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Prevention of Herpes Zoster

Recommendations of the Advisory Committee on Immunization Practices (ACIP)



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Prevention of Herpes Zoster

Recommendations of the Advisory Committee on Immunization Practices (ACIP)

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Summary

These recommendations represent the first statement by the Advisory Committee on Immunization Practices (ACIP) on the use of a live attenuated vaccine for the prevention of herpes zoster (zoster) (i.e., shingles) and its sequelae, which was licensed by the U.S. Food and Drug Administration (FDA) on May 25, 2006. This report summarizes the epidemiology of zoster and its sequelae, describes the zoster vaccine, and provides recommendations for its use among adults aged ≥ 60 years in the United States.

Zoster is a localized, generally painful cutaneous eruption that occurs most frequently among older adults and immunocompromised persons. It is caused by reactivation of latent varicella zoster virus (VZV) decades after initial VZV infection is established. Approximately one in three persons will develop zoster during their lifetime, resulting in an estimated 1 million episodes in the United States annually. A common complication of zoster is postherpetic neuralgia (PHN), a chronic, often debilitating pain condition that can last months or even years. The risk for PHN in patients with zoster is 10%–18%. Another complication of zoster is eye involvement, which occurs in 10%–25% of zoster episodes and can result in prolonged or permanent pain, facial scarring, and loss of vision. Approximately 3% of patients with zoster are hospitalized; many of these episodes involved persons with one or more immunocompromising conditions. Deaths attributable to zoster are uncommon among persons who are not immunocompromised.

Prompt treatment with the oral antiviral agents acyclovir, valacyclovir, and famciclovir decreases the severity and duration of acute pain from zoster. Additional pain control can be achieved in certain patients by supplementing antiviral agents with corticosteroids and with analgesics. Established PHN can be managed in certain patients with analgesics, tricyclic antidepressants, and other agents.

Licensed zoster vaccine is a lyophilized preparation of a live, attenuated strain of VZV, the same strain used in the varicella vaccines. However, its minimum potency is at least 14-times the potency of single-antigen varicella vaccine. In a large clinical trial, zoster vaccine was partially efficacious at preventing zoster. It also was partially efficacious at reducing the severity and duration of pain and at preventing PHN among those developing zoster.

Zoster vaccine is recommended for all persons aged ≥ 60 years who have no contraindications, including persons who report a previous episode of zoster or who have chronic medical conditions. The vaccine should be offered at the patient's first clinical encounter with his or her health-care provider. It is administered as a single 0.65 mL dose subcutaneously in the deltoid region of the arm. A booster dose is not licensed for the vaccine. Zoster vaccination is not indicated to treat acute zoster, to prevent persons with acute zoster from developing PHN, or to treat ongoing PHN. Before administration of zoster vaccine, patients do not need to be asked about their history of varicella (chickenpox) or to have serologic testing conducted to determine varicella immunity.

Introduction

Infection with varicella zoster virus (VZV) causes two distinct clinical conditions. Primary VZV infection causes varicella (i.e., chickenpox), a contagious rash illness that typically occurs among children. A vaccine for preventing initial VZV infection has been available in the United States since 1995, and the Advisory Committee on Immunization Practices (ACIP) recommends routine varicella

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vaccination for all persons aged ≥ 12 months who lack evidence of immunity (1–3). Varicella vaccination has dramatically reduced chickenpox cases among children (3).

VZV can reactivate clinically decades after initial infection to cause herpes zoster (zoster) (i.e., shingles), a localized and generally painful cutaneous eruption that occurs most frequently among older adults. Approximately 1 million new cases of zoster occur in the United States annually. Approximately one in three persons in the general population will develop zoster during their lifetime. A common complication of zoster is postherpetic neuralgia (PHN), a chronic pain condition that can last months or even years. In May 2006, a live, attenuated vaccine for prevention of zoster (ZOSTAVAX[®], manufactured by Merck & Co., Inc.) was licensed in the United States for use in persons aged ≥ 60 years. This report provides recommendations for use of zoster vaccine for prevention of zoster and its sequelae.

Methods

In Spring 2005, Merck & Co., Inc. (Whitehouse Station, New Jersey) submitted a Biologics License Application to the Food and Drug Administration (FDA) for an investigational live, attenuated vaccine for prevention of zoster on the basis of a phase 3 clinical trial. These results were published in June 2005 (4) and presented at the ACIP meeting later that month. In September 2005, ACIP's measles-mumps-rubella and varicella workgroup expanded its membership to include experts in adult medicine and in zoster and began review of relevant data on zoster and the investigational vaccine. Shortly thereafter, this workgroup reformed as the ACIP shingles workgroup and, during subsequent months, held 19 conference calls to review and discuss scientific evidence related to herpes zoster and zoster vaccine, including the epidemiology and natural history of zoster and its sequelae, and the safety, immunogenicity, efficacy, financing, storage, and handling of the zoster vaccine. The workgroup also reviewed several economic analyses on zoster prevention. Workgroup members participated in 10 additional conference calls to develop and discuss recommendation options for preventing zoster. When scientific evidence was lacking, recommendations incorporated expert opinions of the workgroup members.

Presentations of background materials on zoster and the vaccine were made during ACIP meetings in October 2005 and the three meetings in 2006. Following vaccine licensure on May 25, 2006, recommendation options were presented to ACIP in June 2006, and final options were

presented at the October 2006 meeting. During review by CDC and external partners, modifications were made to the proposed recommendations to update and clarify wording in the document. As new information on the epidemiology and prevention of zoster becomes available, it will be reviewed by ACIP and recommendations will be updated as needed.

Background

Biology of VZV

VZV is an exclusively human pathogen that infects approximately 98% of the adult population in the United States (5). The primary infection typically occurs during childhood and causes varicella. During its viremic phase, cell-associated VZV gains access to epidermal cells, causing the typical varicella rash. The virus then enters sensory nerves in mucocutaneous sites and travels through retrograde axonal transport to the sensory dorsal root ganglia adjacent to the spinal cord where the virus establishes permanent latency in neuronal cell bodies (6–7). Latent VZV is present in approximately 1%–7% of sensory ganglion neurons, with <10 genomic copies per infected cell (8–10). Seeding of dorsal root ganglia also might occur during viremia. The magnitude of viremia, the number of skin lesions, and the burden of VZV that establishes latency during primary varicella infection might be linked (11). As with other members of the herpesvirus family, VZV is noninfectious in its latent form but can reactivate at a later time to form intact virions in the involved sensory neurons. These virions then migrate to the skin through axons, spread from cell to cell, and penetrate the epidermis (12). In its full clinical expression, zoster causes pain, which is followed by a vesicular rash distributed across closely overlapping dermatomes of the involved sensory nerve roots.

The triggers for reactivation of VZV have not been identified and probably involve multiple factors. However, specific components of cell-mediated immunity (CMI) have an important role in controlling the development of zoster by preventing reactivation within the neuron or the full clinical expression of reactivated VZV as zoster. The effectiveness of these protective components of CMI is well maintained in immunocompetent persons during childhood and early adulthood. These CMI components are believed to be partially or substantially maintained by periodic immunologic boosting. “Endogenous boosting” might occur in response to subclinical reactivation of latent VZV or to development of zoster itself, and “exogenous boosting” might occur in response to exposure to

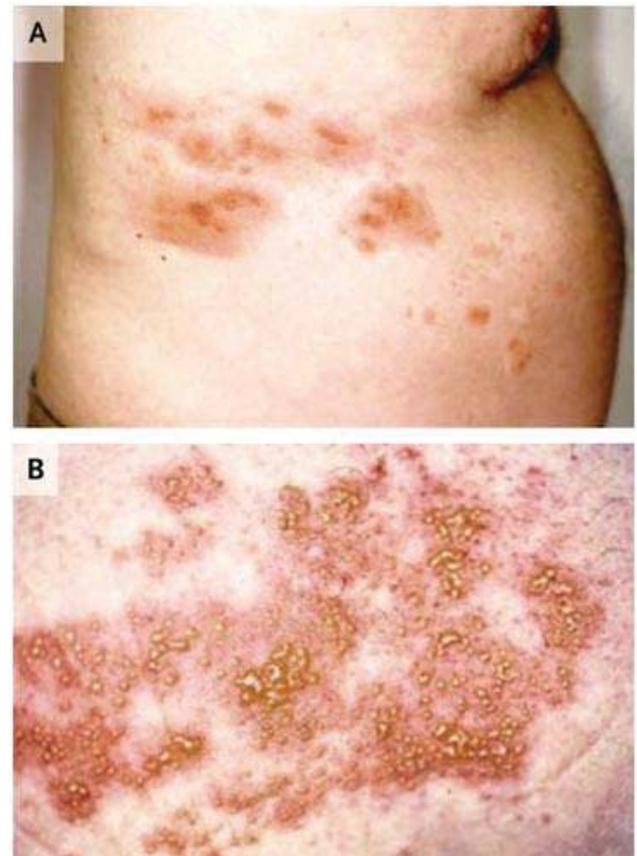
VZV circulating in the population as chickenpox (13–19). Although virtually all adults are infected with VZV (5), specific immunologic parameters have not been identified to distinguish who will develop zoster. Anti-VZV antibody levels per se are not thought to have a role in zoster prevention (20). Parameters that have been monitored and correlate with such protection include anamnestic boost in anti-VZV antibodies in vivo in response to VZV-based vaccination, and the presence of and boost in memory CD4 T cells as measured in vitro by proliferation of peripheral blood mononuclear cells (PBMC), by frequency of proliferating PBMC, or by frequency of interferon- γ (IFN- γ) releasing PBMC, all in response to VZV-antigens (21,22). These latter two parameters are generally assessed using a responder cell frequency (RCF) assay and an IFN- γ enzyme-linked immunosorbent spot-forming cell (ELISPOT) assay, respectively (22). VZV-specific class I-restricted and unrestricted cytotoxicities also have been monitored using target cell lysis (23). Although CMI is necessary for the control of zoster, other nonimmunologic factors also might be involved (24).

Clinical Features of Zoster and PHN

The clinical course of acute zoster is variable. It is usually less severe in children and younger adults. Typically, zoster begins with a prodrome. Headache, photophobia, and malaise might occur, with fever being less common. Abnormal skin sensations and pain of varying severity are the most common symptoms. These symptoms can precede the zoster rash by days to weeks (25) and rarely might be the only clinical manifestation of VZV reactivation (termed zoster sine herpette) (7). Pain is described as aching, burning, stabbing, or shock-like. Altered sensitivity to touch, pain provoked by trivial stimuli, and unbearable itching are all frequently reported.

Zoster rash is typically unilateral and does not cross the mid-line, erupting in one or two adjacent dermatomes. The frequency of zoster occurrence in different dermatomes has been evaluated in certain studies. In general, thoracic, cervical, and ophthalmic involvement are most common (Figure 1) (26–28). Small numbers of lesions can occur outside the primary or adjacent dermatome. The rash is initially erythematous and maculopapular but progresses to form coalescing clusters of clear vesicles containing high concentrations of VZV (Figure 1). The vesicles form over several days and then evolve through pustular, ulcer, and crust stages. The rash usually lasts 7–10 days, with complete healing within 2–4 weeks. However, pigmentation changes and scarring might be permanent. Streptococcal

FIGURE 1. Thoracic distribution of zoster (A), and zoster rash with coalescing clusters of clear vesicles (B)



or staphylococcal superinfections might complicate zoster rash (29).

A common and potentially debilitating consequence of zoster is PHN, a persistent pain after resolution of the rash. Pathologic observations thought to distinguish PHN from uncomplicated zoster include axonal and cell body degeneration, atrophy of the spinal cord dorsal horn, scarring of the dorsal root ganglion, and loss of epidermal innervation of the affected area. Certain experts believe this neuronal damage might be caused by ongoing viral replication (30,31). In addition, consensus is lacking regarding criteria needed to distinguish the quality, duration, or underlying pathophysiology of pain occurring with zoster versus PHN. Therefore, the duration of pain used to define PHN has been inconsistent, ranging from any duration after resolution of the rash to periods from ≥ 30 days to ≥ 6 months after rash onset.

Regardless of definition, the pain of PHN can last for weeks or months and occasionally persists for many years. The nature of PHN pain varies from mild to excruciating

in severity, constant, intermittent, or triggered by trivial stimuli. Approximately half of patients with zoster or PHN describe their pain as “horrible” or “excruciating”, ranging in duration from a few minutes to constant on a daily or almost daily basis (32). The pain can disrupt sleep, mood, work, and activities of daily living, adversely impacting the quality of life and leading to social withdrawal and depression (Table 1) (31–33). Anecdotes of suicide among patients suffering from PHN have been reported (34; Peter Richards, MD, personal communication, 2007). Among persons experiencing zoster, predictors of PHN include the occurrence and severity of pain both before and after onset of the rash, the extent of the rash, trigeminal or ophthalmic distribution (35,36), and the occurrence of viremia (37).

