Longterm Effectiveness of Herpes Zoster Vaccine among Patients with Autoimmune and Inflammatory Diseases

Huifeng Yun, Fenglong Xie, John W. Baddley, Kevin Winthrop, Kenneth G. Saag, and Jeffrey R. Curtis

ABSTRACT. Objective. The protection duration of herpes zoster (HZ) vaccination is unclear among patients with autoimmune (AI) diseases.

Methods. Using 2006–2013 Medicare data, HZ vaccinated patients with AI were matched 1:2 to unvaccinated HZ. Incidence rates (IR) and adjusted risk ratios over time were calculated using Poisson regression.

Results. Of 59,627 vaccinated patients, crude IR increased from 0.75/100 person-years during the first year post-vaccination to 1.25 during the seventh year. Vaccinated patients had a significantly lower risk of HZ compared with the unvaccinated through 5 years.

Conclusion. HZ vaccination was significantly protective only for about 5 years among patients with AI. (First Release March 15 2017; J Rheumatol 2017;44:1083–7; doi:10.3899/jrheum.160685)

Key Indexing Term:
AUTOIMMUNE DISEASES INFECTION VACCINATION HERPES ZOSTER

The pain caused by herpes zoster (HZ), also known as shingles, is sometimes severe and may have a major effect on quality of life[1,2]. Although antiviral treatment of HZ can reduce the severity and duration of HZ, it may not prevent postherpetic neuralgia[3]. To prevent HZ and postherpetic neuralgia, the US Centers for Disease Control recommended the live HZ vaccine for healthy adults aged 60 years and older[4].

The Shingles Prevention Study (SPS) showed that HZ vaccine reduced the incidence of HZ by 51% and remained efficacious for several years among immunocompetent patients[5,6]. In longterm followup of SPS participants, HZ vaccination was shown to lose most of its protective benefit over 10 years[7]. Although observational studies have reported that HZ vaccine significantly reduces HZ and postherpetic neuralgia in patients with autoimmune or inflammatory (AI) conditions[8,9], the duration of protection among patients with AI, who might have an attenuated vaccine response because of immune suppression, is unclear. Therefore, we evaluated the duration of HZ vaccine effectiveness among older patients with AI.

MATERIALS AND METHODS

Data sources and study design. Using 2006–2013 Medicare data, we conducted a retrospective cohort study among 100% of patients with AI diseases, including rheumatoid arthritis (RA), ankylosing spondylitis (AS), inflammatory bowel disease (IBD), psoriasis, and psoriatic arthritis (PsA). Medicare is the US health insurance program for people age 65 or older and for younger people with disabling conditions (e.g., RA). Medicare data include information on diagnoses, procedures, hospitalizations, physician visits, and prescriptions. Both Medicare and the Institutional Review Board of the University of Alabama at Birmingham approved the study: X121029003.

Study population and eligible criteria. After patients with RA (714.x), AS (720.0x), IBD (555.x, 556.x), psoriasis (696.1x), or PsA (696.0x) were identified using ≥ 2 physician International Classification of Diseases, 9th ed (ICD-9) diagnosis codes[10], we identified patients who had HZ vaccinations using current procedural terminology (CPT) code 90736 or National Drug Codes (NDC). The vaccination date was determined as the CPT code date or the NDC date if no corresponding CPT was found within 7 days after the NDC date.

Eligible patients were required to have ≥ 12 months continuous Medicare fee-for-service coverage (baseline) before vaccination and throughout followup. We excluded patients with ICD-9 diagnosis codes or prescriptions for HZ during baseline. Vaccinated patients were matched 1:2 to unvaccinated on calendar year, age, sex, race, AI disease, and use of biologics, disease-modifying antirheumatic drugs (DMARD), and glucocorticoids. Biologic and DMARD were categorized as dichotomous, whereas the

From the University of Alabama at Birmingham, Birmingham, Alabama; Oregon Health and Science University, Portland, Oregon, USA.

H. Yun received research support from Amgen. Dr. Baddley received research support from BMS. Dr. Winthrop received research support from Pfizer. Dr. Saag received research support from Amgen, and consulting fees from Amgen and Astra Zeneca. Dr. Curtis received research support from Amgen, Pfizer, Crescendo, Corrona, and consulting fees from Amgen, Janssen, Pfizer, and Corrona.

