CLINICAL THERAPEUTICS

Varicella–Zoster Vaccine for the Prevention of Herpes Zoster

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This Journal *feature begins with a case vignette that includes a therapeutic recommendation. A discussion of the clinical problem and the mechanism of benefit of this form of therapy follows. Major clinical studies, the clinical use of this therapy, and potential adverse effects are reviewed. Relevant formal guidelines, if they exist, are presented. The article ends with the authors' clinical recommendations.*

A 64-year-old man presents to his internist for his annual examination. He has been in good general health, although he received a diagnosis of pneumonia 8 months ago, for which he was treated with a course of oral antibiotics. At this visit, he inquires about when he should receive the "pneumonia shot" and whether other vaccinations are recommended. Should he receive the varicella–zoster vaccine?

THE CLINICAL PROBLEM

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Varicella–zoster virus (VZV) is a herpesvirus that causes two distinct clinical syndromes. Primary infection is manifested as varicella (chickenpox), whereas reactivation of latent VZV results in a localized eruption known as herpes zoster (shingles) (Fig. 1).[2] VZV is a highly contagious pathogen. Before licensure of the varicella vaccine for children in the United States, 95.5% of people 20 to 29 years of age, 98.9% of people 30 to 39 years of age, and more than 99.6% of people 40 years of age or older had evidence of previous VZV infection.[3]

Herpes zoster develops in approximately 30% of people over a lifetime.[4,5] The annualized incidence of herpes zoster ranges from approximately 1.5 to 4.0 cases per 1000 persons,[6-8] with up to 1 million cases or more each year in the United States.[1,8-10] The risk of disease increases with age, beginning at about 50 years; herpes zoster is 8 to 10 times as likely to develop in people 60 years of age or older as in younger people.[11] One or more episodes of herpes zoster will have developed in up to half of people who are 85 years of age. Herpes zoster also occurs with increased frequency in immunocompromised patients, especially those with human immunodeficiency virus (HIV) infection.[12]

Complications of herpes zoster in immunocompetent hosts include postherpetic neuralgia, encephalitis, myelitis, cranial-nerve palsies, and peripheral-nerve palsies.[11] Postherpetic neuralgia, a persistent pain syndrome occurring after the resolution of the zoster rash, is perhaps the most challenging and debilitating complication; it can last for weeks, months, or even years. Although the development of postherpetic neuralgia can occur at any age, people 50 years of age or older are most likely to have this complication, and more than 40% of people older than 60 years of age who have had zoster have postherpetic neuralgia.[13-18] Approximately 100,000 to 200,000 new cases of postherpetic neuralgia occur in the United States every year.[8]

PATHOPHYSIOLOGY AND EFFECT OF THERAPY

After the primary VZV infection (chickenpox), latent infection is established in the sensory-nerve ganglia (Fig. 2). The trigeminal and thoracic ganglia are the most

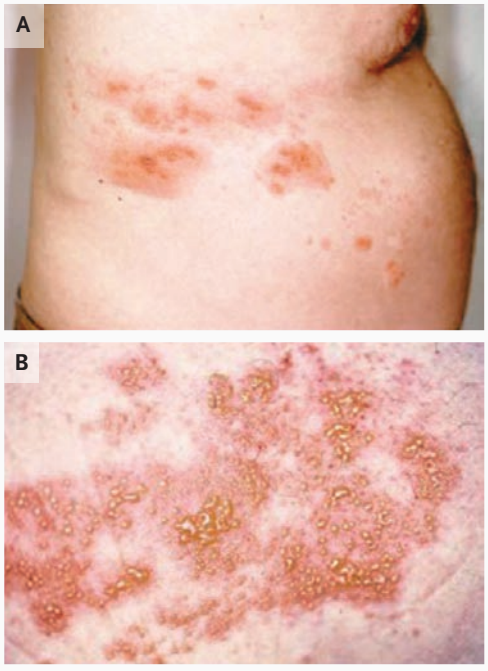

Figure 1. Acute Herpes Zoster.

