

Preventing Herpes Zoster through Vaccination

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Topic: The role of the zoster vaccine in the prevention of herpes zoster and its sequelae, including postherpetic neuralgia (PHN) and herpes zoster ophthalmicus.

Clinical Relevance: Wide administration of the herpes zoster vaccine in accordance with the recommendations of the Centers for Disease Control and Prevention Advisory Committee on Immunization Practices (ACIP) will lead to a decline in the incidence and morbidity of herpes zoster and its complications, including PHN.

Methods: The key study leading to the approval of the zoster vaccine for use, the Centers for Disease Control and Prevention ACIP's recommendations for appropriate use of the zoster vaccine, and predictions regarding the cost efficacy of a zoster vaccination program are reviewed.

Results: The Shingles Prevention Study established that the zoster vaccine was safe, well tolerated, and effective in reducing the burden of illness due to herpes zoster and the incidence of PHN. The ACIP recommended that the zoster vaccine be given to adults 60 and older for the prevention of herpes zoster. Cost-efficacy analyses suggest that the greatest gain in quality-adjusted life-years can be gained by vaccinating individuals at the younger end of the ACIP-recommended age range.

Conclusion: The zoster vaccine promises to reduce the morbidity and mortality of herpes zoster. Administering the vaccine at the younger end of the age range may offer a greater cost benefit. *Ophthalmology* 2008; 115:S35–S38 © 2008 by the American Academy of Ophthalmology.

Herpes zoster is relatively common among older adults: incidence begins to rise at age 50, and 50% of those 85 and above will have herpes zoster in their lifetime. Acute rash can be managed with antiviral agents that decrease the duration and severity of the rash and diminish—but do not abolish—pain and the risk of certain complications. However, these interventions are time sensitive, and most patients do not receive them within 72 hours of rash onset, dramatically limiting their efficacy. For patients who develop postherpetic neuralgia (PHN), ocular complications, or both, the disease course can be long and complicated. Until recently, herpes zoster could not be prevented, and physicians had only a limited number of options to treat acute zoster, prevent ocular complications in patients with herpes zoster ophthalmicus (HZO), and manage pain in patients who developed PHN after their acute rash cleared.

Herpes zoster occurs when the varicella-zoster virus (VZV), which most Americans harbor as a result of early infection that first manifests as chickenpox, becomes reactivated. Normally, cell-mediated immunity continually suppresses VZV from reactivating, but this immunity wanes as

individuals age, increasing the likelihood of a case of herpes zoster. The zoster vaccine, a live attenuated form of the virus, provides the needed boost to cell-mediated immunity to prevent VZV reactivation. As a result, patients are far less likely to develop herpes zoster and, correspondingly, far less likely to develop complications, whether they be ocular complications or PHN. Individuals who do develop herpes zoster despite vaccination experience a milder form of the disease than their unvaccinated counterparts. Thus, the zoster vaccine represents a simple means of reducing the morbidity of herpes zoster and its concomitant complications.

Shingles Prevention Study

The safety and efficacy of the zoster vaccine were established in the Shingles Prevention Study (SPS), a large-scale, randomized, double-blind, placebo-controlled study conducted by the Department of Veterans Affairs Cooperative Studies Program. Immunocompetent adults (N = 38 546) 60 and above (median age, 69 years) who had a history of varicella or who had lived in the United States for at least 30 years and thus could be assumed to have latent VZV were enrolled and randomly assigned to receive either a placebo or active vaccine. The zoster vaccine (Oka/Merck VZV) is a live attenuated vaccine similar in composition to the varicella vaccine but much more potent, ranging from 18 700 to 60 000 plaque-forming units per dose, which is at least 14 times more concentrated than the varicella vaccine. After vaccination, study participants were observed for an average of 3.13 years (range, 1 day–4.90 years).¹

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STATEMENT OF CONFLICT OF INTEREST: this author reports the following conflict of interest with the sponsor of this supplement article. Speakers Bureau: Merck & Co., Inc.

