS
There were 4710 vaccinated members and 16766 unvaccinated members included in the study. Among the vaccinated cohort, members were vaccinated in ≤30 days, 31–59 days, 60–180 days, 181–365 days, and >365 days, respectively, before initiation of chemotherapy. The baseline characteristics of the study cohorts by vaccination status are summarized in Table 1. Age and sex distributions were similar between cohorts. There were fewer black and Hispanic persons in the vaccinated cohort. In the 6 months prior to initiation of chemotherapy, the unvaccinated cohort had a higher proportion of subjects with emergency department visits or hospitalizations, but there were no differences in terms of the more frequent outpatient visits.

The incidence rate of HZ in the vaccinated and the unvaccinated cohort is presented in Table 2. Overall, there were 91 and 583 HZ incident cases in the vaccinated and the unvaccinated cohort, respectively. The incidence rate was 12.87 (95% CI, 10.48–15.80) per 1000 person-years in the vaccinated cohort vs 22.05 (95% CI, 20.33–23.92) in the unvaccinated cohort, yielding a crude incidence rate ratio of 0.58 (95% CI, 0.47–0.73). Although some variations of rate ratio estimate were observed across age, sex, and race group, the overlapping CIs suggested no substantive difference. The 30-month cumulative incidence of HZ after chemotherapy was 3.28% in the vaccinated group and 5.34% in the unvaccinated group (P < .05; Figure 1). The incidence of HZ for cohort members vaccinated ≤30 days, 31–59 days, 60–180 days, 181–365 days, and >365 days before initiation of chemotherapy was 26.71 (95% CI, 10.01–71.21), 19.01 (95% CI, 6.11–59.02), 9.01 (95% CI, 4.05–20.05), 12.34 (95% CI, 7.31–20.84), and 12.89 (95% CI, 10.09–16.47) per 1000 person-years, respectively. In addition, there was no patient hospitalized for HZ in the vaccinated cohort, compared with 6 patients hospitalized for HZ in the unvaccinated group (incidence rate: 0.23 [95% CI, 0.08–0.49] per 1000 person-years). One of them was hospitalized for 26 days, 2 for 3 days, and 3 for 1 day.

The adjusted rate ratio for HZ between the vaccinated and the unvaccinated cohorts was 0.58 (95% CI, 0.46–0.73) and showed no substantial variation across age, sex, or race group (Table 3).

DISCUSSION
Our study demonstrates the effectiveness of zoster vaccine in a cohort of adults aged ≥60 years who subsequently received chemotherapy. The protection was robust by age, sex, and race group; in fact, it was similar to the vaccine protection reported in a comparable but immunocompetent cohort (adjusted HR, 0.58 [95% CI, 0.46–0.73] vs 0.45 [95% CI, 0.24–0.87], respectively) [12]. This comparable performance is surprising because effectiveness in the immunocompetent population was assessed immediately after vaccination, whereas effectiveness in this study was assessed following initiation of chemotherapy, a mean of 2.36 years after vaccination, after more time had elapsed for potential waning of protection. We believe that our results are not likely due to confounding, because the decision by the patients
and their physicians regarding zoster vaccination was made almost randomly, many months to years before cancer was diagnosed. For this same reason, we do not believe that our cohorts differed in terms of the degree of immunosuppression they ultimately experienced.

The 42% protection that we found in our study translates to a large reduction in disease burden given the high incidence of HZ in this high-risk population. The HZ incidence rates that we found in unvaccinated patients receiving chemotherapy were 22.05 per 1000 person-years (95% CI, 20.33–23.92), much higher than the rates in comparable immunocompetent patients (13.0 [95% CI, 12.6–13.3]) [12]. Habel et al [8] reported very similar rates in patients receiving chemotherapy (23.0 [95% CI, 18.9–27.1]). In fact, by preventing HZ-associated hospitalizations, the vaccine also appeared to prevent the severe disease manifestations that often occur in the immunocompromised population. Our study has potentially important policy implications, as the live attenuated zoster vaccine is currently contraindicated in immunocompromised patients, the population at highest risk of HZ and its severe complications. Although observational studies