Panel A shows a cutaneous eruption in the right T7 dermatome, and Panel B shows a close-up view of fresh vesicular lesions. (Both panels reprinted from Gnann and Whitley.[1])

common neuronal sites involved; these dermatomes are also the most common sites of cutaneous herpes zoster.[3] Latent VZV DNA is extrachromosomal, but the overall viral burden in ganglionic cells is low.

As shown in Figure 3, the decline in cell-mediated immunity over time as people age confers a predisposition to the occurrence of herpes zoster in older adults.[4,7,20-26] Second episodes of herpes zoster in immunocompetent people are uncommon, probably because of the immunologic "boosting" effect of the first zoster episode.[4,6,7,27] During reactivation of VZV, the sensory ganglia are sites of viral replication, with subsequent destruction of neurons and satellite cells.[11] This neurologic damage begins before the dermatomal rash of herpes zoster appears.[19] Before the appearance of the zoster rash, VZV travels along the affected sensory nerves to the skin (Fig. 2), evading both innate and adaptive host immune responses to spread from cell to cell and ultimately produce the unilateral, vesicular dermatomal rash that is characteristic of zoster.

The histologic changes in the skin lesions are similar to those of varicella. Multinucleated giant cells and intranuclear inclusions are present in the skin, and a mononuclear inflammatory infiltrate occurs in the dorsal-root ganglion of the affected dermatome. Necrosis of ganglion cells and demyelination of the corresponding axon occur.[28,29]

The VZV vaccine, originally developed and licensed as the "chickenpox vaccine" to prevent varicella, is a live attenuated vaccine that is effective in preventing primary infection with wild-type VZV. However, initial studies suggested that to elicit a significant and durable increase in cell-mediated immunity in older adults, a higher titer of live attenuated virus would be required,[30] probably because of the decreased responsiveness of older people to vaccination in general. As a result, a new VZV vaccine (Zostavax, Merck) was developed specifically for protection against herpes zoster. The commercially available zoster vaccine contains a minimum of 19,400 plaque-forming units per dose.[31] In contrast, the minimum levels of VZV in the commercially available chickenpox vaccines are either 9772 plaque-forming units per dose (in the quadrivalent measles, mumps, rubella, and varicella vaccine [ProQuad, Merck])[32] or 1350 plaque-forming units per dose (in the monovalent varicella vaccine [Varivax, Merck]).[33]

The preventive effect of the zoster vaccine is thought to be a consequence of its boosting effect on an older person's cell-mediated immunity to VZV,[34] mimicking the immunologic benefits of the exposure of a VZV-immune adult to chickenpox. This pharmacologic boost increases cell-mediated immunity to a new set point above the "immunologic threshold" below which a person is at risk for zoster (Fig. 3).

CLINICAL EVIDENCE

Several small clinical studies have shown that immunization with a varicella vaccine boosts waning cell-mediated immunity in older adults.[35-37] A large efficacy study by the Shingles Prevention Study Group evaluated the high-titer, live attenuated zoster vaccine.[10] A total of 38,546 subjects 60 years of age or older were enrolled and followed for a mean period of 3 years. The subjects were stratified according to age at enrollment (60 to 69 years or ≥70 years). More than 95% of the subjects were followed until completion of the study. The