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The number of enrollees in the SPS necessitated the development of novel strategies to screen for and identify potential zoster rashes. An interactive automated telephone response system was adapted to screen the large number of study participants for zoster rash. Study participants, who had been educated about the signs and symptoms of herpes zoster at the beginning of the study, made monthly calls to the automated system and answered a standardized set of questions. If their responses indicated a possible case of herpes zoster, they were asked to contact their study site for follow-up. At the same time, the study site was notified, so that it could contact the study participant directly if he or she failed to make contact with the study site. Additionally, the study site was also notified to follow up with participants who failed to make their scheduled monthly call.¹

Possible cases of herpes zoster were treated according to study protocol, which included the provision of famciclovir, plus the addition of analgesics, and/or other medications as needed. The diagnosis was confirmed by a combination of polymerase chain reaction, viral culture, and clinical evaluation. A total of 1308 cases of suspected zoster were evaluated in this way, yielding 984 confirmed cases of herpes zoster.¹

The primary end point in the SPS was the burden of illness (BOI) due to herpes zoster, a composite measure of the total amount of herpes zoster-associated pain and discomfort experienced by patients in the vaccine or placebo group that included the duration of that pain. Burden of illness was operationalized as the sum of severity-of-illness scores for all study participants (participants who did not develop herpes zoster scored 0 on severity of illness) in the vaccine or placebo group divided by the number of study participants in that group. Severity of illness was the area under a curve of zoster pain, assessed by the Zoster Brief Pain Inventory, graphed over the 182 days after rash onset. Incidence of herpes zoster was also assessed.¹

The secondary end point in the SPS was the incidence of PHN, pain that rated a 3 or above on a scale of 0 (no pain) to 10 (pain as bad as you can imagine) and lasted for more than 90 days after rash onset.¹ Pain scores below 3 were not included in the PHN assessment because it was felt that pain with a score below 3, though reflective of true pain and discomfort, did not interfere significantly with quality of life.

The zoster vaccine reduced the herpes zoster BOI by 61.1% (95% confidence interval [CI], 51.1%–69.1%; $P < 0.001$) (Fig 1). Incidence of herpes zoster was reduced by 51.3% (95% CI, 44.2%–57.6%) from 11.12 cases per thousand patient-years (placebo group) to 5.42 cases per thousand patient-years (vaccine group) ($P < 0.001$). The incidence of PHN was also reduced by 66.5% (95% CI, 47.5%–79.2%) (Fig 2).¹

Patients who developed herpes zoster despite being vaccinated experienced a milder form of zoster of more limited duration than their counterparts in the placebo group: Herpes zoster in the vaccine group was an average of 3 days shorter than in the placebo group (21 days vs. 24 days; $P = 0.03$) and was significantly less severe ($P = 0.008$). No herpes zoster cases tested positive for vaccine-type virus,¹ demonstrating that cases of herpes zoster were unrelated to vaccination.

Herpes zoster is known to increase in both incidence and

severity with age. Secondary analyses of the efficacy of the zoster vaccine across different age groups (e.g., 60–69 years, ≥ 70 years) found that the effect of the vaccine on BOI due to zoster and the incidence of PHN were similar across age strata. However, the reduction in incidence of herpes zoster was greater among those 60 to 69 years old (64%) than among those 70 and over (38%). The overall BOI remained constant across age groups because, although the vaccine was less effective in preventing disease among this older group, it had a greater effect on severity of illness in the older portion of the study sample. Thus, the zoster vaccine maintained its ability to reduce the BOI due to herpes zoster and the incidence of PHN among the oldest members of the study sample (Oxman MN, Williams HM, Levin MJ, et al. The impact of age on the efficacy of zoster vaccine. Poster presented at: Infectious Diseases Society of America 43rd Annual Meeting, October 2005, San Francisco, California).