In addition to PHN, zoster is associated with a variety of other complication. Among persons with zoster, 10%–25% have eye involvement, called herpes zoster ophthalmicus (HZO) (38,39) (Figure 2). HZO can occur when reactivation involves the nasociliary branch of the trigeminal nerve, sometimes preceded by the presence of zoster vesicles on the nose (Hutchinson sign). Keratitis occurs in approximately two thirds of patients with HZO (40), often causing corneal ulceration. Other complications include conjunctivitis, uveitis, episcleritis and scleritis, retinitis, choroiditis, optic neuritis, lid retraction, ptosis, and glaucoma. Extraocular muscle palsies also occur. Prolonged or permanent sequelae of HZO include pain, facial scarring, and loss of vision (41).

An uncommon complication of zoster is Ramsay Hunt syndrome, a peripheral facial nerve palsy accompanied by zoster vesicles on the ear, hard palate, or tongue (42). The pathophysiology of this complication involves reactivation of VZV in the geniculate ganglion of the facial nerve. Additional signs and symptoms of Ramsey Hunt syndrome can include pain, vertigo, hearing loss, sensitivity to sound, tinnitus, and loss of taste. Many patients do not recover

FIGURE 2. Case of herpes zoster ophthalmicus



Photo/MN Oxman, University of California, San Diego

completely (42). Idiopathic facial palsy (Bell's palsy) might be caused by inapparent VZV reactivation (42,43).

Occasionally, zoster can cause motor weakness in noncranial nerve distributions, called zoster paresis (44,45). The mechanism has not been determined. The weakness develops abruptly within 2–3 weeks after onset of the rash and can involve upper or lower extremities. Diaphragmatic paralysis also has been described. The prognosis of zoster paresis is good (46). Zoster also can result in autonomic dysfunction, causing urinary retention and colon pseudo-obstruction.

Rarely, patients will experience acute focal neurologic deficits weeks to months after resolution of the zoster rash, involving the trigeminal distribution contralateral to the initial rash. This ischemic stroke syndrome, termed granulomatous angiitis, is believed to be caused by direct extension of VZV from the trigeminal ganglion to the internal carotid artery or its branches, resulting in inflammation (30). Mortality from this syndrome is substantial. Other rare neurologic complications of zoster include myelitis, aseptic meningitis, and meningoencephalitis. The prognosis for these conditions is good, although encephalomyelitis can be life threatening. Guillain-Barré syndrome also has been reported in association with zoster (47).

In immunocompromised persons, zoster initially might present typically. However, the rash tends to be more severe and its duration prolonged (48,49). One specific risk for persons with some immunosuppressive conditions

TABLE 1. Impact of acute herpes zoster and postherpetic neuralgia on quality of life

Life factor	Impact
Physical	Chronic fatigue Anorexia and weight loss Physical inactivity Insomnia
Psychological	Anxiety Difficulty concentrating Depression, suicidal ideation
Social	Fewer social gatherings Changes in social role
Functional	Interferes with activities of daily living (e.g., dressing, bathing, eating, travel, cooking, and shopping)

is dissemination of the zoster rash. True cutaneous dissemination generally occurs only among immunocompromised patients, occurring in up to 37% of zoster cases in the absence of antiviral treatment (49–54). Dissemination usually begins with a dermatomal rash; however, the rash sometimes begins with no primary dermatomal involvement (54).

Cutaneous dissemination is not life-threatening; however, it is a marker for VZV viremia that can seed the lungs, liver, gut, and brain and cause pneumonia, hepatitis, encephalitis, and disseminated intravascular coagulopathy in 10%–50% of episodes. Visceral dissemination with no skin involvement can occur in profoundly immunocompromised persons. Even with antiviral treatment, the case fatality rate from visceral dissemination is 5%–15%, with most deaths attributable to pneumonia (49,54,55).

The risk for neurologic zoster complications is generally increased in immunocompromised persons. These complications, which can be aggressive and even fatal, include myelitis, chronic encephalitis, ventriculitis, meningoencephalitis, and cranial palsies (30). However, the risk for PHN is not appreciably increased among immunocompromised persons who develop zoster (30).

Compared with other immunocompromised persons, the clinical features of zoster are less severe and visceral dissemination less common among persons infected with human immunodeficiency virus (HIV) (56,57). Some zoster presentations that are unique to persons infected with HIV include atypical skin eruptions (58,59) and an aggressive variant of acute retinal necrosis that generally results in blindness (60). Alveolar bone necrosis and tooth exfoliation also have been reported (61).

Diagnosis

Zoster diagnosis might not be possible in the absence of rash (e.g., before rash or in cases of zoster sine herpete). Patients with localized pain or altered skin sensations might undergo evaluation for kidney stones, gallstones, or coronary artery disease until the zoster rash appears and the correct diagnosis is made (62). In its classical manifestation, the signs and symptoms of zoster are usually distinctive enough to make an accurate clinical diagnosis once the rash has appeared (63). Occasionally, zoster might be confused with impetigo, contact dermatitis, folliculitis, scabies, insect bites, papular urticaria, candidal infection, dermatitis herpetiformis, or drug eruptions. More frequently, zoster is confused with the rash of herpes simplex virus (HSV), including eczema herpeticum (4,31,64–66). The accuracy of diagnosis is lower for children and younger adults in

whom zoster incidence is lower and its symptoms less often classic.

In some cases, particularly in immunosuppressed persons, the location of rash appearance might be atypical, or a neurologic complication might occur well after resolution of the rash. In these instances, laboratory testing might clarify the diagnosis (67–71). Tzanck smears are inexpensive and can be used at the bedside to detect multinucleated giant cells in lesion specimens, but they do not distinguish between infections with VZV and HSV. VZV obtained from lesions can be identified using tissue culture, but this can take several days and false negative results occur because viable virus is difficult to recover from cutaneous lesions. Direct fluorescent antibody (DFA) staining of VZV-infected cells in a scraping of cells from the base of the lesion is rapid and sensitive. DFA and other antigen-detection methods also can be used on biopsy material, and eosinophilic nuclear inclusions (Cowdry type A) are observed on histopathology. Polymerase chain reaction (PCR) techniques performed in an experienced laboratory also can be used to detect VZV DNA rapidly and sensitively in properly-collected lesion material, although VZV PCR testing is not available in all settings. A modification of PCR diagnostic techniques has been used at a few laboratories to distinguish wild-type VZV from the Oka/Merck strain used in the licensed varicella and zoster vaccines.

In immunocompromised persons, even when VZV is detected by laboratory methods in lesion specimens, distinguishing chickenpox from disseminated zoster might not be possible by physical examination (72) or serologically (73–75). In these instances, a history of VZV exposure, a history that the rash began with a dermatomal pattern, and results of VZV antibody testing at or before the time of rash onset might help guide the diagnosis.

Zoster Transmission

Zoster lesions contain high concentrations of VZV that can be spread, presumably by the airborne route (76,77), and cause primary varicella in exposed susceptible persons (77,78–83). Localized zoster is only contagious after the rash erupts and until the lesions crust. Zoster is less contagious than varicella (78). In one study of VZV transmission from zoster, varicella occurred among 15.5% of susceptible household contacts (78). In contrast, following household exposure to varicella, a more recent study demonstrated VZV transmission among 71.5% of susceptible contacts (84). In hospital settings, transmission has been

documented between patients or from patients to health-care personnel, but transmission from health-care personnel to patients has not been documented. Persons with localized zoster are less likely to transmit VZV to susceptible persons in household or occupational settings if their lesions are covered (85).

Epidemiology of Zoster and Complications

Risk Factors

Infection with VZV

Wild-type VZV. Because zoster reflects reactivation of latent VZV, the primary risk factor and a necessary precondition for zoster is previous VZV infection. Approximately 99.5% of the U.S. population aged ≥ 40 years has serologic evidence of previous infection, including all evaluated subgroups; therefore, all older adults are at risk for zoster (5), although many cannot recall a history of varicella (86–90). Varicella vaccine is effective at preventing initial wild-type VZV infection in persons not previously infected. Any wild-type VZV infections prevented cannot reactivate as zoster.

The age at the time of initial VZV infection influences the age at which zoster occurs. Persons acquiring an intrauterine or early childhood infection with VZV are at increased risk for pediatric zoster (91–93). When VZV infections occur before age 2 months, the risk for zoster occurring by the age of 12 years is increased >35 -fold compared with the risk for VZV infections occurring after infancy (92). Other case series suggest that the risk for pediatric zoster also might be increased in children who experienced varicella at older ages (94). Conversely, the risk for zoster might be diminished in persons born in countries (95) or living in communities (96) where varicella infection tends to occur at later ages. These observations suggest that changes in the epidemiology of varicella caused by varicella vaccination or by other factors can alter the epidemiology of zoster, particularly pediatric zoster.

Oka/Merck Strain VZV. Among vaccine recipients, the attenuated Oka/Merck strain of VZV included in varicella vaccine also can establish a latent infection and clinically reactivate as zoster (97). Zoster caused by Oka/Merck strain VZV cannot be distinguished on clinical grounds from zoster caused by wild-type VZV. The risk for zoster caused specifically by Oka/Merck strain VZV is unknown because recipients of varicella vaccine might have already been infected with wild-type VZV or might have become infected with wild-type VZV following vaccination (i.e.,

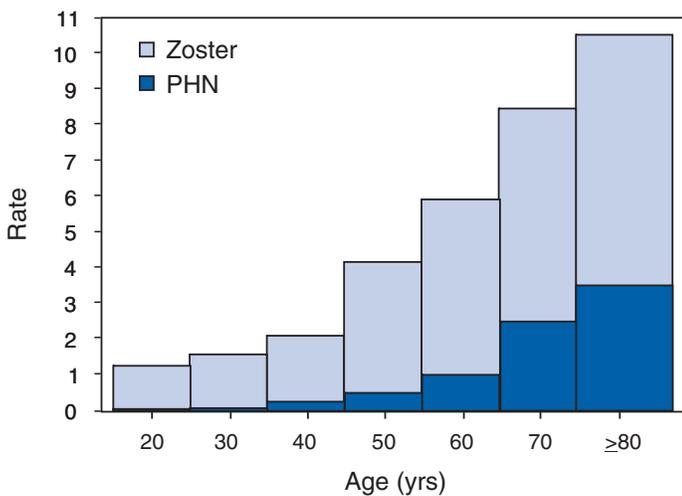
due to vaccine failure) that could also reactivate. Therefore, the rate of all episodes of zoster among varicella vaccine recipients define the upper bound for the risk of the subset of episodes caused by Oka/Merck strain VZV. The risk for zoster in immunocompromised children was approximately 65% less for those who had received the varicella vaccine compared with those with previous wild-type varicella infection (98,99). In immunocompetent children, the risk also appears to be reduced among 1-dose vaccine recipients compared with children with a history of wild-type varicella, although longer follow up is needed (99–101). The risk for zoster in immunocompetent children following 2 doses of varicella vaccine has not been studied. Collectively these studies suggest that the risk for Oka/Merck strain zoster following varicella vaccination is no higher, and likely considerably lower, than that following wild-type varicella infection, even though the acquisition of the Oka/Merck VZV through vaccination generally occurs at a young age (i.e., varicella vaccination is recommended for children aged ≥ 12 months [1–3]), which might be a risk factor for pediatric zoster. As varicella vaccine recipients age, the risk for and manifestation of Oka/Merck strain zoster in older persons at greater risk for zoster complications can be evaluated.

Age

Influence on zoster. Age is the most important risk factor for development of zoster (Figure 3). Virtually all studies conducted in numerous settings and with various study designs have indicated an association between age and increasing zoster incidence, extending to the oldest cohorts (4,62,95,102–104). One study indicated that zoster incidence increased with age by a factor of >10 , from 0.74 per 1000 person years in children aged <10 years to 10.1 per 1000 person years in persons aged 80–89 years, with much of the increase beginning at age 50–60 years (13). Approximately 50% of persons who live to age 85 years will have experienced zoster (105,106).

The important role of age as a risk factor for zoster is presumably related to a loss of components of VZV-specific CMI response because of aging (i.e., immune senescence) possibly combined with waning immunity that might occur over time following initial varicella infection. Loss of specific immunity allows VZV to complete the process of reactivation and spread to the epidermis to produce the fully expressed clinical illness (12). Although precise correlates of protection against zoster have not been identified, certain CMI responses to VZV antigen decline with age (21,22,107,108).