H. Yun, PhD, University of Alabama at Birmingham; F. Xie, MS, University of Alabama at Birmingham; J.W. Baddley, MD, MPH, University of Alabama at Birmingham; K. Winthrop, MD, MPH, Oregon Health and Science University; K.G. Saag, MD, MSc, University of Alabama at Birmingham; J.R. Curtis, MD, MS, MPH, University of Alabama at Birmingham.

Address correspondence to Dr. J.R. Curtis, 510 20th St. South, Faculty Office Towers 802D, Birmingham, Alabama 35294, USA. E-mail: jcurtis@uab.edu

Accepted for publication January 31, 2017.

average glucocorticoid prednisone–equivalent dose during the 6 months before vaccination was categorized as none, < 7.5 mg/day, and ≥ 7.5 mg/day. To understand longterm effectiveness and avoid misclassification related to healthcare associated with vaccine administration, followup started from 30 days after the vaccination date or corresponding calendar date in the matched cohort, and ended at the earliest of first HZ, death, loss of coverage, or December 31, 2013. Matched patients were censored if they were subsequently vaccinated, and then included in the vaccination group and re-matched. The maximum followup time was 7 years post-vaccination.

Outcome. The outcome was first HZ event during followup. We identified HZ using an ICD-9 inpatient diagnosis code alone (053.x) or an outpatient diagnosis code plus antiviral medication (famciclovir, acyclovir, valacyclovir) within 7 days of HZ diagnosis. This previously validated algorithm has high positive predictive value (PPV ≥ 85%)[11,12].

Potential confounders. Besides matching factors, we evaluated other potential confounders including baseline medical conditions and concurrent medications, and updated them in each followup year. Medical conditions include diabetes, chronic obstructive pulmonary disease, renal disease, heart failure, and outpatient infections. Concurrent medications included narcotics, antidepressant drugs, and nonsteroidal antiinflammatory drugs.

Statistical analysis. We conducted descriptive analysis for potential confounders by HZ vaccination status. We calculated incidence rates (IR) for each year of post-vaccination stratified by whether patients were vaccinated. Using matched, unvaccinated patients as referent[13,14], conditional Poisson regression for repeated measures was applied to calculate the adjusted risk ratio (RR) of HZ each year of post-vaccination, controlling for matched variables and additional potential confounders. Analyses were conducted using SAS 9.3 (SAS Institute).

Sensitivity and subgroup analyses. We conducted a sensitivity analysis that identified HZ only using inpatient or outpatient diagnosis codes (053.x) without requiring antiviral drug use. We conducted subgroup analyses to evaluate HZ vaccine effectiveness stratified by age (< 70 and ≥ 70 years) and glucocorticoid dose category.

RESULTS

The vaccinated cohort consisted of 59,627 patients, whereas the matched unvaccinated cohort included 119,254 patients. The factors on which patients were matched were balanced as expected (Table 1). Mean age in both groups was 73.5 years, and 53.1% of the cohort had RA, 31.6% psoriasis, 4.7% PsA, 20.9% IBD, and 1.4% AS.

As shown in Figure 1, HZ IR in the vaccinated group increased from 0.75 per 100 person-years (PY) in the first-year post-vaccination to 1.25 in the seventh year post-vaccination. In contrast, the HZ IR among the unvaccinated remained relatively constant (1.3 to 1.7/100 PY) through 7 years of followup. After adjusting for matched variable and potential confounders (all in Table 1), vaccinated patients had significantly lower risk of HZ compared with unvaccinated patients over 5 years. The relative risk for HZ during years 3–5 ranged from 0.74–0.77, and the upper bound of the 95% CI ranged from 0.87–0.97. This protective effect was not significant during the sixth and seventh years after vaccination (Figure 2).

Both sensitivity analyses that did not require HZ treatment yielded similar results as our main analysis and subgroup analyses that stratified by patient's age and glucocorticoid dosage categories yielded consistent trends with the main analysis (not shown).