### Table 1. Baseline Characteristics of Study Cohorts by Herpes Zoster Vaccination Status

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Vaccinated, No. (%)</th>
<th>Unvaccinated, No. (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60-69</td>
<td>1410 (29.94%)</td>
<td>5628 (33.57%)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>≥70</td>
<td>3300 (70.06%)</td>
<td>11 138 (66.43%)</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>74.55 (6.81)</td>
<td>74.72 (7.92)</td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td>.31</td>
</tr>
<tr>
<td>Female</td>
<td>2783 (59.09%)</td>
<td>9767 (58.25%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1927 (40.91%)</td>
<td>6999 (41.75%)</td>
<td></td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td>&lt;.01</td>
</tr>
<tr>
<td>White</td>
<td>3612 (76.69%)</td>
<td>10 530 (62.81%)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>235 (4.99%)</td>
<td>1792 (10.69%)</td>
<td></td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>311 (6.60%)</td>
<td>969 (5.90%)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>462 (9.81%)</td>
<td>3007 (17.94%)</td>
<td></td>
</tr>
<tr>
<td>Other/multiple/unknown</td>
<td>90 (1.91%)</td>
<td>448 (2.67%)</td>
<td></td>
</tr>
<tr>
<td><strong>No. of outpatient visits during 6 mo prior to chemotherapy treatment</strong></td>
<td></td>
<td></td>
<td>.27</td>
</tr>
<tr>
<td>0</td>
<td>104 (2.21%)</td>
<td>405 (2.42%)</td>
<td></td>
</tr>
<tr>
<td>1–4</td>
<td>1636 (34.73%)</td>
<td>5612 (33.47%)</td>
<td></td>
</tr>
<tr>
<td>5–10</td>
<td>2183 (46.35%)</td>
<td>7809 (46.58%)</td>
<td></td>
</tr>
<tr>
<td>≥11</td>
<td>787 (16.71%)</td>
<td>2940 (17.54%)</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>6.57 (4.40)</td>
<td>6.70 (4.38)</td>
<td></td>
</tr>
<tr>
<td>Median (minimum, maximum)</td>
<td>6 (0, 34)</td>
<td>6 (0, 34)</td>
<td></td>
</tr>
<tr>
<td><strong>No. of emergency visits during visits during 6 mo prior to chemotherapy treatment</strong></td>
<td></td>
<td></td>
<td>&lt;.01</td>
</tr>
<tr>
<td>0</td>
<td>3561 (75.61%)</td>
<td>11 896 (70.95%)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>737 (15.65%)</td>
<td>3029 (18.07%)</td>
<td></td>
</tr>
<tr>
<td>≥2</td>
<td>412 (8.75%)</td>
<td>1841 (10.98%)</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>0.38 (0.83)</td>
<td>0.48 (0.97)</td>
<td></td>
</tr>
<tr>
<td>Median (minimum, maximum)</td>
<td>0 (0, 10)</td>
<td>0 (0, 12)</td>
<td></td>
</tr>
<tr>
<td><strong>No. of hospitalizations visits during 6 mo prior to chemotherapy treatment</strong></td>
<td></td>
<td></td>
<td>&lt;.01</td>
</tr>
<tr>
<td>0</td>
<td>3716 (78.90%)</td>
<td>12 394 (73.92%)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>715 (15.18%)</td>
<td>3023 (18.03%)</td>
<td></td>
</tr>
<tr>
<td>≥2</td>
<td>279 (5.92%)</td>
<td>1349 (8.05%)</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>0.29 (0.65)</td>
<td>0.38 (0.77)</td>
<td></td>
</tr>
<tr>
<td>Median (minimum, maximum)</td>
<td>0 (0, 6)</td>
<td>0 (0, 14)</td>
<td></td>
</tr>
<tr>
<td><strong>Use of antiviral medications during follow-up</strong></td>
<td></td>
<td></td>
<td>.03</td>
</tr>
<tr>
<td>Yes</td>
<td>212 (4.50%)</td>
<td>639 (3.81%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>4498 (95.50%)</td>
<td>16 127 (96.19%)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: SD, standard deviation.
### Table 2. Comparison of Herpes Zoster Incidence in Study Cohorts by Herpes Zoster Vaccination Status