FIGURE 3. Rate* of zoster and postherpetic neuralgia (PHN)†, by age — United States



*Per 1,000 person-years.

†Defined as ≥ 30 days of pain.

Influence on PHN. Among persons experiencing zoster, the primary risk factor for the development of PHN is age. Several studies have indicated that the risk for PHN among persons with zoster increases with age, particularly for persons aged ≥ 50 years (13,35,62,109,110) (Figure 3). In one study, the risk for experiencing at least 2 months of pain from PHN increased 27.4-fold among patients aged ≥ 50 years compared with those aged < 50 years (109). Approximately 80%-85% of PHN occurs in zoster patients aged ≥ 50 years (62).

Sex

Results from a large, randomized, controlled vaccine trial in the United States (4) indicated that the incidence of confirmed zoster cases in a cohort of immunocompetent persons aged ≥ 60 years was 11% higher among the women (11.8 versus 10.7 cases per 1000 person years in women and men, respectively). A prospective cohort study in the Netherlands documented 38% more cases among women than men (odds ratio = 1.38 [95% confidence interval [CI] = 1.22–1.56) after controlling for age and other zoster risk factors (111). Other studies (13,102–104,112) using a variety of methods also demonstrated an age-standardized excess of zoster among women. However, some researchers did not find a difference by sex (36,38,105,113–115). Women with zoster might also be at increased age-specific risk for developing PHN compared with men (35,62).

Race

Certain studies have suggested racial differences in the risk for zoster. In North Carolina, reported lifetime zoster

occurrences and reported incidence were lower in blacks by 65% and 75%, respectively, compared with whites after controlling for relevant confounders (115,116). A study in the United Kingdom indicated that zoster risk in patients was 54% lower among blacks after adjusting for age, sex, country of birth, or household childhood contacts (95). The reasons for these racial differences are unknown.

Geographic or Seasonal Variation

Most studies have not documented a seasonal pattern to zoster incidence (13,38,92,95,105,117). Certain studies have reported summer seasonality, particularly for exposed skin sites. This pattern might be related to ultraviolet irradiation that peaks during summer months and might serve as a trigger for zoster (28,118,119). No studies exist regarding variation in zoster incidence by latitude. Urban/rural status does not appear to be a risk factor for zoster (95).

Altered Immunocompetence

Unlike other vaccine-preventable diseases, zoster epidemiology is not directly related to exposure but to the biology underlying the virus-host relation that allows reactivation of latent VZV. Because CMI plays a key role in controlling both development of zoster and the features of its clinical expression, deficiencies in CMI, regardless of their etiology, are risk factors for both zoster and its severe manifestations. Although the magnitude of zoster risk can be extremely high among immunocompromised persons, the overall population attributable risk is modest because immunosuppression is uncommon (62,103,114).

The incidence of zoster is increased substantially in persons with hematologic malignancies and solid tumors (120). Rates are highest among children with these conditions. The magnitude of risk depends on both the nature of the underlying cancer and the type of treatment (121). Although the incidence of zoster in patients with solid tumors is $< 5\%$, this rate is many-fold higher than that in unaffected age-matched persons (120). Patients with Hodgkin's disease are at particularly high risk for zoster, with cumulative risks during the illness and its treatment as high as 27.3% (51,53,120,122–127).

Zoster is common following hematopoietic stem cell transplantation (HSCT); rates are 13%–55% during the first year (54,128,129). Rates are increased following solid organ transplants (renal, cardiac, liver, and lung) (5%–17%). Incidence is highest during the months immediately following the procedure, and the majority of zoster cases occur within a year of transplantation (130–132).

The risk for zoster and its recurrence is elevated in persons infected with HIV. Zoster rates of 29.4–51.5 per 1000 person years have been reported among HIV-infected adults, reflecting 12- to 17-fold increase compared with HIV-negative persons (56,133–136). For HIV-infected children, the risk is even higher (467 per 1000 person years), especially among children who acquire VZV infection when they are profoundly immunosuppressed (137). Most studies have documented increasing zoster risk as CD4+ T-lymphocyte counts decline, but the risk is increased nine-fold even among HIV-infected women with CD4+ T-lymphocyte counts $>750/\mu\text{L}$ compared with HIV-negative controls (135). However, the risk might decline at CD4+ T-cell counts <50 cells/ μL (136). Persons infected with HIV also are at increased risk for recurrences of zoster.

Other Co-morbidities

The risk for zoster appears to be elevated in persons with inflammatory diseases; however, for most of these conditions, data are insufficient to determine how much of the risk is attributable to the underlying disease versus its treatment. Zoster has been associated with systemic lupus erythematosus (SLE), with rates of 15–91 per 1000 person years (138–143). The risk for zoster also is increased among persons with rheumatoid arthritis (adjusted hazard ratio = 1.9 [95% CI = 1.8–2.0]), with an incidence of approximately 10 cases of per 1000 person years reported (144,145). Patients with Wegener's granulomatosis have a reported incidence of 45 zoster cases per 1000 person years (146), and recurrences in these patients are common. In one study, Crohn's disease and ulcerative colitis were both associated with a significantly increased risk for zoster (incident rate ratios = 1.6 and 1.2, respectively). The increase was, in part, caused by use of immunosuppressive medications (147). For all these conditions, zoster is generally not life-threatening, although cutaneous dissemination is more common, and deaths have been reported in such patients (138,141,142).

Certain studies have evaluated the risk for zoster in persons with other noninflammatory co-morbid conditions, although findings have not been consistent. Two studies have documented an association between zoster and diabetes mellitus (148,149). However, this association was not indicated in two other studies (150,151). Another study documented an increased risk for zoster in persons who subsequently had multiple sclerosis diagnosed (152).

Exposure to VZV/External Boosting

VZV can be transmitted from zoster lesions to cause primary varicella in susceptible persons. Although some

experts have suggested that zoster can be caused directly by exposure to VZV from varicella or from other cases of zoster (72,153,154), in general, zoster is not associated with epidemics of varicella. In addition, zoster does not have a seasonal pattern to suggest it is spread directly from varicella (13,28,38,92,105,117). Theoretically, reactivation of latent VZV might be triggered by exposure to exogenous VZV (123,153); however, no evidence suggests that such episodes occur more frequently than would be expected to occur by chance.

Conversely, exposure to varicella might reduce the risk for zoster (13). Protection might be partially maintained by exposure to varicella circulating in the population and the resulting exogenous boosting of VZV-specific immunity (15,117,155). An analysis of surveillance data from the United Kingdom indicated an inverse relation between annual varicella incidence in children aged <5 years and zoster incidence in adults aged 15–44 years (117). A case-control study in the United Kingdom (15) documented a graded reduction in zoster risk as a function of number of varicella contacts over a 10-year period. Multivariate analysis suggested a 74% reduction in risk for zoster among persons with three to four varicella exposures compared with those with no exposures, with a significant trend suggesting some reduction with fewer than three exposures. Social contacts with children (as a proxy for varicella exposure) and occupational contact with sick children were protective (15). A cohort analysis based on data from a sentinel physician network in the United Kingdom (155) suggested that adults living with children had both increased varicella exposure and a 25% decrease in zoster incidence. The analysis estimated that this boosting effect lasted an average of 20 years (95% CI = 7–41 years). However, persons living or interacting with children might have different underlying health compared with persons without exposure to children, which might be a confounder in these studies. Other evidence that varicella exposure might protect against zoster includes possible effects household exposure to varicella had against subsequent development of zoster among children with leukemia (156). Finally, the efficacy of the zoster vaccine (4) supports the concept that exposure to exogenous VZV can reduce risk for zoster, presumably by boosting specific immunity against VZV.

Contrary evidence also exists that varicella exposure does not reduce the risk for zoster. Women are at greater risk for zoster (13,102,103,110,111) despite the fact that women probably have more exposure to young children who experience varicella. A Japanese study indicated that the risk for zoster in children was not diminished by repeated varicella exposures (92).

Although a sufficient number of varicella exposures could reduce the risk for zoster in select populations, it is unclear whether such levels of exposure play an epidemiologically important role in reducing the risk for zoster among the general population of older adults who are at the highest risk for the disease, and, if so, how long such effects would last in the elderly.

Other Risk Factors

As with orofacial and genital flairs of HSV, zoster has been anecdotally linked to stress. However, only two rigorous evaluations of the role of psychological stress on zoster have been conducted. A case-control study documented a significant association with number of stressful life events within 6 months of reported zoster ($p = 0.012$) (157). A prospective cohort study indicated a nonsignificant association ($p = 0.078$) between zoster risk and negative life events.

Trauma or surgery could lead to reactivation of VZV in the affected dorsal root ganglion and increase the risk for zoster rash in that dermatome. Such a development would seem to be specific and easily ascertained, and certain reports and case series describe such events (158–161). One case-control study collected information about recent trauma and/or surgery in patients who developed zoster and in matched controls. The frequency of trauma in nonzoster sites was similar between the two groups, but zoster patients were significantly more likely than controls to report trauma at the site of their zoster during the month before zoster onset (adjusted OR = 12.1 [95% CI = 1.5–97.6]; $p = 0.002$) (24). The basis by which these stimuli provoke zoster is unclear, but they suggest that nonimmunologic factors can play important roles in the pathophysiology of zoster.

Finally, one study indicated that dietary micronutrient intake was protective against zoster. Body mass index did not appear to be associated with zoster risk (162). Genetic predisposition for zoster also has been reported (163).

Population Rates of Zoster and PHN

Zoster

Zoster is not a reportable condition in the United States; therefore, incidence has been inferred from a variety of studies. Observed rates have varied substantially on the basis of methods for case ascertainment, access to health care, and case definitions. The age distribution in the population being studied also is an important consideration when comparing these studies because zoster can vary dramatically across study sites. Conclusions cannot be drawn from cross-study comparisons without adjusting for age or comparing

age-specific rates directly. Differences in the prevalence of immunosuppression or in racial makeup also can influence population-wide zoster incidence. In addition, the incidence of zoster appears to have been increasing over recent decades, even after adjusting for other factors, although this increase has not been observed consistently.

Despite these limitations, certain analyses of zoster incidence in the United States have been conducted. The incidence in all studies ranged from 3.2–4.2 per 1000 population per year (age-adjusted to the 2000 U.S. population) (62,103,104,114,164,165), translating into an estimated 1 million cases annually. In all studies, a substantial increase in zoster incidence occurred with age and extended to the oldest strata; for all persons aged ≥ 60 years, the annual incidence was approximately 10 per 1000 persons (62,103,104,114,164,165), similar to the annual incidence of 11.1 per 1000 observed during the zoster vaccine trial (4). On the basis of these data, an estimated 32% of persons in the United States will experience zoster during their lifetime (CDC unpublished data, 2007).

Certain studies provide evidence of increasing age-specific zoster incidence in the United States (38,62,165,166), although other studies have shown no such trend (104). The observed increases cannot be solely attributed to changes in the epidemiology of varicella, because documentation of increases predated licensure of varicella vaccine in the United States in 1995 (38) and because age-specific increases over time also are being reported in certain international settings, including in the absence of varicella vaccination programs (105,167,168). Because the basis for this increase remains unclear, predicting whether the age-specific risk for zoster will continue to increase in the future is difficult.

Recurrent Zoster

Effectively evaluating the risks for recurrent zoster (i.e., second or subsequent episodes) in immunocompetent persons requires large populations, long-term follow up, adequate duration, and laboratory confirmation. Although data are limited, certain studies suggest a recurrence rate that is comparable to the rate of initial episodes (13,38,114). A community-based study of clinician-diagnosed zoster was conducted in Olmsted County, Minnesota. The observational period lasted 6 years. Of 1,669 persons that experienced an episode of zoster during that period, 24 experienced a second episode, suggesting a high incidence of zoster recurrence and providing no evidence that an episode of zoster protects against recurrence (62). Similar observations were noted in an older survey-based study (169). In the Shingles Prevention Study, two of approximately 20,000

vaccine placebo recipients had two episodes of zoster within 3 years of the initial episode. These cases provide the first laboratory-confirmed evidence that zoster can recur in immunocompetent persons, even soon after the initial episode (4).

Zoster Hospitalizations and Deaths

Hospitalizations. Conclusions about hospitalization for zoster should be interpreted carefully if they are derived from administrative data. Hospital administrative data often do not distinguish zoster episodes that were reasons for hospitalizations from those episodes that were incidental to the hospitalization or that occurred during prolonged hospital stay. PHN at the time of an unrelated hospitalization also might be coded as zoster. In addition, underlying immunosuppressive conditions might not be available or might not be collected from administrative data. These factors preclude determination of the portion of hospitalizations that could be prevented by a live-attenuated vaccine that is contraindicated for immunosuppressed persons.