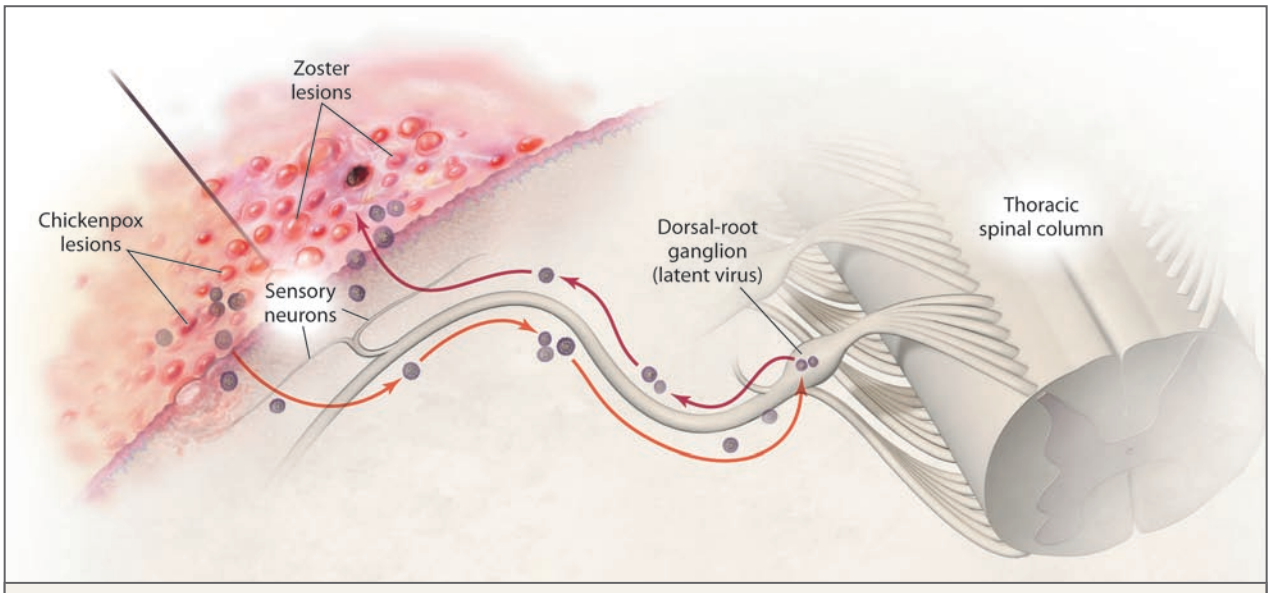

Figure 2. Establishment of VZV Latency in Sensory-Nerve Ganglia.
After a primary VZV infection (chickenpox), latent VZV infection is established in the dorsal-root ganglia, and zoster occurs with subsequent reactivation of the virus.

incidence of herpes zoster was 51% lower in the group of subjects who received the vaccine than in the group of subjects who received placebo (5.4 cases per 1000 person-years vs. 11.1 cases per 1000 person-years, P<0.001). Vaccine-strain DNA was not detected in any of the subjects with zoster. The incidence of postherpetic neuralgia was 67% lower among subjects who received the vaccine than among those who received placebo (0.5 case per 1000 person-years vs. 1.4 cases per 1000 person-years, P<0.001). The median duration of pain among subjects in whom herpes zoster developed was shorter in the vaccine group than in the placebo group (21 days vs. 24 days, P=0.03), and the degree of pain also was lower among the vaccine recipients (P=0.008).

The vaccine was more efficacious in preventing herpes zoster among persons who were 60 to 69 years of age than among those who were 70 years or older. However, it prevented postherpetic neuralgia to a greater extent among those who were 70 years or older than among those who were 60 to 69 years old.

CLINICAL USE

On May 25, 2006, the Food and Drug Administration licensed the zoster vaccine for the prevention of herpes zoster in persons 60 years of age or older.[10,31] It is not indicated for the treatment of herpes zoster or postherpetic neuralgia.

The zoster vaccine should not be administered to persons with a history of anaphylactic or anaphylactoid reactions to gelatin, neomycin, or any other vaccine component. People with a history of primary or acquired immunodeficiency conditions or those receiving immunosuppressive therapy, including corticosteroids, should not receive the vaccine. Zoster vaccination is also contraindicated in people with active, untreated tuberculosis and in pregnant women.

There are no alternatives to the zoster vaccine for prophylaxis. The other available varicella-containing vaccines, Varivax and ProQuad, contain significantly lower titers of live attenuated virus and therefore are of insufficient potency to elicit an increase in cell-mediated immunity to VZV in older adults. These vaccines should not be administered to older adults to prevent herpes zoster or postherpetic neuralgia.

Antiviral therapy decreases "zoster-associated pain" (the continuum of pain measured from its onset to final resolution, including postherpetic neuralgia),[38] but it does not prevent the development of postherpetic neuralgia.[1,20] Opioids, tricyclic antidepressants, and gabapentin have been

shown to have limited effectiveness in reducing the severity or duration of postherpetic neuralgia,[39-43] with variable and frequently inadequate results clinically.