In the SPS, similar proportions of patients within the vaccine and placebo groups developed HZO (10.9% and 10.5%, respectively). However, as described above, the overall incidence of herpes zoster was lowered by 51% in the vaccine group. The vaccine reduced the incidence of HZO by 49% and reduced the overall severity of HZO in patients who did develop it (Oxman MN, Williams HM, Levin MJ, et al. Efficacy of zoster vaccine according to dermatome region. Poster presented at: 45th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy, December 2005, Washington, DC).

The vaccine was generally safe and well tolerated. In the overall study population, the rate of serious adverse events was 1.4% in both the vaccine and placebo groups for the first 42 days after vaccination. The adverse events substudy, a more detailed investigation of the incidence and type of adverse events conducted in approximately 17% of the vaccine ($n = 3345$) and placebo ($n = 3271$) groups, revealed some differences in the incidence of certain adverse events. Individuals who received active vaccine were more likely to have injection site reactions (48% vs. 17%; $P < 0.05$): erythema, injection site pain or tenderness, swelling, pruritus, and warmth all occurred with greater frequency ($P < 0.05$) among patients receiving active vaccine. These injection site reactions were more common in the vaccine group than the placebo group but are typical of what would be expected from other vaccines, such as those for tetanus, influenza, or pneumococcal disease. Within the substudy, serious adverse events were also more common among recipients of active vaccine (1.9% vs. 1.3%; $P = 0.03$). However, there were no significant differences in the type or location of serious adverse events.¹

Based on the findings from the SPS, the zoster vaccine was approved by the U.S. Food and Drug Administration for use in adults 60 and older. In addition, the Centers for Disease Control and Prevention Advisory Committee on Immunization Practices (ACIP) recommended that the zoster vaccine be administered to adults 60 and above for the prevention of herpes zoster, including those who have already had a case of zoster.

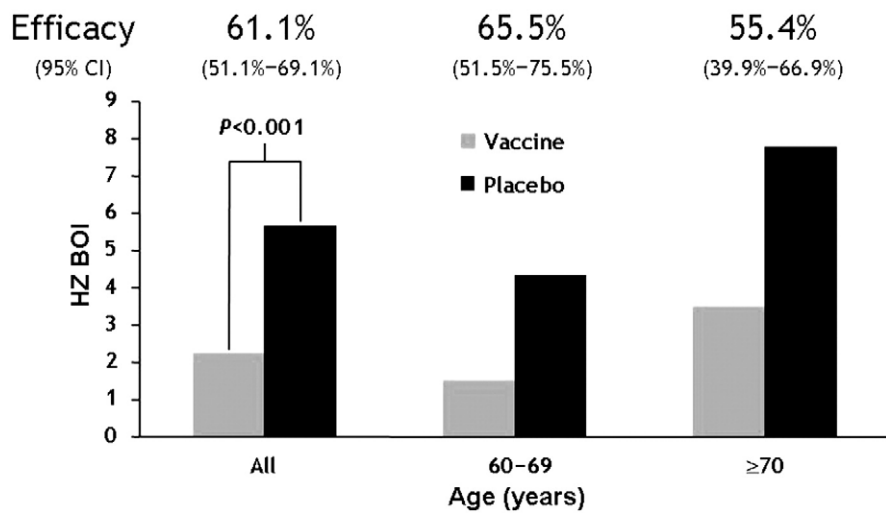


Figure 1. Efficacy of zoster vaccine in reducing the herpes zoster (HZ)-related burden of illness (BOI). CI = confidence interval.