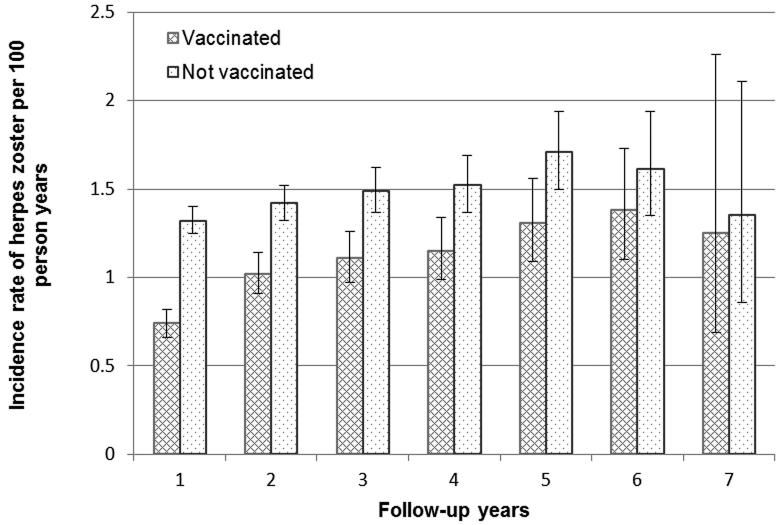
Table 1. Baseline characteristics for the vaccinated cohort and matched unvaccinated cohort. Values are % unless otherwise specified.

Characteristics	Vaccinated Cohort, n = 59,627	Unvaccinated Cohort, n = 119,254
Matched variables		
Age, yrs, mean (SD)	73.5 (7.3)	73.5 (7.3)
Female	69.7	69.7
Race		
White	93.1	93.1
African American	2.9	2.9
Asian	1.6	1.6
Hispanic	1.0	1.0
Other	1.5	1.5
Index yr of vaccination or start of followup		
2007	6.8	6.8
2008	8.3	8.3
2009	12.1	12.1
2010	7.5	7.5
2011	11.9	11.9
2012	25.9	25.9
2013	27.6	27.6
Autoimmune disease		
RA	53.1	53.1
AS	1.4	1.4
IBD	20.9	20.9
Psoriasis	31.6	31.6
PsA	4.7	4.7
Any biologic use prior to index date	11.0	11.0
DMARD	46.1	46.1
Glucocorticoids		
None	83.5	83.5
< 7.5 mg/day	14.0	14.0
≥ 7.5 mg/day	2.5	2.5
Variables not matched on		
Diabetes	26.7	22.3
COPD	24.9	21.0
Renal disease	10.4	8.5
Heart failure	11.3	7.3
Outpatient infection during baseline	44.8	42.9
Narcotics	50.7	47.4
Antidepressant	27.7	26.2
NSAID	21.8	23.5

RA: rheumatoid arthritis; AS: ankylosing spondylitis; IBD: inflammatory bowel disease; PsA: psoriatic arthritis; DMARD: disease-modifying antirheumatic drugs; COPD: chronic obstructive pulmonary disease; NSAID: nonsteroidal antiinflammatory drugs.

DISCUSSION

There has been some concern that patients with AI conditions might have a lower immunogenic response to HZ vaccination, especially when treated with immunosuppressive medications such as glucocorticoids[15,16]. Reassuringly, we found that in older patients with autoimmune diseases, the HZ vaccine was effective in the short term, and that its effectiveness waned over time. HZ risk was most reduced in the first-year post-vaccination and increased back to the unvaccinated rate over about 5–7 years.



Vaccinated	year 1	year 2	year 3	year 4	year 5	year 6	year 7
Events	328	315	225	169	120	74	11
Person Years	44472	30939	20308	14718	9178	5381	877
IR per 100	0.74	1.02	1.11	1.15	1.31	1.38	1.25
Not vaccinated							
Events	1138	819	514	347	229	117	19
Person Years	86149	57855	34490	22847	13405	7245	1411
IR per 100	1.32	1.42	1.49	1.52	1.71	1.61	1.35