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Vaccinated (n = 4710)</th>
<th>Unvaccinated (n = 16,766)</th>
<th>Rate Ratio</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>4710 91 7071.82 12.87 10.48–15.80</td>
<td>16,766 583 26,439.08 22.05 20.33–23.92</td>
<td>0.58</td>
<td>.47–.73</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Age, y</td>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60–69</td>
<td>1410 30 2245.96 13.36 9.34–19.10</td>
<td>5628 188 9397.70 20.00 17.34–23.08</td>
<td>0.67</td>
<td>.45–.98</td>
<td>.04</td>
</tr>
<tr>
<td>≥70</td>
<td>3300 61 4825.86 12.64 9.83–16.25</td>
<td>11,138 395 17,041.37 23.18 21.00–25.58</td>
<td>0.55</td>
<td>.42–.71</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Sex</td>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>2783 64 4278.34 14.96 11.71–19.11</td>
<td>9767 365 15,776.32 23.14 20.88–25.64</td>
<td>0.65</td>
<td>.50–.84</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Male</td>
<td>1927 27 2793.48 9.67 6.63–14.09</td>
<td>6999 218 10,662.76 20.44 17.90–23.35</td>
<td>0.47</td>
<td>.32–.71</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Race</td>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>3612 74 5519.64 13.41 10.68–16.84</td>
<td>10,530 357 16,942.12 21.07 19.00–23.37</td>
<td>0.64</td>
<td>.50–.82</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Black</td>
<td>235 2 327.56 6.11 1.53–24.41</td>
<td>1792 50 2752.34 18.17 13.77–23.97</td>
<td>0.34</td>
<td>.08–1.38</td>
<td>.13</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>311 10 446.85 22.38 12.04–41.59</td>
<td>989 41 1515.36 27.06 19.92–36.75</td>
<td>0.83</td>
<td>.41–1.65</td>
<td>.59</td>
</tr>
<tr>
<td>Hispanic</td>
<td>462 5 660.29 7.57 3.15–18.19</td>
<td>3007 125 4614.86 27.09 22.73–32.28</td>
<td>0.28</td>
<td>.11–.68</td>
<td>.01</td>
</tr>
<tr>
<td>Other/multiple/unknown</td>
<td>90 0 117.47 0.00 . . .</td>
<td>448 10 614.40 16.28 8.76–30.25</td>
<td>. . .</td>
<td>. . .</td>
<td>. . .</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; PY, person-years.
provide evidence that Zostavax may be effective and safe in these patients [11, 19], additional studies are needed to provide reassurance that this practice would be safe. Our data suggest that VZV-specific immunity is well maintained in the presence of chemotherapy-induced immunosuppression. Physicians can therefore be assured that patients will retain significant protection following vaccination even if they must subsequently undergo chemotherapy. With a lifetime cancer risk of close to 40% among 60-year-old adults [20], our results provide an additional rationale for offering HZ vaccination to patients in a timely manner, adding to the benefit of the vaccine [21].

The ACIP currently recommends that zoster vaccine be specifically offered to patients at least 14–30 days before they undergo immunocompromising treatments in order to obtain the benefits of vaccine protection without the risks of dissemination of this live attenuated vaccine [14]. However, this recommendation has never been formally evaluated for safety and efficacy. Notably, in our study, only 152 patients (3.2%) started chemotherapy within 60 days after vaccination, fewer patients than were vaccinated during other windows of time.

More importantly, in contrast to HZ rates that were considerably lower in most vaccine recipients, who subsequently underwent chemotherapy compared with nonrecipients, this pattern was not seen for those patients who received chemotherapy within 60 days after vaccination. Given the small number of patients in this group, the lack of an observed reduction in HZ risk may be a random, artifactual finding. Alternatively, it may be a real phenomenon; perhaps immunogenicity is unable to fully develop when chemotherapy is administered within weeks following vaccination. We believe, however, that the higher HZ rates seen in this group reflect residual confounding: For patients anticipating chemotherapy, the nature of the cancer and the treatment regimen would likely play a key role in the decision to vaccinate, leading to confounding by indication. This bias is not plausible among patients who develop cancer months or years in the future. Our findings suggest that zoster vaccination continues to benefit patients who develop cancer and require chemotherapy ≥60 days in the future. In addition to the potential bias noted above, there are other limitations to our study. First, electronic health data can only capture information on medically attended HZ. In a population-based survey, 95% of 141 patients aged ≥60 years who experienced HZ sought medical attention [22]. Our immunocompromised patients had ready access to healthcare in the KPSC system and were frequent healthcare utilizers; they would have been even more likely to seek care for their HZ episodes. However, it is possible that there were some differences in HZ ascertainment as a function of vaccination status. The vaccine recipients may have also differed in their underlying risk of HZ.