The zoster vaccine, which is frozen for storage, is administered subcutaneously as a single 0.65-ml dose. To minimize the loss of potency, it should be administered immediately after reconstitution with the supplied diluent; if not used within 30 minutes after reconstitution, the vaccine should be discarded. There are insufficient data to suggest that repeated administration of the zoster vaccine is safe or confers an additional benefit.

On the basis of a cost of $150 for the single-shot vaccine, a preliminary Centers for Disease Control and Prevention (CDC) analysis has shown that the estimated "societal perspective" cost per quality-adjusted life-year ranges from $14,877 to $34,852. Approximately 17 people would need to be vaccinated in order to prevent one case of herpes zoster, and approximately 31 would need to be vaccinated in order to prevent one case of postherpetic neuralgia.[8] The cost per case of herpes zoster prevented is estimated to be $3,330, and the cost per case of postherpetic neuralgia prevented is estimated to be $6,405.[8]

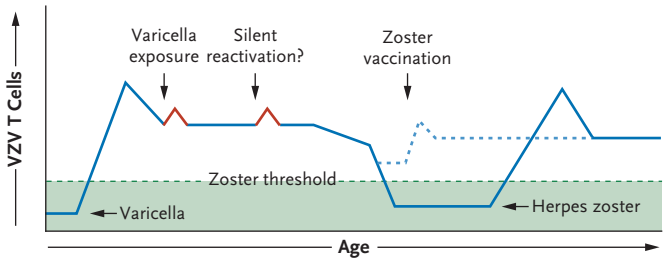

Figure 3. Host Factors in Latent VZV Infection and Reactivation.
Varicella is the primary infection caused by VZV, and its resolution is associated with the induction of VZV-specific memory T cells (blue line). Memory immunity to VZV may be boosted periodically by exposure to varicella or silent reactivation from latency (red peaks). VZV-specific memory T cells decline with age. The decline below a threshold (dashed green line) correlates with an increased risk of zoster. The occurrence of zoster, in turn, is associated with an increase in VZV-specific T cells. The administration of zoster vaccine to older persons may prevent VZV-specific T cells from dropping below the threshold for the occurrence of zoster (dashed blue line). (Reprinted from Arvin.[19])

ADVERSE EFFECTS

Most of the information regarding the adverse effects of the zoster vaccine comes from the Shingles Prevention Study.[10] Within the first 42 days after vaccination, varicella-like rashes at the injection site were more likely to develop in vaccine recipients than in placebo recipients (0.1% vs. 0.04%, $P<0.05$). Other symptoms and signs at the site of injection that occurred more frequently in the first 42 days in vaccine recipients than in placebo recipients included erythema (36% vs. 7%), localized pain or tenderness (35% vs. 9%), swelling (26% vs. 5%), and pruritus (7% vs. 1%) ($P<0.05$ for all four comparisons). The number and types of serious adverse events in the first 42 days were similar between the two groups. According to the package insert, cardiac events occurred more often among the vaccine recipients than among the placebo recipients in the Shingles Prevention Study (0.6% vs. 0.4%)[31]; whether this increased occurrence was due to the zoster vaccine and, if so, the reason or reasons for it are not known.

Since the zoster vaccine has been clinically available for less than 1 year, the potential risk of rare adverse events is unknown. The longer experience with the pediatric varicella vaccine (more than 10 years) suggests that this risk may be small, although the potency of the zoster vaccine is higher and the target population is quite different.

AREAS OF UNCERTAINTY

There are several areas of uncertainty. First, ongoing analyses of cost-effectiveness probably will influence recommendations for zoster immunization for people 60 years of age or older.

Second, it is unclear whether people 50 to 59 years of age should receive the vaccine. This would be an off-label use of the product. An argument for such use is the fact that the burden of herpes zoster in this population is substantial, since the incidence of zoster increases among people 50 years of age or older. Furthermore, the efficacy of the vaccine against herpes zoster is higher among persons 60 to 69 years of age than among those 70 years or older, suggesting that it may be more immunogenic in people 50 to 59 years of age as well. However, no efficacy data are available for this population, and the available immunogenicity data are based only on small numbers of people in this age group.