Given these limitations, crude annual rates of zoster hospitalization have ranged from 2.1 per 100,000 population in a Northern California managed care population (170) to 4.4 per 100,000 population in England (171). A crude rate of 16.1 per 100,000 population was identified in an analysis of Connecticut-wide hospitalization data that included all zoster episodes, not just primary discharge diagnosis (172).

In a community-based study in Olmsted County, Minnesota, approximately 3% of patients with zoster were hospitalized for the illness (62). Although values differ substantially, all studies indicate that zoster hospitalization rates increase with age (170,172–174). In the Connecticut study, zoster hospitalization rates were approximately 75-fold greater among persons aged ≥ 85 years than in persons aged < 30 years (172). Although precise denominators are not available, risks for hospitalization also increased among persons with altered immunocompetence; approximately 30% of all persons hospitalized with zoster episodes had one or more immunocompromising conditions, primarily malignancies (82%) and HIV infection (8%) (62,172). Central nervous system and ophthalmologic complications accounted for most of the reported complications among hospitalized zoster cases (172–174), although bacterial superinfection was common in one series (175). Another study indicated that 0.5% of patients with confirmed zoster were hospitalized before their zoster rash developed for prodromal pain syndromes including suspected myocardial infarction, severe new-onset headache,

back pain, and abdominal pain resulting in appendectomy (62).

Deaths. On the basis of clinical experience and in the absence of zoster-related deaths in cohort studies, certain experts believe that zoster mortality appears to be uncommon, particularly among healthy persons (176). Vital records might not distinguish deaths attributed to zoster from incidental deaths occurring merely in the presence of zoster, and they might not capture information on the immunologic status among those deaths. An Australian study using administrative data indicated that 1% of patients hospitalized with a primary zoster diagnosis died; the number of deaths directly attributable to zoster was not validated (174). Certain analyses have indicated that almost all zoster deaths occur in the elderly, with a rate ≥ 10 -fold higher among persons aged > 65 years (171,173,174). Immunosuppression also appears to be a risk factor for zoster mortality. In one study, 52% of patients hospitalized with zoster who died had one or more immunocompromising condition (e.g., malignancies, leukemia, and HIV). In that study, the risk for death in persons with immunocompromising conditions was 8.7%; the risk in persons without these conditions was 3.7% (172).

PHN

Drawing conclusions from studies on the risk for PHN is difficult because definitions for PHN vary and results are influenced by many factors, including the source and age of the study population. Among zoster patients treated with a placebo in clinical trials of antiviral drugs, approximately one third still had pain after 3 months and approximately one fourth had pain at 6 months (177,178). However, these trials might include a population of patients with more severe zoster pain, thereby introducing a detection bias that could inflate estimated risks for PHN. In a phase 3 clinical trial of zoster vaccine (4), zoster occurred among 642 placebo recipients; the risk for pain persisting at least 30, 60, 90, 120 or 180 days among these person was 30.3%, 17.6%, 12.5%, 8.4%, and 5.1%, respectively. Results from the trial might not reflect risks for progression to PHN in community settings because ascertainment, diagnosis, and antiviral treatment of zoster were standardized and thorough. However, in a community-based study in Olmsted County, Minnesota, in which almost all medical events were captured, the risk for PHN in patients with zoster was 18%, 13%, and 10% when defining PHN as at least 30, 60, and 90 days of pain, respectively (62).

Treatment and Nonspecific Management of Zoster and PHN

The treatment of acute zoster, the prevention of PHN development among patients with acute zoster, and the treatment of patients with current PHN are complex clinical problems with ongoing uncertainties and active research (31). Acyclovir, famciclovir, and valacyclovir are approved by the FDA for treatment of zoster in immunocompetent patients. All three are nucleoside analogs that inhibit replication of human herpes viruses, including VZV. Clinical trials have indicated that these agents, taken orally, reduce the duration of viral shedding and lesion formation, reduce the time to rash healing, and decrease the severity and duration of acute pain from zoster and the risk for progression to PHN. Because all three antiviral agents are safe and well tolerated, many experts recommend that treatment should be considered for all eligible patients with zoster, and specifically recommend treatment for persons aged ≥ 50 years who have moderate or severe pain, moderate or severe rash, or involvement of nontruncal dermatomes (31). In clinical trials, treatment has been initiated within 72 hours of rash onset, a biologically arbitrary time point that often is not feasible in clinical practice. The benefits of later treatment have not been studied (31). If treatment cannot be initiated within 72 hours of rash onset, experts recommend that it should be initiated as soon as possible, particularly in the presence of new vesicle formation or of complications.

Two clinical trials have assessed the role of corticosteroids in combination with acyclovir for treatment of zoster and prevention of subsequent PHN (179,180). Patients at risk for steroid-related toxicities (e.g., those with diabetes mellitus or gastritis) were excluded from the trials. A 3-week tapering course of corticosteroids diminished acute zoster pain and decreased the time to cutaneous healing, cessation of analgesic therapy, and return of uninterrupted sleep and normal daily activities. However, no evidence indicated that use of corticosteroids prevented development of PHN. Theoretically, corticosteroids should be equally effective in combination with valacyclovir or famciclovir; however, combinations of these agents have not been studied in clinical trials. No evidence indicates that topical antiviral therapy or corticosteroids without systemic antiviral therapy have a role in treatment of zoster.

A variety of approaches have been used with varying degrees of success for control of acute zoster pain, including acetaminophen, nonsteroidal anti-inflammatory agents, tricyclic antidepressants, opiates, anticonvulsants, capsaicin, and topical anesthetics (31). In more severe instances of

pain, referral to a pain specialist, or even hospitalization and administration of epidural analgesics, is often considered. Many of these same modalities are used with varying degrees of success for control of chronic PHN pain (26,181,182). Elderly persons, who already have reduced physiologic reserve and typically take multiple medications for pre-existing chronic conditions, might be unable to tolerate psychotropic and other medications for management of their acute zoster or chronic PHN pain (31,33).

Patients with uncomplicated zoster should be advised to keep the rash clean and dry, to avoid topical antibiotics, and, if possible, to keep the rash covered. They should alert their physician if the rash worsens or they have fever, which could indicate bacterial superinfection (31).

Prevention of Transmission from Zoster

Some health-care institutions might exclude personnel with zoster from work until their lesions dry and crust (85). Persons with localized zoster should avoid contact with susceptible persons at high risk for severe varicella in household and occupational settings until lesions are crusted. Such persons include pregnant women, all premature infants born to susceptible mothers, infants born at <28 weeks' gestation or who weigh ≤ 1000 g regardless of maternal immune status, and immunocompromised persons of all ages (85). Persons with opportunities for contact with such high risk-persons in household or occupational settings should be informed about how to recognize the signs and symptoms of zoster. If a person susceptible to varicella infection has close exposure to a persons with zoster, postexposure prophylaxis with varicella vaccine or VARIZIGTM should be considered (3,85,183).

Zoster Vaccine

Vaccine Composition, Dosage, and Administration

The zoster vaccine licensed in the United States (ZOSTAVAX[®], Merck & Co., Inc.) is a lyophilized preparation of the Oka/Merck strain of live, attenuated VZV, the same strain used in the varicella vaccines (VARIVAX[®], PROQUAD[®]). The Oka strain was isolated in Japan (184) in the early 1970s from vesicular fluid from a healthy child who had varicella; the strain was attenuated through sequential propagation in cultures of human embryonic lung cells, embryonic guinea-pig cells, and human diploid cells (WI-38). Further passage of the virus was performed at Merck Research Laboratories in human diploid cell

cultures (MRC-5). The cells, virus seeds, virus bulks, and bovine serum used in the manufacturing are all tested to provide assurance that the final product is free of adventitious agents.

Zoster vaccine, when reconstituted as directed in the package label using the supplied diluent, is a sterile preparation for subcutaneous administration. Each 0.65-mL dose contains a minimum of 19,400 PFU ($4.29 \log_{10}$) of Oka/Merck strain of VZV when reconstituted and stored at room temperature for up to 30 minutes. Zoster vaccine is similar to VARIVAX[®]. However, its minimum potency is at least 14-times the potency of VARIVAX[®], which contains a minimum of 1,350 (approximately $3.13 \log_{10}$) PFU. PROQUAD[®] contains $3.993 \log_{10}$ PFU, similar in potency to ZOSTAVAX[®]. Each dose of zoster vaccine also contains additional VZV antigenic component from non-viable Oka/Merck VZV. Additional vaccine components in each dose include 31.16 mg of sucrose, 15.58 mg of hydrolyzed porcine gelatin, 3.99 mg of sodium chloride, 0.62 mg of monosodium L-glutamate, 0.57 mg of sodium phosphate dibasic, 0.10 mg of potassium phosphate monobasic, 0.10 mg of potassium chloride; residual components of MRC-5 cells including DNA and protein; and trace quantities of neomycin and bovine calf serum. The product contains no thimerosal or other preservatives.

Zoster vaccine should be administered as a single 0.65-mL dose subcutaneously in the deltoid region of the upper arm; a booster dose is not licensed for the vaccine. The vaccine should not be injected intravascularly or intramuscularly and should only be reconstituted and injected using a sterile syringe free of preservatives, anti-septics, and detergents, which can inactivate the vaccine virus.

Storage and Handling

To maintain potency, lyophilized zoster vaccine must be stored frozen at an average temperature of $\leq 5^{\circ}\text{F}$ ($\leq -15^{\circ}\text{C}$) until it is reconstituted for injection. Any freezer that has a separate sealed freezer door and reliably maintains an average temperature of $\leq 5^{\circ}\text{F}$ ($\leq -15^{\circ}\text{C}$) is acceptable for storing zoster vaccine. Providers should check the adequacy of their freezer by verifying its temperature before obtaining vaccine. In general, the freezer compartments of dormitory style units are incapable of reliably maintaining temperatures cold enough to store zoster vaccine and are unacceptable for storage. For certain refrigerator/freezer models, it is necessary to reduce the temperature to the coldest setting to maintain zoster vaccine at the correct temperature. However, this might reduce the temperature in the refrigerator

compartment and result in freezing of any vaccines or other pharmaceutical products being refrigerated. As a result, both the refrigerator and freezer temperatures should be monitored and the temperature recorded at least twice a day. Any out-of-range temperature readings require immediate and documented corrective action. When a freezer is temporarily unavailable (e.g., during transport or equipment failure), zoster vaccine should be stored in a suitable container (i.e., the original shipping container or a comparable container with a properly fitting lid) with an adequate quantity of dry ice (i.e., a minimum of six pound per box) so that dry ice would persist in the container if unreconstituted vaccine must be transported back to the freezer. Dry ice placed in a suitable container will maintain a temperature of $\leq 5^{\circ}\text{F}$ ($\leq -15^{\circ}\text{C}$). The diluent, which does not contain preservative or other antiviral substances that could inactivate the vaccine virus, should be stored separately, either at room temperature or in the refrigerator. The vaccine should be reconstituted according to the directions in the package label and only with the diluent supplied. Before reconstitution, zoster vaccine should be protected from light. Once reconstituted, the vaccine should be used immediately to minimize loss of potency. The vaccine must be discarded if not used within 30 minutes after reconstitution. Information regarding stability under conditions other than those recommended is available from the manufacturer at 800-637-2590.

Efficacy

The efficacy of zoster vaccine was evaluated in a phase 3 vaccine trial termed the Shingles Prevention Study, a double-blind randomized, placebo-controlled trial involving 38,546 healthy adults aged ≥ 60 years who had a history of varicella or at least 30 years of residence in the continental United States (as a marker of previous infection). Persons excluded from the trial included those with a history of zoster, with allergies to components of the vaccine, with immunocompromising conditions, or with conditions that might have interfered with study evaluations (e.g., cognitive impairment, < 5 year life expectancy, dermatologic disorders, chronic pain, hearing loss, or lack of mobility). The study population ranged in age from 59–99 years (median: 69.4 years), and comprised 41.0% females, 95.4% white, 2.1% blacks, 1.3% Hispanics, and 1.2% other or unknown race/ethnicity. On enrollment, approximately 90% of the participants had at least one underlying chronic medical condition.