The ACIP currently recommends that zoster vaccine be specifically offered to patients at least 14–30 days before they undergo immunocompromising treatments in order to obtain the benefits of vaccine protection without the risks of dissemination of this live attenuated vaccine [14]. However, this recommendation has never been formally evaluated for safety and efficacy. Notably, in our study, only 152 patients (3.2%) started chemotherapy within 60 days after vaccination, fewer patients than were vaccinated during other windows of time.

More importantly, in contrast to HZ rates that were considerably lower in most vaccine recipients, who subsequently underwent chemotherapy compared with nonrecipients, this pattern was not seen for those patients who received chemotherapy within 60 days after vaccination. Given the small number of patients in this group, the lack of an observed reduction in HZ risk may be a random, artifactual finding. Alternatively, it may be a real phenomenon; perhaps immunogenicity is unable to fully develop when chemotherapy is administered within weeks following vaccination. We believe, however, that the higher HZ rates seen in this group reflect residual confounding: For patients anticipating chemotherapy, the nature of the cancer and the treatment regimen would likely play a key role in the decision to vaccinate, leading to confounding by indication. This bias is not plausible among patients who develop cancer months or years in the future. Our findings suggest that zoster vaccination continues to benefit patients who develop cancer and require chemotherapy ≥60 days in the future. In addition to the potential bias noted above, there are other limitations to our study. First, electronic health data can only capture information on medically attended HZ. In a population-based survey, 95% of 141 patients aged ≥60 years who experienced HZ sought medical attention [22]. Our immunocompromised patients had ready access to healthcare in the KPSC system and were frequent healthcare utilizers; they would have been even more likely to seek care for their HZ episodes. However, it is possible that there were some differences in HZ ascertainment as a function of vaccination status. The vaccine recipients may have also differed in their underlying risk of HZ.

We controlled for the use of anti-VZV prophylaxis in our analysis, but occasional patients may have received other anti-VZV medications and this may have varied by vaccination status.

Given the size of the study population, we were also unable to validate the ICD-9-based HZ diagnoses in the cohorts. Prior studies have shown that the 85%–100% of ICD-9-based HZ proved to be HZ upon record review [23, 24]. Furthermore, we have shown elsewhere that physician-diagnosed HZ at KPSC was correctly diagnosed regardless of HZ vaccination status, based on polymerase chain reaction confirmation of specimens taken from the patients’ skin lesions [25]. We were also not able to explore potential HZ risk factors and outcomes using

### Table 3. Hazard Ratio of Herpes Zoster Comparing the Vaccinated and the Unvaccinated Cohorts

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>0.58</td>
<td>.46–.72</td>
<td>0.58</td>
<td>.46–.73</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60–69</td>
<td>0.68</td>
<td>.46–.99</td>
<td>0.70</td>
<td>.47–1.03</td>
</tr>
<tr>
<td>≥70</td>
<td>0.54</td>
<td>.41–.70</td>
<td>0.54</td>
<td>.41–.70</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>0.64</td>
<td>.49–.84</td>
<td>0.62</td>
<td>.47–.81</td>
</tr>
<tr>
<td>Male</td>
<td>0.47</td>
<td>.32–.71</td>
<td>0.50</td>
<td>.34–.75</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>0.63</td>
<td>.49–.81</td>
<td>0.62</td>
<td>.48–.80</td>
</tr>
<tr>
<td>Black</td>
<td>0.35</td>
<td>.09–1.43</td>
<td>0.37</td>
<td>.09–1.51</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>0.83</td>
<td>.42–1.66</td>
<td>0.81</td>
<td>.40–1.62</td>
</tr>
<tr>
<td>Hispanic</td>
<td>0.28</td>
<td>.12–.69</td>
<td>0.28</td>
<td>.12–.70</td>
</tr>
<tr>
<td>Other/multiple/unknown</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval.  
* Rate ratio adjusted for age, sex, race, healthcare utilization in the 6 months prior to follow-up, and use of antiviral medications during follow-up.
record reviews. As a result, we were unable to assess rates of post-
herpetic neuralgia or rates of potential adverse safety events. 
Finally, although we were able to identify patients being hospital-
ized for HZ, we were not able to assess the severity of their disease.