Third, wild-type VZV infections are declining

as a result of universal vaccination in childhood, including a second dose of vaccine at 4 to 6 years of age, as recommended recently by the CDC Advisory Committee on Immunization Practices (ACIP) and by the Committee on Infectious Diseases of the American Academy of Pediatrics.[44,45] As a consequence, the likelihood that older people will be "boosted" by exposure to a child with chickenpox is declining. The effect that this shift in the epidemiology of VZV will have at a time when older people are also receiving the zoster vaccine will require careful postlicensure monitoring over a period of many years. Questions to be answered include the incidence of herpes zoster over time and the longevity of protection conferred by the one dose of the zoster vaccine currently indicated. As these questions are being investigated, persons who have previously received Varivax or ProQuad should be considered to be candidates for zoster vaccination as they grow older, unless there is an applicable precaution or contraindication.

Fourth, the zoster vaccine is not licensed for use in immunocompromised people. However, this population is at especially high risk for the development of herpes zoster. This group includes people who are mildly immunosuppressed, such as people with diabetes and people receiving low-dose corticosteroids, tumor-necrosis-factor blockers, and other immunomodulatory drugs. In addition, the safety and efficacy of the vaccine have not been established in immunocompetent people for whom immunosuppressive therapy is anticipated and who will therefore be at at high risk for herpes zoster. This group includes patients who are awaiting organ transplantation, patients with early-stage HIV infection who are asymptomatic, and patients who will be receiving chemotherapy for cancer or immunosuppressive therapy for rheumatoid arthritis, lupus, or other autoimmune diseases.

Finally, the efficacy of the vaccine in people who have had a previous episode of herpes zoster is unknown, since this population was excluded from the large zoster vaccine trial.

GUIDELINES

In October 2006, the ACIP voted to recommend a single dose of zoster vaccine for adults 60 years of age or older, whether or not they have had a previous episode of herpes zoster.[46] Furthermore, persons with chronic medical conditions may be vaccinated unless there is an applicable precaution or contraindication. Because virtually all adults 60 years of age or older will have had clinical or subclinical primary VZV infection (chickenpox),[3] it is not necessary to determine whether there is a history of chickenpox for routine vaccination of people in this age group.

RECOMMENDATIONS

The patient described in the vignette is a healthy, immunocompetent person who is 60 years of age or older and is therefore an appropriate candidate for immunization with the zoster vaccine. We recommend that the vaccine be universally administered to such persons, provided there is no contraindication. We do not recommend routine vaccination of people 50 to 59 years of age because of the lack of efficacy data and cost-effectiveness information for this population.

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Dr. Whitley reports chairing the data and safety monitoring board for the Shingles Prevention Study, serving on the Gilead Sciences Scientific Advisory Board, and receiving speaking fees from Novartis and GlaxoSmithKline. Dr. Kimberlin reports serving as the liaison from the Committee on Infectious Diseases of the American Academy of Pediatrics to the CDC ACIP. No other potential conflict of interest relevant to this article was reported.

We dedicate this review to Stephen Straus, M.D. Dr. Straus's career achievements in herpes virology in general and in VZV in particular have been seminal to advancing our understanding of disease pathogenesis, treatment, and prevention.

REFERENCES

1. Gnann JW Jr, Whitley RJ. Herpes zoster. N Engl J Med 2002;347:340-6.
2. Straus SE, Reinhold W, Smith HA, et al. Endonuclease analysis of viral DNA from varicella and subsequent zoster infections in the same patient. N Engl J Med 1984;311:1362-4.
3. Kilgore PE, Kruszon-Moran D, Seward JF, et al. Varicella in Americans from NHANES III: implications for control through routine immunization. J Med Virol 2003;70:Suppl 1:S111-S118.
4. Hope-Simpson RE. The nature of herpes zoster: a long term study and a new hypothesis. Proc R Soc Med 1965;58:9-20.
5. Brisson M, Edmunds WJ, Law B, et al. Epidemiology of varicella zoster virus infection in Canada and the United Kingdom. Epidemiol Infect 2001;127:305-14.
6. Donahue JG, Choo PW, Manson JE, Platt R. The incidence of herpes zoster. Arch Intern Med 1995;155:1605-9.
7. Ragozzino MW, Melton LJ III, Kurland LT, Chu CP, Perry HO. Population-