If this vaccine is utilized widely by the age group for which it is indicated, there should be an accompanying substantial decline in the incidence and morbidity of herpes zoster. Currently, it is estimated that there are at least 1 million cases of herpes zoster each year in the U.S.¹ If all ≥ 60 -year-olds are vaccinated against herpes zoster in accordance with the ACIP recommendation, the vaccine could prevent a quarter of a million cases of herpes zoster each year and dramatically reduce the severity and duration of the remainder of the cases in vaccinated individuals. The impact on the incidence of HZO would be similar: if approximately 10% of cases of herpes zoster result in HZO (Oxman MN, Williams HM, Levin MJ, et al. Efficacy of zoster vaccine according to dermatome region. Poster presented at: 45th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy, December 2005, Washington, DC), universal vaccination of ≥ 60 -year-olds, who represent 50% of all cases of herpes zoster, could prevent 25 000 cases of HZO each year.

Cost Efficacy of a Herpes Zoster Vaccine

Cost-efficacy analyses suggest that the zoster vaccine will be more cost effective at the younger end of the age spectrum for which it is indicated (e.g., 60–64 years) than at the older end (≥ 80). The clinical and economic benefits of vaccinating older adults against herpes zoster were compared with the effects of no vaccination in a model based on data from the SPS. The age-related incidence of herpes zoster, BOI associated with herpes zoster (as defined by the SPS), and incidence and average duration of PHN were combined with varying values for unknown variables, such as the length of protection provided by the vaccine and the cost of vaccination. Cost-efficacy estimates were generated by varying inputs to produce estimates for cost efficacy in quality-adjusted life-years (QALYs) across a range of scenarios.²

Although zoster incidence increases with age, the ability of the zoster vaccine to prevent herpes zoster decreases as

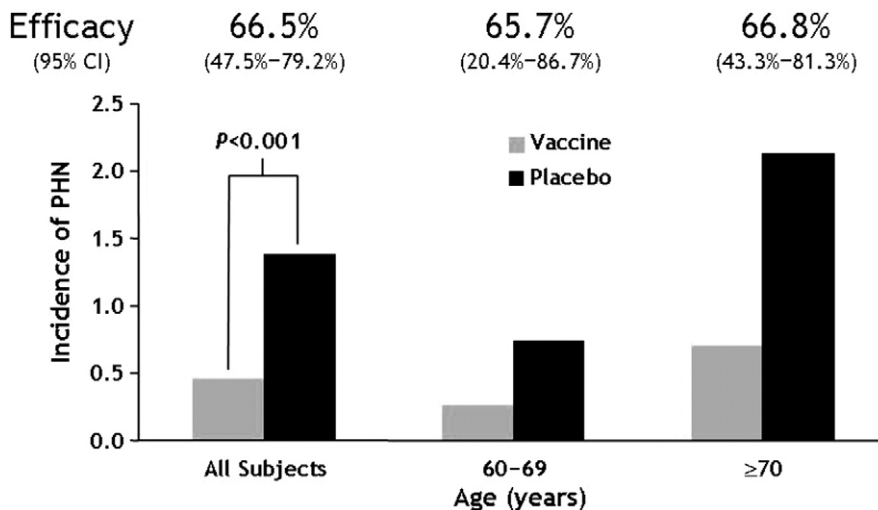


Figure 2. Efficacy of zoster vaccine in reducing incidence of postherpetic neuralgia (PHN). CI = confidence interval.