Persons were randomized to receive a single subcutaneous dose of zoster vaccine or placebo; the mean duration of

follow up was 3.1 years. Active case ascertainment was conducted through monthly telephone contact supplemented by a close-out interview. Zoster cases were confirmed by PCR testing (93%), viral culture (1%), or evaluation by a panel of five physicians with expertise in zoster diagnosis (6%). Patients with confirmed zoster were followed for at least 182 days to assess the outcome of the condition, including presence and severity of pain. Approximately 95% of persons were followed to completion of the study. Outcomes evaluated included incidence of zoster, incidence of PHN (defined as pain level of three or more [on a numerical rating scale of 0-10] persisting at least 90 days after rash onset), and burden of illness (BOI), measured using a mean value of severity-by-duration index for each treatment group, thus incorporating the incidence, severity, and duration of pain and discomfort from zoster). A total of 957 confirmed cases of zoster occurred among study participants: 315 among vaccine recipients and 642 among placebo recipients. The proportion of vaccine and placebo recipients that received antiviral treatment within 72 hours of rash onset, as clinically indicated, was 64.1% and 65.9%, respectively.

The vaccine reduced the risk for developing zoster by 51.3% (95% CI = 44.2–57.6; $p < 0.001$ (Table 2) (4). The vaccine was 66.5% (95% CI = 47.5–79.2; $p < 0.001$) efficacious for preventing PHN. When the definition of PHN was changed from 30 days of pain to 182 days of pain following rash onset, vaccine efficacy increased from 58.9% to 72.9% (Table 3). Zoster vaccine had an independent effect of reducing PHN among patients who developed zoster (39% [95% CI = 7%–59%]) (Table 2). The mean severity-by-duration of zoster was reduced by 57% ($p = 0.016$) in vaccine recipients who developed PHN.

Zoster vaccine reduced BOI by 61.1% (95% CI = 51.1–69.1; $p < 0.001$) (Table 2). The vaccine reduced the degree of interference in activities of daily living (ADLI) caused by zoster, in part because of the reduction in zoster itself, but also because of a decrease in ADLI among those vaccine recipients who did develop zoster (185). No evidence indicated that vaccine recipients experiencing zoster were protected from other sequelae such as scarring, bacterial superinfection, palsies, or ocular or visceral complications (186).

In general, with increasing age at vaccination, the vaccine retained efficacy against severity of zoster better than against zoster itself. Thus, efficacy for the prevention of zoster was highest among persons aged 60–69 years and declined with increasing age (Table 2). Declines in efficacy of preventing zoster were observed with each 5-year increase in age throughout the age range of participants (187). However, no significant differences were observed among persons aged 60–69 years versus those aged ≥ 70 years in vaccine efficacy at reducing BOI or PHN, probably because the independent effect of reducing PHN among patients who developed zoster was greatest among persons aged 70–79 years (Table 2). For persons aged ≥ 80 years, efficacy against zoster was 18% (Table 2), but efficacy against PHN (39%) was better retained (186). No significant differences by sex were observed in the efficacy of the vaccine at reducing BOI, PHN, or zoster (4). No evidence indicated that the vaccine was less efficacious for prevention of zoster (vaccine efficacy: 51.6%; 95% CI = 41.4–60.1), PHN (vaccine efficacy: 60.9%; 95% CI = 31.3–78.7), or for reduction in BOI (vaccine efficacy: 60.1%; 95% CI = 46.1–70.4) among subjects with functional limitations (188).

TABLE 2. Efficacy of ZOSTAVAX[®] compared with a placebo, by age group — Shingles Prevention Study*

Age group (yrs) [†]	ZOSTAVAX [®]				Placebo				Efficacy			
	No. subjects	HZ cases	PHN cases [§]	% HZ cases with PHN [§]	No. subjects	HZ cases	PHN cases [§]	% HZ cases with PHN [§]	HZ % (95% CI)**	PHN [§] % (95% CI)	PHN [§] with HZ % (95% CI)	Burden of illness (BOI) % (95% CI)
60–69	10,370	122	8	6.6	10,356	334	23	6.9	64 (56–71)	65.7 (20.4–86.7)	5 (-107–56)	65.5 (51.5–75.5)
70–79	7,621	156	12	7.7	7,559	261	45	17.2	41 (28–52)	66.8 (43.3–81.3)	55 (18–76)	55.4 (39.9–66.9)
≥ 80	1,263	37	7	18.9	1,332	47	12	25.5	18 (-29–48)	— [¶]	26 (-69–68)	— [¶]
Total	19,254	315	27	8.6	19,247	642	80	12.5	51 (44–58)	66.5 (47.5–79.2)	39^{††} (7–59)	61.1 (51.1–69.1)

* The analysis was performed on the Modified Intent-To-Treat (MITT) population that included all subjects randomized in the study who were followed for at least 30 days postvaccination and did not develop an evaluable case of herpes zoster (HZ) within the first 30 days postvaccination.

[†] Age strata at randomization were aged 60–69 years and ≥ 70 years.

[§] Postherpetic neuralgia (PHN) was defined as HZ-associated pain rated as three or more, on a scale ranging from 0 (no pain) to 10 (pain as bad as you can imagine), persisting or appearing more than 90 days after onset of HZ rash using Zoster Brief Pain Inventory.

[¶] VE for PHN and BOI calculated for the age groups 60–69 and ≥ 70 years.

** Confidence interval.

^{††} Age-adjusted estimate based on the age strata (age 60–69 years and ≥ 70 years) at randomization.

Sources: Oxman MJ, Levin MJ, Johnson GR, et al. Zoster Prevention Study Group. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *N Engl J Med* 2005;352:2271–84; ZOSTAVAX[®]. Package Insert. Merck & Co., Inc, Whitehouse Station, NJ 08889.

TABLE 3. Efficacy of zoster vaccine on the incidence of postherpetic neuralgia (PHN) among persons aged ≥ 60 years, by duration of pain* — Shingles Prevention Study

Persistence of PHN among all subjects [†]	Vaccine group		Placebo group		Efficacy [¶]	
	No. confirmed cases of HZ with PHN	Incidence per 1,000 person/yr [§]	No. confirmed cases of HZ with PHN	Incidence per 1,000 person/yr [§]	%	(95% CI ^{**})
30 days	81	1.39	196	3.39	58.9	(46.6–68.7)
60 days	45	0.77	113	1.96	60.4	(43.6–72.6)
90 days	27	0.46	80	1.38	66.5	(47.5–79.2) ^{††}
120 days	17	0.29	54	0.93	68.7	(45.2–83.0)
182 days	9	0.16	33	0.57	72.9	(42.1–88.6)

* For the secondary end point, PHN was defined as the pain and discomfort associated with herpes zoster rated as three or more, on a scale ranging from 0 (no pain) to 10 (pain as bad as you can imagine), persisting or appearing more than 90 days after the onset of herpes zoster rash. Efficacy analyses were performed with the use of a follow-up interval that excluded the first 30 days after vaccination and the modified intention-to-treat population, which excluded persons who withdrew or in whom a confirmed case of herpes zoster developed, within the first 30 days after vaccination. Of the three persons who developed more than 1 confirmed case of herpes zoster, only the first case was included.

[†] PHN was defined as the pain and discomfort associated with herpes zoster that was rated as three or more persisting or appearing more than 30, 60, 90, 120, and 182 days after the onset of herpes zoster rash.

[§] For the total population and the subgroups stratified according to sex, the incidence of PHN in each treatment group (vaccine or placebo) was the weighted average of the observed incidence of PHN stratified according to age group, with weights proportional to the total number of person-years of follow-up in each age group.

[¶] Vaccine efficacy for the incidence of PHN and 95% confidence interval (CI).

** Confidence interval.

^{††} Vaccine efficacy for the incidence of PHN for all persons was the protocol-specified secondary end point.

Source: Oxman MN, Levin MJ, Johnson GR, et al. Zoster Prevention Study Group. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *N Engl J Med* 2005;352:2271–84.

Twelve clinical lots of zoster vaccine were used in the Shingles Prevention Study, nine of which were heat treated to accelerate aging of the vaccine. Potency upon shipment to study sites ranged from 21,000–62,000 PFUs/dose, but potency and accelerated aging did not significantly influence vaccine efficacy with regard to zoster, PHN, or BOI.

Immunogenicity

A substudy of the Shingles Prevention Study was conducted among 1,395 persons to assess VZV-specific immunity at baseline and 6 weeks following administration of zoster vaccine or placebo. The longer-term duration of immunogenicity also was assessed. Anamnestic antibody response was evaluated using gpELISA to measure increases in VZV antibody levels after vaccination. RCF and IFN- γ ELISPOT were used to measure the number of memory T-cells. With all three assays, VZV-specific immunity measured 6 weeks after vaccination increased following receipt of vaccine but not placebo. In both vaccine and placebo recipients, immune responses were inversely related to the risk for developing zoster; this association with protection was greatest for anamnestic antibody response following vaccination for which gpELISA Geometric Mean Titers (GMTs) increased 1.7-fold (95% CI = 1.6–1.8). However, for all three assays, no threshold level of immunity that predicted complete protection from zoster was observed.

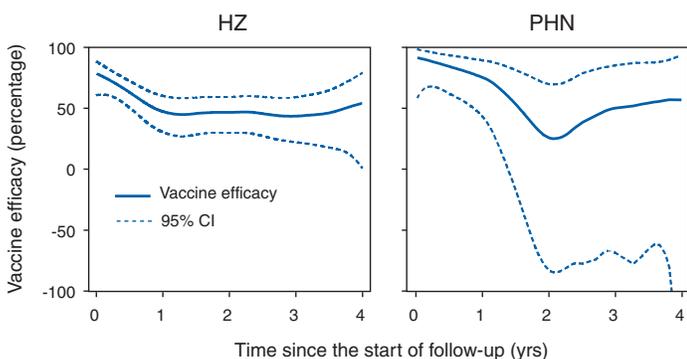
No clear dose response for increases in GMTs was observed; similar increases were achieved in vaccine

recipients throughout the dosage range used in the Shingles Prevention Study (189). Peak CMI responses were present 1–3 weeks following vaccination (187,190,191), as would be expected for anamnestic responses that would occur in persons with previous VZV infection. The impact of age on CMI response to vaccination also was evaluated. RCF and IFN- γ ELISPOT responses were greater in persons aged 60–69 years than in persons aged ≥ 70 years ($p < 0.01$) (192). The increase in GMTs as a measure of anamnestic antibody response in persons aged 50–59 years was comparable to that in persons aged ≥ 60 years (193). In a prelicensure study, subjects aged 55–70 years acquired VZV-specific class I-restricted and unrestricted cytotoxicity following vaccination with even low levels (4,000 PFUs) of either live or heat-inactivated Oka/Merck strain of VZV (23).

Duration of Efficacy and of Immunity

Vaccine efficacy for zoster prevention declined during the first year following vaccination, but remained stable through the remaining 3 years of follow up (Figure 4). Vaccine efficacy for PHN prevention had a similar pattern, with an initial decline and subsequent stabilization. After conclusion of the Shingles Prevention Study, approximately 7,500 vaccine recipients will be followed to extend observation to 10 years. Because placebo recipients were offered zoster vaccine at the conclusion of the Shingles Prevention Study, zoster rates in these 7,500 persons will be compared with

FIGURE 4. Duration of zoster vaccine efficacy for preventing zoster and postherpetic neuralgia (PHN)



historic controls. Increases in RCF and IFN- γ ELISPOT responses persisted for 3–6 years following vaccination (192,194).

Safety and Adverse Events

Serious Adverse Events

Adverse events were monitored in the Shingles Prevention Study population, with more comprehensive ascertainment in a safety substudy comprising 6,616 persons (3,345 vaccine recipients and 3,271 placebo recipients) (Table 4). In the Shingles Prevention Study population, the number and types of serious adverse events (4) during the 42 days after receipt of vaccine or placebo were similar (1.4%). However, rates of serious adverse events in the safety substudy were higher in vaccine recipients (1.9%) than in placebo recipients (1.3%), with a relative risk of 1.5 (95% CI = 1.0–2.3). Nonetheless, no temporal or clinical patterns of adverse events were observed in vaccine recipients to suggest a causal relation (4,186). The incidence of death and hospitalizations was similar in the two treatment groups throughout the observation time (4,186).

Mild Local and Systemic Reactions

In the Shingles Prevention Study safety substudy, self-reported injection site adverse events (e.g., erythema, pain, swelling, warmth, and pruritis) were more common among vaccine recipients (48.3%) than placebo recipients (16.6%) ($p < 0.05$) (Table 4) (4); the risk for these events was higher in vaccine recipients aged 60–69 years (58.3%) than in persons aged ≥ 70 years (41.3%) (189). Most injection site adverse events were mild and resolved within 4 days (187). Less-serious systemic adverse events, including headaches, were more common in vaccine recipients (6.3%) than in placebo recipients (4.9%) ($p < 0.05$) (Table 4) (4). The risk

for fevers after vaccination did not differ between vaccine recipients and controls.