based study of herpes zoster and its sequelae. Medicine (Baltimore) 1982;61:310-6.
8. Advisory Committee on Immunization Practices. Considerations for shingles vaccine recommendations in the U.S.: record of the proceedings. Atlanta: Centers for Disease Control and Prevention, 2006. (Accessed March 12, 2007, at http://www.cdc.gov/nip/acip/minutes/acip-min-jun06.pdf.)
9. Gershon AA, Perkin RT. Herpes zoster. N Engl J Med 2000;343:222.
10. Oxman MN, Levin MJ, Johnson GR, et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. N Engl J Med 2005;352:2271-84.
11. Gilden DH, Kleinschmidt-DeMasters BK, LaGuardia JJ, Mahalingam R, Cohrs RJ. Neurologic complications of the reactivation of varicella–zoster virus. N Engl J Med 2000;342:635-45. [Erratum, N Engl J Med 2000;342:1063.]
12. Locksley RM, Flournoy N, Sullivan KM, Meyers JD. Infection with varicella-zoster virus after marrow transplantation. J Infect Dis 1985;152:1172-81.
13. Rogers RS III, Tindall JP. Geriatric herpes zoster. J Am Geriatr Soc 1971;19:495-504.
14. Brown GR. Herpes zoster: correlation of age, sex, distribution, neuralgia, and associated disorders. South Med J 1976;69:576-8.
15. Edmunds WJ, Brisson M, Rose JD. The epidemiology of herpes zoster and potential cost-effectiveness of vaccination in England and Wales. Vaccine 2001;19:3076-90.
16. Haanpaa M, Laippala P, Nurmikko T. Allodynia and pinprick hypesthesia in acute herpes zoster, and the development of postherpetic neuralgia. J Pain Symptom Manage 2000;20:50-8.
17. Scott FT, Leedham-Green ME, Barrett-Muir WY, et al. A study of shingles and the development of postherpetic neuralgia in East London. J Med Virol 2003;70:Suppl 1:S24-S30.
18. Scott FT, Johnson RW, Leedham-Green M, Davies E, Edmunds WJ, Breuer J. The burden of herpes zoster: a prospective population based study. Vaccine 2006;24:1308-14.
19. Arvin A. Aging, immunity, and the varicella–zoster virus. N Engl J Med 2005;352:2266-7.
20. Kost RG, Straus SE. Postherpetic neuralgia — pathogenesis, treatment, and prevention. N Engl J Med 1996;335:32-42.
21. Berger R, Florent G, Just M. Decrease of the lymphoproliferative response to varicella-zoster virus antigen in the aged. Infect Immun 1981;32:24-7.
22. Burke BL, Steele RW, Beard OW, Wood JS, Cain TD, Marmer DJ. Immune responses to varicella-zoster in the aged. Arch Intern Med 1982;142:291-3.
23. Dolin R, Reichman RC, Mazur MH, Whitley RJ. NIH conference: herpes zoster–varicella infections in immunosuppressed patients. Ann Intern Med 1978;89:375-88.
24. Galil K, Choo PW, Donahue JG, Platt R. The sequelae of herpes zoster. Arch Intern Med 1997;157:1209-13.
25. Wilson A, Sharp M, Koropchak CM, Ting SF, Arvin AM. Subclinical varicella-zoster virus viremia, herpes zoster, and T lymphocyte immunity to varicella-zoster viral antigens after bone marrow transplantation. J Infect Dis 1992;165:119-26.
26. Buchbinder SP, Katz MH, Hessol NA, et al. Herpes zoster and human immunodeficiency virus infection. J Infect Dis 1992;166:1153-6.
27. Weller TH. Varicella and herpes zoster: changing concepts of the natural history, control, and importance of a not-so-benign virus. N Engl J Med 1983;309:1434-40.
28. Lungu O, Annunziato PW, Gershon A, et al. Reactivated and latent varicella-zoster virus in human dorsal root ganglia. Proc Natl Acad Sci U S A 1995;92:10980-4.
