Shingles Vaccine: Effective and Costly or Cost-Effective?

The epidemiology and clinical impact of the varicella-zoster virus (VZV) changed dramatically with the introduction in 1995 of the varicella vaccine, after which the incidence of varicella in children plummeted (1). Nevertheless, the entire adult U.S. population remains at risk for shingles, a late complication of earlier varicella infection, and that risk is likely to increase as the baby boom generation ages and life expectancy increases. Shingles is characterized by a painful vesicular eruption in a dermatomal distribution and is caused by the reactivation of latent VZV in sensory ganglia. Approximately 25% of the U.S. population will have a shingles episode during their lifetime. Risk for occurrence is greatest in immunosuppressed persons and elderly persons, with the increased risk accelerating from 50 years of age. Among patients with shingles, 10% to 33% develop postherpetic neuralgia (PHN), a chronic and often severely painful condition with no effective treatment. The risk for PHN after shingles increases with age, especially after 60 years of age (2).

Fortunately, a new vaccine (Zostavax, Merck & Co., Whitehouse Station, New Jersey) specifically targets shingles. This vaccine was evaluated in a major phase III trial that involved 38 546 persons 60 years of age or older (3). The vaccine reduced the risk for shingles and PHN by 51% and 67%, respectively, suggesting added benefits to persons who develop shingles despite being vaccinated. The efficacy against shingles decreased with the age of the person vaccinated to 18% for persons 80 years of age or older, although this small benefit may be particularly important because the oldest group is probably the most vulnerable to shingles and its sequelae. Protection declined somewhat during the first year after vaccination but remained stable for the final 3 years of follow-up. The vaccine seemed safe in the 19 270 persons vaccinated. The cost for the 1-dose vaccine is $150.

Vaccine prices (4) have risen for all vaccines, with more recently developed vaccines among the more expensive. Manufacturers attribute the increased prices partly to the higher costs of conducting clinical trials, the larger studies needed to evaluate new vaccines, and an unpredictable fluctuating market. Adult vaccine costs are approximately $11 to $15 for influenza, $24 for pneumococcus, $180 for the 3-dose series of hepatitis B, $120 for the 2-dose series of hepatitis A, and $134 for the 2-dose series of varicella.

Is using the new VZV vaccine "worthwhile"? The current standard for such evaluation is an economic analysis, specifically a cost-effectiveness analysis. In this issue, Hornberger and Robertus's study (5) is such an analysis. The authors use a method that conforms to accepted standards of economic analysis. It takes a societal perspective and expresses results as costs per quality-adjusted life-year (QALY) gained. In conducting such analyses, the investigators' choice of structural framework, assumptions used, and values assigned can make an enormous difference in the conclusions.

Hornberger and Robertus did an excellent job in highlighting the uncertainties of their study. In their sensitivity analysis, they demonstrate that assumptions about age distribution of the vaccinated population, cost of the vaccine, QALY weights assigned to zoster and PHN, and duration of vaccine efficacy each substantially alter the cost per QALY results independently (see Hornberger and Robertus's Figure 3). Some key variables are known. The vaccine price is now set, and experts could reach agreement about the assumed age distribution of vaccinees. Other variables are not known, such as consensus on the value of averted pain from shingles and PHN, although intangible factors like this represent the greatest costs of these conditions. Moreover, the durability of protection is speculative at this time. Therefore, we must interpret the cost–utility ratios proposed in the analysis with substantial caution.

While these factors, inherent to any cost–utility analysis of shingles, probably dominate the uncertainties in Hornberger and Robertus's study, other costs and benefits of shingles and shingles vaccine are hard to measure and may also contribute to the uncertainties. In its current formulation, shingles vaccine requires freezer storage. Many internists and family physicians are unfamiliar with such frozen products, and therefore, added up-front costs might include training, purchase of freezer units, and initial vaccine losses. Other costs that Hornberger and Robertus did not consider separately from vaccine cost were for vaccine administration, patient travel time, time receiving vaccine, and treatment of adverse events. The authors used the human capital approach to placing a monetary value on the time spent at less than full health. By only valuing time according to work productivity, the authors do not capture the value of leisure time, which is so important in this target population that is mostly retired. Furthermore, the analysis does not account for increases in the retirement age that are projected by many analysts, nor does it account for the projected increases in the incidence of shingles and PHN as the average age of the population increases.