The safety and tolerability of zoster vaccine was evaluated in a separate study among persons aged 50–59 years, including 62 persons who received the standard potency (approximately 58,000 PFUs) and 123 persons who received high potency (approximately 207,000 PFUs) (195). Although the numbers of persons was small, both vaccines were safe and well tolerated; however, injection site reactions were more common (69.4% and 82.9%, respectively) than those observed in person aged ≥ 60 years in the Shingles Prevention Study (48.3%).

Vaccine Virus Rash and Transmission

Varicella-like rashes, including injection site varicella-like lesions, generalized varicella-like rashes, and zoster-like rashes, were evaluated in the Shingles Prevention Study during the first 42 days of observation (Table 4). Twenty vaccine recipients and seven placebo recipients had lesions at the injection site ($p < 0.05$) (4); the lesions were tested for VZV by PCR in one of these persons in each group, and results were negative in both. Among the vaccine recipients, lesions occurred a median of 3–4 days after vaccination and lasted a median of 5 days.

Generalized varicella-like rashes occurred at similar rates in the two groups (Table 4). Zoster-like rashes were less common in vaccine versus placebo recipients during this 42-day period ($p < 0.05$). Oka/Merck strain VZV was not detected in any of 10 lesion specimens from vaccine recipients available for PCR testing. In early studies conducted as part of the manufacturer's clinical program for development of zoster vaccine, samples from rashes in two vaccinated persons were confirmed to be Oka/Merck-strain VZV (186). Both experienced noninjection-site varicella-like rashes; one had 21 lesions on day 17 lasting 8 days and the other developed five lesions on day 8 that lasted 16 days. No varicella-like rashes were documented during any clinical zoster vaccine trials of laboratory-confirmed zoster attributed to Oka/Merck strain VZV. In addition, no evidence existed of transmission of vaccine virus from vaccine recipients to contacts.

The Economic Burden of Zoster and Cost-Effectiveness of Vaccination

The economic burden of zoster in the elderly is substantial and includes direct costs attributed to health-care use and indirect costs attributed to losses in productivity from temporary or more permanent disability. In addition,

TABLE 4. Adverse events among all persons and among persons in an adverse-events substudy*

Event	Vaccine group		Placebo group		Difference in risk	
	No.	(%)	No.	(%)	%	(95% CI) [†]
No. in group	19,270		19,276			
Day of vaccination to end of study						
Death	793	(4.1)	795	(4.1)	0.01	(-1.2–1.2) [§]
Death by age group (yrs)						
60–69	218	(2.1)	246	(2.4)	-0.80	(-2.0–0.4) [§]
≥70	575	(6.5)	549	(6.2)	0.95	(-1.2–3.1) [§]
Vaccine-related serious adverse event [¶]	2	(<0.1)	3	(<0.1)	NC	
Day of vaccination to day 42						
Death	14	(0.1)	16	(0.1)	-0.01	(-0.1–0.1)
≥1 serious adverse events	255	(1.4)	254	(1.4)	0.01	(-0.2–0.3)
Varicella-like rash at injection site	20	(0.1)	7	(0.04)	0.07	(0.02–0.13)**
Varicella-like rash not at injection site	18	(0.1)	14	(0.1)	0.02	(-0.04–0.09)
Herpes zoster-like rash	17	(0.1)	36	(0.2)	-0.10	(-0.18– -0.03)**
Rash unrelated to herpes zoster	595	(3.2)	620	(3.3)	-0.13	(-0.49–0.23)
Confirmed case of herpes zoster	7	(<0.1)	24	(0.1)	-0.09	(-0.16– -0.03)**
Persons in the adverse event substudy	3345		3271			
Day of vaccination to end of study						
Person hospitalized	1,137	(34.0)	1,115	(34.1)	0.1	(-8.8–9.0) [§]
Hospitalization related to herpes zoster	5	(0.2)	6	(0.2)	-0.1	(-0.7–0.5) [§]
Day of vaccination to day 42						
≥1 serious adverse events	64	(1.9)	41	(1.3)	0.7	(0.1–1.3)**
≥1 adverse events	1,929	(58.1)	1,117	(34.3)	23.7	(21.3–26.0)**
≥1 systemic adverse events	820	(24.7)	768	(23.6)	1.0	(-1.0–3.1)
≥1 vaccine-related systemic adverse events [¶]	209	(6.3)	160	(4.9)	1.4	(0.3–2.5)**
Documented temperature ≥38.3°C (≥100.9°F)	27	(0.8)	27	(0.9)	0	(-0.5–0.4)
Self-reports of feeling abnormal temperature ^{††}	231	(7.2)	190	(6.0)	1.2	(0.0–2.4)
≥1 adverse event at injection site ^{§§}	1,604	(48.3)	539	(16.6)	31.7	(28.3–32.6)**
Erythema	1,188	(35.8)	227	(7.0)	28.8	(26.9–30.6)**
Pain or tenderness	1,147	(34.5)	278	(8.5)	26.0	(24.1–27.9)**
Swelling	871	(26.2)	147	(4.5)	21.7	(20.1–23.4)**
Pruritus	237	(7.1)	33	(1.0)	6.1	(5.2–7.1)**
Warmth	57	(1.7)	11	(0.3)	1.4	(0.9–1.9)**
Hematoma	53	(1.6)	46	(1.4)	0.2	(-0.4–0.8)
Rash	10	(0.3)	3	(0.1)	0.2	(0.0–0.5)

* The rates of death and of hospitalization are percentages of persons in each treatment group. Otherwise, percentages are rates weighted in proportion to the number of persons with safety follow-up in each age group. NC denotes not calculated. Three persons who had withdrawn from the study because of worsening health and subsequently died were included in the safety analysis.

† Confidence interval.

§ The difference in risk (vaccine group versus placebo group) and the 95% confidence intervals (CIs) for deaths and hospitalizations are based on the rates per 1000 persons-years of follow-up to account for differential follow-up among the study participants as a result of staggered enrollment. Otherwise, the differences in risk and 95% CIs are based on an asymptotic method for the difference of two binomial proportions where the proportions are weighted according to the number of persons with safety follow-up in each age group. Negative values for the difference in risk result when the rate in the placebo group is larger than that in the vaccine group.

¶ Events classified as possibly related to vaccination were assessed by a blinded investigator at each site.

** P<0.05 for the comparison with the placebo group.

†† A temperature of ≥38.3°C (≥100.9°F) was not documented.

§§ None of the adverse events related to the injection site were considered to be serious adverse events.

Source: Oxman MN, Levin MJ, Johnson GR, et al. Zoster Prevention Study Group. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *N Engl J Med* 2005;352:2271–4.

much of the economic burden of zoster is borne by individual patients as reduced quality of life because of pain and suffering. Certain studies provide a range of estimates for health-care use among persons aged ≥60 years for treatment of zoster and PHN. The estimates vary widely because of differing assumptions regarding the risk for PHN and of complications resulting from zoster. Estimated health-care use per case of zoster ranges from 1.3–3.1 for the number of outpatient visits, 0.005–0.12 for the number of

emergency department visits, and 1–5 for the number of medications prescribed. Approximately 1%–4% of zoster episodes result in hospitalization, with a mean duration of 4.8 days. (196–199). Health-care use for zoster and PHN increases substantially with the age of patients (196–198).

Costs associated with acute zoster have been evaluated. Among patients with acute episodes of zoster, average expenditures ranged from \$112–\$287 per episode of outpatient care, \$73–\$180 per antiviral treatment, and

\$3,221–\$7,206 per hospitalization (2006 dollars). Additional costs associated with managing non-PHN complications (e.g., ocular, neurologic, and cutaneous) ranged from \$1,158–\$11,255 per complication, and from \$566–\$1,914 per episode of PHN. Among the subset of patients with PHN persisting from 30 days to 12 months, annualized health-care costs, including costs of the acute episode, ranged from \$2,159 to \$5,387 (200,201). Although indirect costs from death can occur with zoster, these costs result mostly from losses in work time caused by temporary or more permanent disability. Patients with zoster (including those progressing to PHN) lose an average of >129 hours of work per episode (197,198), including losses of 12 or more hours of work time and 69 hours of leisure time during the first 30 days (196). Data on the national economic impacts of zoster and its complications on quality of life have not been reported.

Five studies have estimated the cost-effectiveness of a 1-dose routine vaccination program of immunocompetent persons aged ≥ 60 years (196,197,199,202,203) (Table 5). One of these studies has not been published (196). All five studies used a Markov cohort model (105), followed a cost-utility analytic approach that included a societal perspective (204,205), and used quality-adjusted life-year (QALY) scores to assess the incremental impact of the vaccine program on quality of life. Costs and health benefits were measured in 2005–2006 U.S. dollars, and a 3% discount rate was used to adjust health outcomes and costs. Model assumptions varied regarding duration of vaccine protection, the efficacy of the vaccine for preventing PHN among vaccine recipients who developed zoster, costs associated with vaccine adverse events, and costs attributed to losses in work productivity. None of the five models incorporated costs for losses in leisure time. Assuming a routine vaccination program with 100% coverage, the estimated QALYs gained ranged from 0.0016 (0.6 days) to 0.0087 (3 days). At a vaccine cost of \$150 per dose, the societal costs of routinely vaccinating immunocompetent persons aged ≥ 60 years range from \$27,000 to \$112,000 per QALY gained. In the sensitivity analyses, variables with the strongest influence on outcomes include vaccine costs, duration of vaccine efficacy, risks for PHN as a complication, and costs and QALY scores for zoster and its complications.

Although costs per QALY gained are most appropriately used to prioritize among competing programs for purposes of resource allocation, policymakers often decide whether or not to support programs by comparing their cost per QALY against a standard threshold. A threshold suggested by the World Health Organization is three times the gross domestic product per capita, which would be \$94,431 for

the United States (206). Alternatively, policymakers often decide about supporting programs by comparing their cost per QALY with the values for other widely accepted interventions. Compilations of such cost effectiveness data have been published and maintained in on-line registries (207,208). The estimated cost per QALY for zoster vaccination covers a wide range that appears acceptable in comparison to either standard thresholds or to other established interventions, but it is at the intermediate-to-high end of that range.

Summary of Rationale for Zoster Vaccine Recommendations

The availability of a safe and effective vaccine for zoster offers an opportunity to decrease the burden of this disease and its complications among persons with high levels of risk. In the United States, the vaccine is licensed for use among persons aged ≥ 60 years, and routine vaccination of this population is recommended for several reasons. First, zoster causes substantial morbidity in the United States, with approximately 1,000,000 new cases occurring annually (62). Many of these cases cause debilitating pain, and when PHN develops, the pain can last for months or even years. Other complications include involvement of the eye that can threaten sight, bacterial superinfections, and disfiguring facial scarring. Second, although effective antiviral medications for treatment of zoster are available, administration must be initiated within 72 hours of rash onset for maximum benefit. Many patients might not obtain such rapid diagnosis and treatment, and even when they do, the treatment is only partially effective at alleviating the symptoms and shortening their duration. Third, available treatments for PHN often do not completely alleviate the pain and might be poorly tolerated by the older patients (31,33). Finally, available evidence suggests the cost-effectiveness of zoster vaccine is within the range of some other public health interventions.