29. Esiri MM, Tomlinson AH. Herpes zoster: demonstration of virus in trigeminal nerve and ganglion by immunofluorescence and electron microscopy. J Neurol Sci 1972;15:35-48.
30. Levin MJ. Use of varicella vaccines to prevent herpes zoster in older individuals. Arch Virol Suppl 2001;17:151-60.
31. Zostavax. Whitehouse Station, NJ: Merck & Co., 2006 (package insert). (Accessed March 5, 2007, at http://www.fda.gov/CbER/label/zosmer052506LB.pdf.)
32. ProQuad. Whitehouse Station, NJ: Merck & Co., 2005 (package insert). (Accessed March 5, 2007, at http://www.fda.gov/CbER/label/mmrvmer090605LB.pdf.)
33. Varivax. Whitehouse Station, NJ: Merck & Co., 2005 (package insert). (Accessed March 5, 2007, at http://www.fda.gov/cber/label/varmer040505LBr.pdf.)
34. Levin MJ, Murray M, Rotbart HA, Zerbe GO, White CJ, Hayward AR. Immune response of elderly individuals to a live attenuated varicella vaccine. J Infect Dis 1992;166:253-9.
35. Oxman MN. Immunization to reduce the frequency and severity of herpes zoster and its complications. Neurology 1995;45:Suppl 8:S41-S46.
36. Levin MJ, Barber D, Goldblatt E, et al. Use of a live attenuated varicella vaccine to boost varicella-specific immune responses in seropositive people 55 years of age and older: duration of booster effect. J Infect Dis 1998;178:Suppl 1:S109-S112.
37. Trannoy E, Berger R, Hollander G, et al. Vaccination of immunocompetent elderly subjects with a live attenuated Oka strain of varicella zoster virus: a randomized, controlled, dose-response trial. Vaccine 2000;18:1700-6.
38. Wood MJ, Kay R, Dworkin RH, Soong SJ, Whitley RJ. Oral acyclovir therapy accelerates pain resolution in patients with herpes zoster: a meta-analysis of placebo-controlled trials. Clin Infect Dis 1996;22:341-7.
39. Kanazi GE, Johnson RW, Dworkin RH. Treatment of postherpetic neuralgia: an update. Drugs 2000;59:1113-26.
40. Max MB, Schafer SC, Culnane M, Smoller B, Dubner R, Gracely RH. Amitriptyline, but not lorazepam, relieves postherpetic neuralgia. Neurology 1988;38:1427-32.
41. Kishore-Kumar R, Max MB, Schafer SC, et al. Desipramine relieves postherpetic neuralgia. Clin Pharmacol Ther 1990;47:305-12.
42. Rowbotham M, Harden N, Stacey B, Bernstein P, Magnus-Miller L. Gabapentin for the treatment of postherpetic neuralgia: a randomized controlled trial. JAMA 1998;280:1837-42.
43. Watson CP, Babul N. Efficacy of oxycodone in neuropathic pain: a randomized trial in postherpetic neuralgia. Neurology 1998;50:1837-41.
44. ACIP provisional recommendations for prevention of varicella. Atlanta: Centers for Disease Control and Prevention, 2006. (Accessed March 5, 2007, at http://www.cdc.gov/nip/vaccine/varicella/varicella_acip_recs_prov_june_2006.pdf.)
45. American Academy of Pediatrics Committee on Infectious Diseases. Prevention of varicella: recommendations for use of varicella vaccines in children, including a recommendation for a routine two-dose varicella immunization schedule. Pediatrics (in press).
46. ACIP provisional recommendations for the use of zoster vaccine. Atlanta: Centers for Disease Control and Prevention, 2006. (Accessed March 5, 2007, at http://www.cdc.gov/nip/recs/provisional_recs/zoster-11-20-06.pdf.)