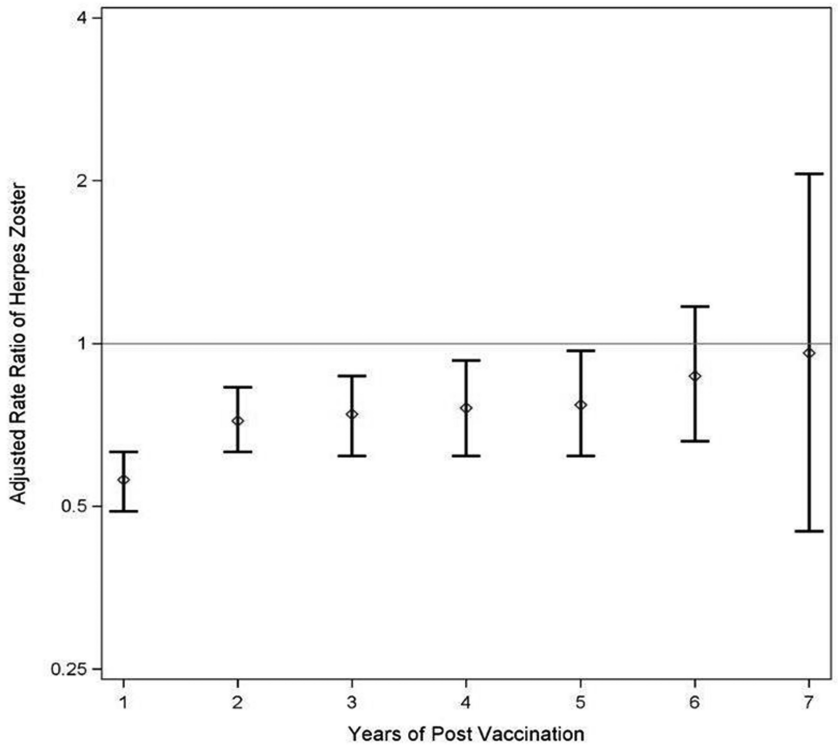
Figure 1. IR and 95% CI for herpes zoster over time among vaccinated patients compared with the matched unvaccinated patients. IR: incidence rate.

The attenuating effectiveness over time of HZ vaccination observed in our analysis has been reported in the general population, although in healthy older people, the protection associated with vaccination appears to last somewhat longer. A previous analysis reported that the vaccine efficacy declined after the first year post-vaccination, but remained significantly protective for at least 5 years[6]. Likewise, the subsequently published Long Term Persistence Substudy showed that vaccine effectiveness continued to decline, but remained statistically significant through Year 8 post-vaccination[7]. In addition, an observational study conducted among healthy older members of the Kaiser Permanente Northern California in 2007–2013 also found that HZ vaccine effectiveness in routine use waned over time. In that observational analysis, the protective effects of vaccination remained significant over 7 years following vaccination[17]. Our study found that HZ vaccination was significantly protective in the short term. The nonsignificant effectiveness during years 6–7 post-vaccination may result from small numbers, but the effect estimates of the vaccine's benefit by Year 7 were negligible (IRR 0.96), irrespective of the 95% CI.

As expected, our study conducted in patients with AI diseases had higher absolute incidence rates of HZ in each post-vaccination year than those reported in the general population. In unvaccinated healthy older people in the SPS, the absolute IR was 1.1 per 100 PY in patients aged 70 and older. Rates in our study were about 50% increased, consistent with prior observations that have found elevated rates of HZ in patients with AI[18].

Unlike randomized trials, our observational study lacked detailed information on disease activity and clinical factors, and thus residual confounding is possible. Although the claims-based algorithm for HZ has been shown to have good PPV, medical records were not available to confirm HZ, so misclassification was possible, although unlikely to be differential by vaccination status. Additionally, misclassification of HZ vaccination was possible if individuals paid for their vaccination without using insurance coverage. However, because all patients were required to have full coverage and given the expense of the vaccine (> $200), vaccination administration not identified by Medicare should have been rare. Finally, the insignificant effectiveness during years 6–7 may be due to the limited events and person-time; however, the clinical benefits in these 2 years are limited, and the reported RR estimates were close to 1.