In a large, placebo-controlled clinical trial, the zoster vaccine reduced BOI attributed to zoster by 61.1 % and the incidence of PHN by 66.5 %. The vaccine reduced the overall incidence of zoster by 51.3 % and substantially reduced its associated pain (4). Although the vaccine was more efficacious in persons aged 60–69 years, substantial efficacy against zoster was observed in persons aged ≥ 70 years, and PHN was prevented in older age groups. Prevention of zoster and its sequelae is particularly important among the oldest persons because they experience the highest incidence of zoster and PHN, they might be least

TABLE 5. Economic burden and projected cost-effectiveness of a herpes zoster vaccination program, by selected studies* — United States

	Study No. 1 [†]	Study No. 2	Study No. 3	Study No. 4	Study No. 5 [§]
Costs					
Acute zoster					
Outpatient care	\$246–\$312 [¶]	\$214 (SD** = \$52.7)	\$287 (\$221–\$422)	\$112 (\$56–\$224)	\$289 (\$178–\$527)
Antiviral medicines	\$73–\$135	\$155	NA ^{††}	\$180 (\$135–\$238)	NA
Hospitalization	\$6,815 (SD = \$11,608)	\$8,521	\$7,206 (\$6,529–\$8,401)	\$6,884	\$3,221 (\$130–\$5,200)
Out-of-pocket ^{§§}	\$7–\$20	NA	NA	NA	N/A
Complications (nonpostherpetic neuralgia [PHN]) ^{¶¶}					
Ocular	\$1,158 (SD = \$2,231)	\$1,827 (SD = \$2,844)	\$11,255 (\$9,255–\$13,255)	NA	NA
Neurologic	\$1,642 (SD = \$3,483)	\$2,623 (SD = \$3,965)	NA	NA	NA
Cutaneous	\$1,851 (SD = \$1,838)	\$3,739 (SD = \$5,684)	NA	NA	NA
PHN ^{***}					
Outpatient care and prescriptions	\$903–\$1071	\$1,914 (SD = \$2,667)	\$566 (\$483–\$673)	\$996	NA
Out-of-pocket	\$29–\$118	NA	NA	NA	NA
Productivity losses per case ^{†††}	\$1,062	\$2,437	\$782 (0–\$1,000)	\$744 (\$185–\$1,934)	NA
Cost-Effectiveness					
Outcomes prevented per million person-years					
Zoster	58,000	66,000	NA	NA	NA
Complications (non-PHN)	7,000	8,500	NA	NA	NA
PHN	32,000	20,000	NA	NA	NA
Premature deaths	5	37	NA	NA	NA
Resource-use averted per million person-years					
Outpatient visits	285,000	274,000	NA	NA	NA
Emergency department visits	28,000	8,700	NA	NA	NA
Hospitalization days	6,000	8,900	NA	NA	NA
Prescription fills	176,000	354,000	NA	NA	NA
QALYs gained per person-year ^{§§§}	0.0087	0.0057	0.0021	0.0016	NA
Vaccine cost per dose ^{¶¶¶}	\$150 (\$50–\$200)	\$150	\$145 (\$50–\$150)	\$200 (\$50–\$500)	\$170 (\$123–\$245)
Cost per QALY ^{****,§§§}	\$55,000	\$27,000	\$112,000	\$100,000	\$50,000

* Study No. 1: Ortega-Sanchez IR. Projected cost-effectiveness of vaccinating US elderly to prevent shingles. Oral presentation to the Advisory Committee for Immunization Practices (ACIP) Meeting, June 2006; Study No. 2: Pellissier JM, Brisson M, Levin MJ. Evaluation of the cost-effectiveness in the United States of a vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *Vaccine* 2007;25:8326–37; Study No. 3: Rothberg MB, Virapongse A, Smith KJ. Cost-effectiveness of a vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *Clin Infect Dis* 2007;44:1280–8; Study No. 4: 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; Study No. 5: Ho A, Coplan PM, Lee A, et al. Cost-effectiveness of vaccination against herpes zoster in the elderly population. *Canadian J Anesthesia (Suppl 1)*: 26394. Studies used a Markov cohort model. Except for Study 5, which considered vaccinating immunocompetent persons aged ≥ 65 years, studies No. 1–4 evaluated a routine vaccination program of immunocompetent persons aged ≥ 60 years. Baseline for comparison in all studies was “no vaccination.” Study No. 5 measured medical costs of zoster in 2002 U.S. dollars and Studies No. 1–4 measured age-specific costs in 2005–2006 U.S. dollars.

[†] For rates of zoster incidence and medical costs, Study No. 1 used data mainly from MedStat. For rates of zoster incidence and complications, the study used: Yawn BP, Saddier S, Wollan P, Sauver JS, Kurland M, Sy L. A population-based study of the incidence and complication rates of herpes zoster before zoster vaccine introduction. *Mayo Clin Proc* 2007;82:1341–9. For quality-of-life scores with zoster, out-of-pocket, and productivity costs, the study used: Lieu TA, Ortega-Sanchez IR, Ray GT, et al. Community and patient values for preventing zoster. *Pharmacoeconomics* 2008;26:235–49.

[§] For incidence of zoster, Study No. 5 used data mainly from: 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; CDC. Prevention of varicella: updated recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2007;56(No. RR-4). Medical costs from 1995 were updated to 2002 U.S. dollars.

[¶] Ranges in medical costs described age-specific costs for zoster or PHN cases among persons aged ≥ 60 years. High and low medical costs also were used for sensitivity analysis.

** SD = Standard deviation. In addition to reported mean costs, SD values were used for sensitivity analysis.

^{††} NA = not available.

^{§§} Out-of-pocket costs are monetary expenses associated with zoster or PHN as reported by patients and include medical and nonmedical payments, over-the-counter medications, travel expenses, and other monetary expenses.

^{¶¶} Study Nos. 1–3 included costs of frequent non-PHN complications observed ≤ 30 days after zoster reactivation (i.e., ocular, neurologic, and cutaneous complications).

^{***} Study Nos. 1 and 2 used costs attributable to PHN cases lasting ≥ 90 days, and study No. 4 used cost attributable to PHN cases lasting 182 days (\$166 per month). Although Study No. 3 assumed that 43%–56% of PHN cases lasted ≥ 12 months, attributable costs were not explicitly defined.

^{†††} Productivity losses (i.e., indirect costs) in cases of zoster and PHN were related to monetary value of time of work missed or income lost. Losses from leisure time or unpaid activities were not included. Although zoster can cause death, no productivity costs associated with premature deaths were included.

^{§§§} Source of quality-of-life values to estimate quality-adjusted life years (QALYs) differed across studies. Source of quality-of-life values to estimate quality-adjusted life years (QALYs) differed across studies. For all five studies, quality-of-life values are based on published data with valuation by representative samples of community members. In addition, study No. 1 also used published quality-of-life values using valuation by zoster patients, yielding values of QALYs gained per person-year of 0.019 and cost per QALY of \$23,000.

^{¶¶¶} Range in vaccine costs were used for sensitivity analyses. Study No. 4 reported an aggregated cost for the vaccine and vaccine administration equal to \$200. Except for Study No. 5, vaccine administration costs also were included (i.e., \$3.50 in Study No. 3, \$18 in Study No. 2, and \$15–\$30 in Study No. 1).

^{****} Estimates of cost per QALY saved assumed that PHN cases were avoided only through the prevention of zoster cases. When PHN cases were prevented in persons with zoster for whom the vaccine failed to prevent zoster (i.e., burden of illness), a societal cost of \$35,000 per QALY saved was estimated by Study No. 1.

able to seek medical attention for zoster and PHN and to request treatment of ongoing pain, they might be least able to tolerate the medications and procedures commonly used

to treat PHN, they might have the least reserve to tolerate zoster and its complications, and they are most likely to suffer social and psychological consequences from PHN.

Recommendations for Use of Zoster Vaccine

Routine Vaccination of Persons Aged ≥ 60 Years

ACIP recommends routine vaccination of all persons aged ≥ 60 years with 1 dose of zoster vaccine. Persons who report a previous episode of zoster and persons with chronic medical conditions (e.g., chronic renal failure, diabetes mellitus, rheumatoid arthritis, and chronic pulmonary disease) can be vaccinated unless those conditions are contraindications or precautions. Zoster vaccination is not indicated to treat acute zoster, to prevent persons with acute zoster from developing PHN, or to treat ongoing PHN. Before routine administration of zoster vaccine, it is not necessary to ask patients about their history of varicella (chickenpox) or to conduct serologic testing for varicella immunity.

Simultaneous Administration with Other Adult Vaccines

Immunogenicity of zoster vaccine and trivalent inactivated influenza vaccine is not compromised when the two vaccines are administered simultaneously (186). However, no data exist on administration of zoster vaccine with other vaccines routinely recommended for persons aged ≥ 60 years, which are all inactivated. In general, the simultaneous administration of most widely used live, attenuated and inactivated vaccines has not resulted in impaired immune response or an increased rate of adverse events (209). Therefore, zoster vaccine can be administered with other indicated vaccines during the same visit (e.g., Td, Tdap, and pneumococcal polysaccharide vaccines). Each vaccine must be administered using a separate syringe at a different anatomic site. If simultaneous administration is not possible, zoster vaccine can be administered at any time before or after an inactivated vaccine, but at least 4 weeks before or after another live, attenuated vaccine (209).

Groups for Which Vaccine is Not Licensed

Vaccination of Persons Aged < 60 Years

The vaccine is not licensed for persons aged < 60 years, and no recommendation exists for routine vaccination of persons aged < 60 years. In the clinical trial, the zoster vaccine was evaluated among persons aged ≥ 60 years. The vaccine was most effective and well tolerated in the youngest persons (Table 1) (4). Although the vaccine would

probably be safe and effective in persons aged < 60 years, data are insufficient to recommend vaccination of these persons at this time.

Vaccination of Persons Who Have Received Varicella Vaccine

Zoster vaccination is not recommended for persons of any age who have received varicella vaccine. However, health-care providers do not need to inquire about varicella vaccination history before administering zoster vaccine because virtually all persons currently or soon to be in the recommended age group have not received varicella vaccine. In the United States, varicella vaccination began in 1995. Since that time, few adults aged ≥ 40 years would have been susceptible to varicella and thus eligible to receive varicella vaccine (5). The number of persons eligible for zoster vaccination who have received varicella vaccine is extremely small and will remain so for at least a decade.

Special Groups and Circumstances

Persons with a Reported History of Zoster

Persons with a reported history of zoster can be vaccinated. Repeated zoster has been confirmed in immunocompetent persons soon after a previous episode (4). Although the precise risk for and severity of zoster as a function of time following an earlier episode are unknown, some studies suggest it may be comparable to the risk in persons without a history of zoster (62,169). Furthermore, no laboratory evaluations exist to test for the previous occurrence of zoster, and any reported diagnosis or history might be erroneous (4,64,65). Although the safety and efficacy of zoster vaccine have not been assessed in persons with a history of zoster, different safety concerns are not expected in this group.

Persons Anticipating Immunosuppression

The risk for zoster and its severe morbidity and mortality is much greater among persons who are immunosuppressed. Review of vaccination status for zoster and other vaccines should be a key component of the medical assessment for immunocompetent patients aged ≥ 60 years who might be anticipating initiation of immunosuppressive treatments or who have diseases that might lead to immunodeficiency. Such patients without a history of zoster vaccination should receive 1 dose of zoster vaccine at the first possible clinical encounter while their immunity is intact. Zoster vaccine should be administered at least 14 days before initiation of immunosuppressive therapy, although some

experts advise waiting 1 month after zoster vaccination to begin immunosuppressive therapy if delay is possible (210).

Persons Receiving Antiviral Medications

Licensed antiviral medications active against members of the herpesvirus family include acyclovir, famciclovir, and valacyclovir. These agents might interfere with replication of the live, VZV-based zoster vaccine. All three agents have relatively short serum half-lives and are quickly cleared from the body. Persons taking chronic acyclovir, famciclovir, or valacyclovir should discontinue these medications at least 24 hours before administration of zoster vaccine, if possible (209). These medications should not be used for at least 14 days after vaccination, by which time the immunologic effect should be established (209).

Persons Receiving Blood Products

Zoster vaccine can be administered to persons at any time before, concurrent with, or after receiving blood or other antibody-containing blood product because persons with a history of varicella indefinitely maintain high levels of antibody to VZV, and the levels are comparable to those found in donated blood and antibody-containing blood products (e.g., whole blood, packed red blood cells, and plasma immune globulin, hyperimmune globulin, and intravenous immune globulin) (192,211).

Nursing Mothers

Most live vaccines, including varicella vaccine, are not secreted in breast milk (209,212). Therefore, breast feeding is not a contraindication for zoster vaccination. However, this situation will be extremely rare in the target age group for this vaccine.

Contraindications

Allergy to Vaccine Components

Zoster vaccine is contraindicated for persons who have a history of anaphylactic reaction to any component of the vaccine, including gelatin and neomycin. Neomycin allergy is usually manifested as a contact dermatitis, which represents a delayed-type immune response. A history of contact dermatitis to neomycin is not a contraindication for receiving zoster vaccine (209).

Immunocompromised Persons

Zoster vaccine should not be administered to persons with primary or acquired immunodeficiency including:

- Persons with leukemia, lymphomas, or other malignant neoplasms affecting the bone marrow or lymphatic

system. However, patients whose leukemia is in remission and who have not received chemotherapy (e.g., alkylating drugs or antimetabolites) or radiation for at least 3 months can receive zoster vaccine (209).