The uncertainties in Hornberger and Robertus's analysis notwithstanding, what do we mean by "cost-effective"? A conventional threshold for cost-effectiveness has been $50 000 per QALY or less (6). This threshold is largely arbitrary, although the cost per QALY of widely accepted practices probably influences it. The threshold has crept upward toward $100 000 per QALY as more therapies and procedures enter common medical practice at much greater dollars per QALY saved. Many examples are found on the Tufts-New England Medical Center Cost-Effectiveness Analysis (CEA) Registry (7). The World Health Organization suggests that the threshold for cost-effectiveness

should be 3 times the gross domestic product per capita, which would be $94 431 for the United States (8). By this standard, the shingles vaccine in Hornberger and Robertus's study is in an intermediate cost-effectiveness category, at least at its current price and with the assumptions in the authors' model.

We can expect more economic analyses of the herpes zoster vaccine that use variations of this technique and make different assumptions. Physicians who have treated patients with shingles will want to use this vaccine and have it reimbursed by third-party payers. So will many of us who are 60 years of age or older. All interested parties would be reassured if this effective and seemingly safe vaccine, used for a relatively common and often debilitating condition, were also shown to be cost-effective. Given the many uncertainties, the conclusions about cost-effectiveness remain to be definitively demonstrated. But even before economic conclusions are established, policymaking bodies may decide to make a recommendation for routine administration of the shingles vaccine, and insurers may follow by providing insurance coverage for the vaccine. They will be making a "willingness-to-pay" determination based on a common recognition of disease burden, vaccine efficacy, safety, and consumer need.

Jeffrey P. Koplan, MD, MPH
Woodruff Health Sciences Center, Emory University
Atlanta, GA 30322

Rafael Harpaz, MD, MPH
National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention
Atlanta, GA 30333

Potential Financial Conflicts of Interest: *Grants received:* J.P. Koplan (Centers for Disease Control and Prevention).

Requests for Single Reprints: Jeffrey P. Koplan, MD, MPH, Woodruff Health Sciences Center, Emory University, 1440 Clifton Road, NE, Suite 410, Atlanta, GA 30322.

Current author addresses are available at www.annals.org.

Ann Intern Med. 2006;145:386-387.

References

1. **Seward JF, Watson BM, Peterson CL, Mascola L, Pelosi JW, Zhang JX, et al.** Varicella disease after introduction of varicella vaccine in the United States, 1995-2000. JAMA. 2002;287:606-11. [PMID: 11829699]
2. **Plotkin SA, Orenstein WA, eds.** Vaccines. 4th ed. Philadelphia: Saunders; 2004:783-823.
3. **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. [PMID: 15930418]
4. **Centers for Disease Control and Prevention.** CDC Vaccine Price List. Accessed at www.cdc.gov/nip/vfc/cdc_vac_price_list.htm on 29 June 2006.
5. **Hornberger J, Robertus K.** Cost-effectiveness of a vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. Ann Intern Med. 2006;145:317-25.
6. Primer on cost-effectiveness analysis. Eff Clin Pract. 2000;3:253-5. Accessed at www.acponline.org/journal/ecp/sepoct00/primer.htm on 17 July 2006.
7. The CEA Registry. Tufts-New England Medical Center Institute for Clinical Research and Health Policy Studies. Accessed at www.tufts-nemc.org/cearegistry on 17 July 2006.
8. **World Health Organization.** Choosing Interventions That Are Cost-Effective. Table: Threshold Values for Intervention Cost-Effectiveness by Region. Accessed at www.who.int/choice/costs/CER_levels/en/index.html on 17 July 2006.

© 2006 American College of Physicians

Current Author Addresses: Dr. Koplan: Woodruff Health Sciences Center, Emory University, 1440 Clifton Road, NE, Suite 410, Atlanta, GA 30322.

Dr. Harpaz: National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, 1600 Clifton Road, Mail Stop A-47, Atlanta, GA 30333.