We only assessed the impact of vaccination on HZ rates fol-
lowing chemotherapy; although the results are reassuring, we 
cannot assume that they would hold for other types of iatrogen-
ic immunosuppression. The effectiveness of zoster vaccine in 
patients undergoing various types of immunosuppression will 
become increasingly important as the number of indications 
for immunosuppression increases.

In conclusion, in our study, persons treated with chemotherapy 
who are at high risk of HZ and its sequelae received sub-
stantial protection through zoster vaccination. As high 
proportion of adults develop cancer during their lifetime and 
require chemotherapy, our findings provide an additional ra-
nale for offering zoster vaccine to adults for whom it is indicat-
ed, before the vaccine becomes contraindicated.

Supplementary Data

Supplementary materials are available at Clinical Infectious Diseases online 
(http://cid.oxfordjournals.org). Supplementary materials consist of data 
provided by the author that are published to benefit the reader. The posted 
materials are not copyrighted. The contents of all supplementary data are the 
sole responsibility of the authors. Questions or messages regarding errors 
should be addressed to the author.

Notes

Author contributions. H. F. T. has full access to all of the data in the study 
and takes responsibility for the integrity of the data and the accuracy of the 
results.

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

Financial support. This study was supported by the Kaiser Permanente 
Southern California internal research fund.

Potential conflicts of interest. H. F. T. and S. J. J. have received research 
support from Novartis Vaccines. S. J. J. has served as an unpaid consultant 
for Merck. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the 
content of the manuscript have been disclosed.

References

1. Blank IJ, Polydefkis MJ, Moore RD, Gebo KA. Herpes zoster among 
persons living with HIV in the current antiretroviral therapy era. J Ac-
2. Veetil BM, Myasoedova E, Matteson EL, Gabriel SE, Green AB, Crowson 
CS. Incidence and time trends of herpes zoster in rheumatoid arthritis: a 
3. Ranganathan P. Herpes zoster infection risk in patients with rheumatoid 
with rheumatoid arthritis treated with anti-TNF-alpha agents. JAMA 
2009; 301:737–44.
multicenter cohort of solid organ transplant recipients. Transplant Infect 
infection in the post-hematopoietic stem cell transplant pediatric pop-
ulation may be preceded by transaminitis: an institutional experience. 
7. Christiansen NP, Haake RJ, Hurd DD. Early herpes zoster infection in 
adult patients with Hodgkin’s disease undergoing autologous bone 
zoster in patients with newly diagnosed cancer. Cancer Epidemiol Bio-
in breast cancer patients after radiotherapy. Strahlenther Onkol 2000; 
176:313–6.
10. Gnann JW, Whiteley RJ. Natural history and treatment of varicella-
317–29.
11. Langan SM, Smeeth L, Margolis DJ, Thomas SL. Herpes zoster vaccine 
effectiveness against incident herpes zoster and post-herpetic neuralgia 
zoster vaccine in older adults and the risk of subsequent herpes zoster 
352:2271–84.
14. Harpaz R, Ortega-Sanchez IR, Seward JF. Prevention of herpes zoster: 
recommendations of the Advisory Committee on Immunization Practi-
strain varicella zoster virus in an immunocompetent recipient of zoster 
characteristics of members of a large, integrated health care system: 
17. Sommer AL, Wachel BK, Smith JA. Evaluation of vaccine dosing in 
patients with solid tumors receiving myelosuppressive chemotherapy. 
18. National Comprehensive Cancer Network. NCCN clinical practice 
guidelines in oncology (NCCN guidelines). Prevention and treatment 
of cancer-related infections. Version 1. Fort Washington, Pennsylvania: 
pes zoster and risk of herpes zoster infection among older patients with 
lifetime risk of being diagnosed with cancer, 2014. Available at: http:// 
in the United States of a vaccine to prevent herpes zoster and posther-
22. Lu PJ, Euler GL, Jumaan AO, Harpaz R. Herpes zoster vaccination 
among adults aged 60 years or older in the United States, 2007: uptake 
23. Yawn BP, Wollan P, St Sauver J. Comparing shingles incidence and 
complication rates from medical record review and administrative 
database estimates: how close are they? Am J Epidemiol 2011; 174: 
1054–61.
24. Donahue JG, Choo PW, Manson JE, Platt R. The incidence of herpes 
clinical diagnosis of herpes zoster by polymerase chain reaction. In: ID-