- Persons with AIDS or other clinical manifestations of HIV, including persons with CD4+ T-lymphocyte values ≤ 200 per mm^3 or $\leq 15\%$ of total lymphocytes.
- Persons on immunosuppressive therapy, including high-dose corticosteroids (≥ 20 mg/day of prednisone or equivalent) lasting two or more weeks. Zoster vaccination should be deferred for at least 1 month after discontinuation of such therapy (209). Short-term corticosteroid therapy (< 14 days); low-to-moderate dose (< 20 mg/day of prednisone or equivalent); topical (e.g., nasal, skin, inhaled); intra-articular, bursal, or tendon injections; or long-term alternate-day treatment with low to moderate doses of short-acting systemic corticosteroids are not considered to be sufficiently immunosuppressive to cause concerns for vaccine safety. Persons receiving this dose or schedule can receive zoster vaccine. Therapy with low-doses of methotrexate (≤ 0.4 mg/Kg/week), azathioprine (≤ 3.0 mg/Kg/day), or 6-mercaptopurine (≤ 1.5 mg/Kg/day) for treatment of rheumatoid arthritis, psoriasis, polymyositis, sarcoidosis, inflammatory bowel disease, and other conditions are also not considered sufficiently immunosuppressive to create vaccine safety concerns and are not contraindications for administration of zoster vaccine.
- Persons with clinical or laboratory evidence of other unspecified cellular immunodeficiency. However, persons with impaired humoral immunity (e.g., hypogammaglobulinemia or dysgammaglobulinemia) can receive zoster vaccine.
- Persons undergoing hematopoietic stem cell transplantation (HSCT). The experience of HSCT recipients with VZV-containing vaccines (e.g., zoster vaccine) is limited. Physicians should assess the immune status of the recipient on a case-by-case basis to determine the relevant risks. If a decision is made to vaccinate with zoster vaccine, the vaccine should be administered at least 24 months after transplantation (209).
- Persons receiving recombinant human immune mediators and immune modulators, especially the antitumor necrosis factor agents adalimumab, infliximab, and etanercept. The safety and efficacy of zoster vaccine administered concurrently with these agents is unknown. If it is not possible to administer zoster vaccine to patients before initiation of therapy, physicians should assess the immune status of the recipient on a case-by-case basis to determine the relevant risks and

benefits. Otherwise, vaccination with zoster vaccine should be deferred for at least 1 month after discontinuation of such therapy.

Pregnancy

Zoster vaccine is not recommended for use in pregnant women, although these women are unlikely to be in the vaccine target age group. The effects of the live, attenuated VZV-based zoster vaccine on the fetus are unknown. Women should avoid becoming pregnant for 4 weeks following zoster vaccination. Having a pregnant household member is not a contraindication to zoster vaccination. If a pregnant woman is vaccinated or becomes pregnant within 1 month of vaccination, she should be counseled about potential effects on the fetus. Wild-type VZV poses a small risk to the fetus (3), and the fetal risk from the attenuated zoster vaccine is probably even lower. Furthermore, virtually all persons receiving the vaccine will have preexisting VZV immunity, which is expected to limit viral replication and presumably further reduce fetal risk. In most circumstances, the decision to terminate a pregnancy should not be based on whether zoster vaccine was administered during pregnancy. Merck & Co., Inc., in collaboration with CDC, has established a pregnancy registry to monitor the maternal-fetal outcomes of pregnant women who are inadvertently administered live-attenuated VZV-based vaccines within 1 month of pregnancy (telephone: 800-986-8999). Patients and health-care providers should report any exposure to zoster vaccine during pregnancy to this registry.

Precautions

Moderate to Severe Illness

Zoster vaccination of persons who have severe acute illness should be postponed until recovery. The decision to delay vaccination depends on the severity of symptoms and the etiology of the disease. Zoster vaccine can be administered to persons who have mild acute illnesses with or without fever (209).

Program Implementation Issues

Following Good Adult Vaccination Practices

Zoster vaccine should be offered to patients aged ≥ 60 years at the first available clinical encounter with their provider. The average adult in this age group has 5–8 clinical encounters with their provider annually (213). Strategies to promote zoster vaccination include linking delivery of zoster vaccine to delivery of other indicated adult vaccines

(e.g., influenza) and preventive-health interventions (214–217), standing orders so that patients will automatically be offered indicated vaccines rather than requiring case-by-case physicians' orders (218), and practice-based audits and/or physician-reminder systems (218). Residents of nursing homes and other long-term-care facilities who are at least aged 60 years and without contraindications should be included in routine zoster vaccination activities. When administering zoster vaccine, health-care providers should review the patient's vaccination status for all indicated adult vaccines (219,220).

ACIP recommends that health-care providers keep permanent documentation of all administered vaccines, including zoster vaccine, in the vaccine recipient's permanent medical record (209). The type of the vaccine, manufacturer, anatomic site, route of delivery, date of administration, lot number, and name of the administering facility should be recorded. To help avoid the administration of unnecessary doses, every patient should be given a record of the vaccination.

Administration Errors

The zoster vaccine, ZOSTAVAX[®], is a live, attenuated vaccine containing Oka/Merck strain VZV. The vaccine is similar to the varicella vaccine, VARIVAX[®], except the minimum PFU-content of the ZOSTAVAX[®] is at least 14-fold higher than the minimum PFU-content of VARIVAX[®]. Opportunities for administration errors are possible.

For providers who serve both children and adults, physical separation of products, careful visual inspection and reading of labels, and preparation of vaccine for patient use only at time of vaccination can help prevent errors. If a provider mistakenly administers high-potency zoster vaccine to a child indicated for varicella vaccine, the level of protection against varicella would probably be at least the same as for conventional doses of varicella vaccine. This erroneous dose should count as a single valid dose of varicella vaccine. If the erroneous dose was administered in lieu of the first dose of varicella vaccine, a second dose of varicella vaccine is required. Administration errors involving zoster vaccine should be reported to VAERS whether or not an adverse event occurs.

Early clinical trials for prevention of varicella were conducted in susceptible children using a formulation of live-attenuated Oka/Merck strain VZV at doses of 17,430 PFU, approaching the range of PFU in zoster vaccine ($\geq 19,400$ PFU). This high-dose formulation was well tolerated and efficacious (221). The more recently licensed live, attenuated Oka-strain VZV vaccine (PROQUAD[®]) prepared in

combination with measles, mumps, and rubella vaccine (MMRV) is formulated with a broad range of titers that extend to over 60,000 PFU (222,223).

Varicella vaccine (VARIVAX[®]) is not indicated for prevention of zoster. MMRV vaccine (PROQUAD[®]) is not licensed for use in persons aged ≥ 13 years. If a provider mistakenly administers varicella vaccine to persons indicated for zoster vaccine, no specific safety concerns exists, but the dose should not be considered valid and the patient should be administered a dose of zoster vaccine during that same visit. If the error is not immediately detected, a dose of zoster vaccine should be administered as soon as possible but not within 28 days of the varicella vaccine dose to prevent potential interference of 2 doses of live attenuated virus.

Risk for Transmission of Oka/Merck Strain after Receiving Zoster Vaccine

Persons having close household or occupational contact with persons at risk for severe varicella need not take any precautions after receiving zoster vaccine except in rare instances in which a varicella-like rash develops, when standard contact precautions are adequate. Although transmission of Oka/Merck strain VZV has been documented following varicella vaccination, such transmission is rare and has only been documented when the vaccine recipient first developed a varicella-like rash. Rates of varicella-like rash appear to be less common following zoster vaccination than following varicella vaccination (4), and transmission of the Oka/Merck strain VZV from recipients of zoster vaccine has not been detected. The risk for transmitting the attenuated vaccine virus to susceptible persons should be weighed against the risk for developing wild-type zoster that could be transmitted to a susceptible person. If a susceptible, immunocompromised person is inadvertently exposed to a person who has a vaccine-related rash, VARIZIG[™] need not be administered because disease associated with this type of transmission is expected to be mild. Acyclovir, valacyclovir, and famciclovir are active against live-attenuated Oka/Merck strain VZV and can be used in the unlikely situations in which a severe illness develops in the susceptible contact.

Reporting of Adverse Events after Vaccination

As with any newly licensed vaccine, surveillance for rare adverse events associated with administration of zoster vaccine is important for assessing its safety in widespread use. Vaccine safety surveillance in the age group for which zoster vaccine is recommended (aged ≥ 60 years) will present chal-

lenges because of the high prevalence of chronic conditions, the frequent use of multiple medications, and the common occurrence of medical events. Coincident adverse events can be anticipated following zoster vaccination, but many of these could be caused by the vaccine as well. All clinically significant adverse events should be reported to VAERS even if causal relation to vaccination is not certain. VAERS reporting forms and information are available electronically at <http://www.vaers.hhs.gov> or by telephone (800-822-7967). Web-based reporting is also available, and providers are encouraged to report electronically at <https://secure.vaers.org/VaersDataEntryintro.htm>.

Future Research and Directions

Key questions remain regarding optimal implementation of zoster vaccination and preventing zoster and its complications. Areas that need particular focus include:

- Surveillance for zoster and its complications. Zoster is not a notifiable condition. Other strategies will be needed to monitor zoster and its complications include using administrative databases, population-based surveys, or active surveillance in sentinel sites. Because the primary disease burden associated with zoster is pain, capturing this condition will be particularly challenging using any surveillance strategy.
- Durability of protection against zoster and its complications afforded by the zoster vaccine. In a persistence substudy ongoing at 12 of 22 of the original zoster vaccine study sites, follow up of vaccine recipients will be extended to an observation time of 10 years. However, no concurrent randomized placebo group exists to which these vaccine recipients can be compared, and results will be compared against historic controls. Large administrative databases also will be important in evaluating changes in vaccine effectiveness over time. These and other available data will help to determine changes in vaccine policy (e.g. a booster dose). However, both of these approaches might be confounded by secular changes in the incidence of zoster.
- Increased understanding of the epidemiology of zoster. Better knowledge of age-adjusted changes in the incidence of zoster and risk factors for any such changes will help determine the long-term effectiveness of the zoster vaccine and clarify whether changes in VZV circulation caused by varicella vaccination might be affecting zoster incidence. A better understanding of the epidemiology and risk factors for zoster might also lead to changes in policy regarding use of zoster vaccine (e.g., targeting the vaccine to selected risk groups).

that are not now covered by the vaccine recommendations or lowering the targeted age group). Additional information is needed to define risks for zoster in varicella-vaccinated adults attributed to Oka/Merck strain VZV from the vaccine itself or to wild-type VZV from breakthrough varicella. Although studies involving both immunocompromised and immunocompetent children provided evidence that the risks for zoster are lower in varicella-vaccinated children than in children with naturally acquired varicella (3,99,100,224), characterization of these risks in older adults will involve longer follow up.

- Better prevention and treatment strategies for zoster and PHN. Although licensure of zoster vaccine represents an important milestone in prevention of zoster, the vaccine remains only partially efficacious and is not licensed for all populations and age groups at risk. Although available treatments for zoster and PHN have improved, treatment of these conditions remains inadequate. Improved prevention and treatment strategies, including better vaccines, are needed to reduce the disease burden of zoster. ZOSTAVAX[®] or other active or inactive formulations of zoster vaccine should be evaluated in additional cohorts of persons (e.g., persons aged 50–59 years and immunosuppressed persons at the highest risk for zoster and its complications). Patients infected with HIV, with or without AIDS, could benefit substantially from the prevention of zoster. A better understanding of immunologic correlates of protection against zoster would help facilitate the development and evaluation of such new zoster prevention strategies.
- The epidemiology of zoster in persons with a history of varicella vaccination. Available data suggest that children vaccinated with varicella vaccines are at reduced risk for Oka/Merck strain zoster as compared with the risk for zoster from wild-type VZV in children with a history of chickenpox. However, this evidence does not extend to vaccine recipients as they become older. Nor does it include decades of time after vaccination, particularly in the absence of circulating VZV that could externally boost immunity. Data also are lacking regarding the risk for zoster from wild-type VZV in vaccinated persons with a history of breakthrough varicella. These issues should be addressed in future studies to develop zoster vaccination policy for cohorts of vaccine recipients as they age.
- Safety of zoster vaccination. Postlicensure studies to evaluate further the safety of the zoster vaccine are

under development and will be conducted by the manufacturer. Clinical trials have been completed to assess the safety and immunogenicity of simultaneous administration of zoster vaccine and formulations of influenza vaccine. In addition, independent studies are being developed by CDC to monitor safety through VAERS and the CDC Vaccine Safety Datalink.

Additional Information About Zoster and Zoster Vaccine

Additional information about zoster and zoster vaccine is available from several sources, and new information will be available in the future. Updated information about zoster, PHN, and zoster vaccine is available at <http://www.cdc.gov/vaccines/vpd-vac/shingles/default.htm>.

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