The duration of HZ vaccine effectiveness waned over about 5 years among older patients with AI conditions, many of whom were treated with immunosuppressive and



Adjusted RR	0.56	0.72	0.74	0.76	0.77	0.87	0.96
95% CI, lower limit	0.49	0.63	0.62	0.62	0.62	0.66	0.46
95% CI, higher limit	0.63	0.83	0.87	0.93	0.97	1.17	2.06

Figure 2. Adjusted RR of herpes zoster by years of post-vaccination compared with the matched unvaccinated patients. RR: risk ratio.

immunomodulatory agents. This finding raises the possibility that patients might benefit from a booster vaccine at some point after initial vaccination, although no recommendation currently exists that would support such a practice. Further research is needed to determine when and if such a strategy is effective.

REFERENCES

1. Cohen JI. Herpes zoster. N Engl J Med 2013;369:1766-7.
2. Langan SM, Smeeth L, Margolis DJ, Thomas SL. Herpes zoster vaccine effectiveness against incident herpes zoster and post-herpetic neuralgia in an older US population: a cohort study. PLoS Med 2013;10:e1001420.
3. Dworkin RH, Schmader KE. Treatment and prevention of postherpetic neuralgia. Clin Infect Dis 2003;36:877-82.
4. Centers for Disease Control and Prevention. Prevention of herpes zoster. Recommendations of the Advisory Committee on Immunization Practices (ACIP). [Internet. Accessed February 8, 2017.] Available from: www.cdc.gov/Mmwr/preview/mmwrhtml/rr57e0515a1.htm
5. Oxman MN, Levin MJ, Johnson GR, Schmader KE, Straus SE, Gelb LD, et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. N Engl J Med 2005;352:2271-84.
6. Schmader KE, Oxman MN, Levin MJ, Johnson G, Zhang JH, Betts R, et al; Shingles Prevention Study Group. Persistence of the efficacy of zoster vaccine in the shingles prevention study and the short-term persistence substudy. Clin Infect Dis 2012;55:1320-8.
7. Morrison VA, Johnson GR, Schmader KE, Levin MJ, Zhang JH, Looney DJ, et al; Shingles Prevention Study Group. Long-term persistence of zoster vaccine efficacy. Clin Infect Dis 2015; 60:900-9.
8. Zhang J, Xie F, Delzell E, Chen L, Winthrop KL, Lewis JD, et al. Association between vaccination for herpes zoster and risk of herpes zoster infection among older patients with selected immune-mediated diseases. JAMA 2012;308:43-9.
9. Zhang J, Delzell E, Curtis JR. Postherpetic neuralgia after herpes zoster vaccination—reply. JAMA 2012;308:1427-8.
10. Herrinton LJ, Curtis JR, Chen L, Liu L, Delzell E, Lewis JD, et al. Study design for a comprehensive assessment of biologic safety using multiple healthcare data systems. Pharmacoepidemiol Drug Saf 2011;20:1199-209.
11. Donahue JG, Choo PW, Manson JE, Platt R. The incidence of herpes zoster. Arch Intern Med 1995;155:1605-9.
12. Mullooly JP, Riedlinger K, Chun C, Weinmann S, Houston H. Incidence of herpes zoster, 1997-2002. Epidemiol Infect 2005;133:245-53.
13. Farrington CP. Relative incidence estimation from case series for vaccine safety evaluation. Biometrics 1995;51:228-35.
14. Cameron AC, Trivedi PK. Regression analysis of count data. New York: Cambridge University Press; 1998.
15. Adler S, Krivine A, Weix J, Rozenberg F, Launay O, Huesler J, et al.

Protective effect of A/H1N1 vaccination in immune-mediated disease—a prospectively controlled vaccination study. Rheumatology 2012;51:695-700.
16. Bingham CO 3rd, Looney RJ, Deodhar A, Halsey N, Greenwald M, Codding C, et al. Immunization responses in rheumatoid arthritis patients treated with rituximab: results from a controlled clinical trial. Arthritis Rheum 2010;62:64-74.
17. Tseng HF, Harpaz R, Luo Y, Hales CM, Sy LS, Tartof SY, et al. Declining effectiveness of herpes zoster vaccine in adults aged ≥60 years. J Infect Dis 2016;213:1872-5.
18. Yun H, Yang S, Chen L, Xie F, Winthrop K, Baddley JW, et al. Risk of herpes zoster in autoimmune and inflammatory diseases: implications for vaccination. Arthritis Rheumatol 2016;68:2328-37.