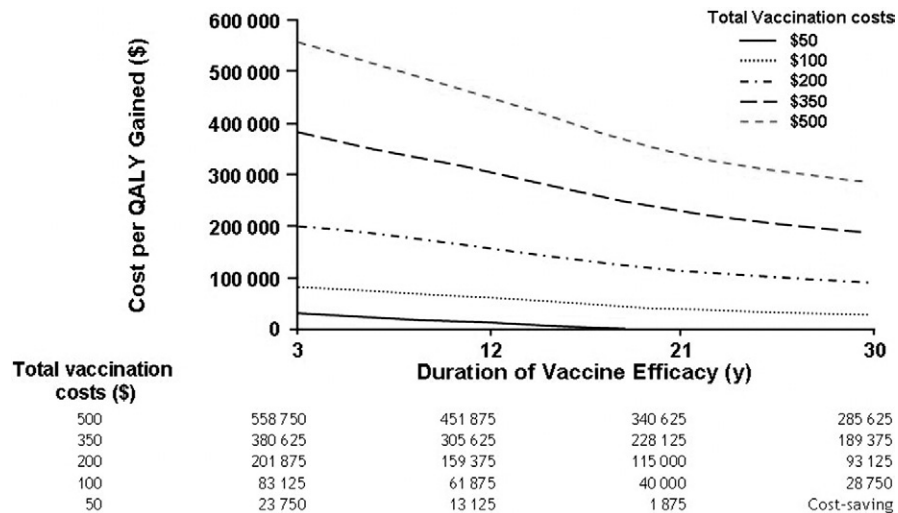


Figure 3. Cost per quality-adjusted life-year (QALY) gained by vaccinating against herpes zoster as a function of vaccine cost and duration of efficacy.

the age of the vaccinee increases. As a result, cost-efficacy analyses strongly favor vaccinating “younger” older adults as opposed to “older” older adults: a 60-year-old vaccinated against herpes zoster gains 0.0024 QALY, whereas an 80-year-old gains less than a third of that figure, only 0.0007 QALY. The younger vaccinee also accrues greater savings in treatment and lost productivity costs.²

The exact cost of the QALYs gained by vaccinating against herpes zoster varies as a function of vaccine cost and duration of protection offered by the vaccine. The cost per QALY across these 2 variables is demonstrated in Figure 3. Increases in QALYs are gained at a lower cost by vaccines that cost less and offer a greater period of protection from disease.²

Although vaccine cost is known (~\$150), the duration of protection offered by the vaccine is still unknown. In the SPS, study participants were observed for an average of 3.13 years (range, 1 day–4.90 years), but as with any new vaccine, the full duration of protection offered by the zoster vaccine still remains to be seen. The varicella vaccine, a less potent form of the zoster vaccine given to children to prevent initial varicella disease, has been shown to offer protection for at least 14 or 25 years, depending on whether data from the U.S. or from Japan, where the vaccine has been in use much longer, are utilized.²

The cost efficacy of the zoster vaccine fell below \$50 000 per QALY for a vaccine that costs \$100 and provided a minimum of 20 years’ protection against herpes zoster, and falls under \$100 000 per QALY when vaccines cost \$200 (or less) and offer protection of at least 20 years’ duration. The greatest benefits in QALYs gained will be seen when “younger” older adults are vaccinated.² These benefits may be expanded by immunizing adults just as they turn 60 or, possibly, when they are in their 50s, especially if the zoster vaccine is determined to provide a longer period of protection.

Summary and Conclusions

If the zoster vaccine is widely administered in accordance with the ACIP recommendations, there will be a resulting decline in the incidence and morbidity of herpes zoster and its complications, including PHN. Current ACIP recommendations suggest administering the vaccine to ≥60-year-olds whether or not they have had a previous episode of herpes zoster. Although no efficacy data are available, immunogenicity is suggested in 50- to 59-year-olds, as the SPS demonstrated greater vaccine efficacy among 60- to 69-year-olds than among ≥70-year-olds.

Cost-effectiveness analyses based on the outcomes of the SPS suggest that the price of the vaccine and duration of the protection it offers are key variables in the cost per QALY gained by vaccine administration. However, across scenarios, models that vaccinated individuals closer to age 60 offered a greater cost efficacy than models that vaccinated individuals at older ages.

The data from the SPS, results of the Hornberger cost-efficacy analysis, and established data on the age-related incidence of herpes zoster together provide a strong case for vaccinating “younger” older adults, as opposed to “older” older adults. Although all immunocompetent ≥60-year-olds who have not recently developed herpes zoster should be vaccinated, the greatest benefits will be accrued by vaccinating earlier rather than later.

References

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