Although herpes zoster is not a reportable condition in the United States, its incidence has been inferred from a variety of studies to range from 3.2 to 4.2 per 1,000 patient-years.¹ This incidence translates into an estimated 1 million cases of herpes zoster annually. Overall, an estimated 32% of persons in the United States will have herpes zoster during their lifetimes.¹⁻³

In a recent population-based study in Olmsted County, Minn., researchers found that the incidence of herpes zoster was 3.6 per 1,000 patient-years.² The researchers also found that the incidence and rate of complications increased with age, with 68% of cases occurring in those aged 50 years and older. There is a substantial increase in herpes zoster incidence for individuals aged 60 years and older, making the annual incidence in this population approximately 10 per 1,000 patient-years.²⁻⁴

Herpesviridae have been known to science for many years. The family contains more than 100 types of viruses that infect vertebrates, though only eight types are known to infect humans—herpes simplex virus type 1, herpes simplex virus type 2, varicella-zoster virus (VZV), Epstein-Barr virus, cytomegalovirus, and human herpesviruses 6, 7 and 8.

Varicella-zoster virus is highly contagious and causes two distinct clinical syndromes—a primary infection that is manifested as varicella (ie, chicken pox) and a secondary latent infection that is manifested as herpes zoster (ie, shingles).

**Disease progression**

The earliest symptoms of herpes zoster are nonspecific and include fever, headache and malaise, followed by changes of sensation, burning pain and itching. The pain may be mild to extreme in the affected dermatome.²⁻⁵

This early, nonspecific phase of herpes zoster is followed by the appearance of the condition’s characteristic skin rash. The rash occurs most commonly on the torso, but it can also appear on the face, eyes or other parts of the body. The rash initially appears similar to urticaria (ie, hives), but herpes zoster is distinguished by the rash being limited to one side of the body and not crossing the body midline.

Physicians should keep in mind that some patients may have a condition called zoster sine herpete, in which herpes zoster infection is present without the characteristic rash.²⁻³ VZV analyses should include tests for both anti-VZV IgG and PCR-amplifiable VZV DNA in CSF, as well as examination of blood MNCs for VZV DNA.⁶
As herpes zoster progresses, the hive-like rash changes into vesicles, which become cloudy and then fill with blood. Like a childhood infection of varicella, the herpes zoster lesions crust over within seven to 10 days, and the skin heals. However, if severe blistering occurs, scarring and discolored skin may remain.

The most common complication of herpes zoster is postherpetic neuralgia (PHN), a neuropathic pain syndrome that lingers after the rash has resolved. This painful syndrome can have a substantial adverse impact on an individual's mood and ability to conduct daily living activities.7-11 Other complications of herpes zoster can include bacterial superinfection, cerebral vasculitis, esophagitis, meningencephalitis, motor paralysis, myocarditis, pneumonia, and transverse myelitis.7-11

Depending on the extent of dermatomal involvement, patients with herpes zoster may experience loss of vision or hearing. Herpes zoster ophthalmicus, which affects approximately 10% to 25% of patients with herpes zoster, occurs when VZV reactivates in the ophthalmic division of the trigeminal nerve.12

The symptoms of herpes zoster ophthalmicus may include conjunctivitis, keratitis, optic nerve palsies and uveitis. In addition, herpes zoster ophthalmicus can result in chronic ocular inflammation, loss of vision and debilitating pain.

Herpes zoster oticus (ie, Ramsay Hunt syndrome type 2), which involves the ear, is thought to occur when the reactivated VZV spreads from the facial nerve to the vestibulocochlear nerve. The symptoms of this condition include hearing loss and rotational vertigo.7-11

**Cell-mediated immunity**

In the March 2007 supplement to *JAOA—The Journal of the American Osteopathic Association*, Weaver et al4 outlined the importance of cell-mediated immunity (CMI) to protect against herpes zoster. When CMI to VZV becomes insufficient to keep the virus under control, the virus reemerges from the dorsal root ganglia, usually causing the acute herpes zoster rash and severe pain.

The chief factor that compromises CMI is advancing age, with accompanying immunosenescence. Stress and physical trauma also appear to play roles in determining the timing and, possibly, the location of herpes zoster.1

Kimberlin et al13 noted that the prophylactic effect of the herpes zoster vaccine is thought to be a consequence of its boosting effect on an older person's CMI to VZV—mimicking the immunologic benefits of the exposure of a VZV-immune adult to chicken pox. This pharmacologic boost raises CMI to a new “set point” above the “immunologic threshold,” below which a person is at risk for herpes zoster.1,4,14-17


Historical perspective

Conditions caused by herpesviruses have been described throughout the centuries. The word herpes is derived from an ancient Greek word meaning “creeping” or “crawling”—referring to the spread of herpes rashes. Hippocrates discusses herpeslike conditions in some of his writings. Descriptions of what appear to be herpesvirus infections can be found in the Ebers papyrus, an ancient Egyptian medical document from 1500 BC.18

In the 16th century, Shakespeare described the effects of herpesvirus infection in Romeo and Juliet. In Mercutio’s speech about Queen Mab, Shakespeare wrote, “O’er ladies lips, who straight on kisses dream, which oft of the angry Mab with blisters plagues.”19

During the 1760s, English physician William Heberden created detailed clinical descriptions to facilitate differentiation between cases of chicken pox and smallpox.10

In 1831, English physician Richard Bright hypothesized that herpes zoster arose from the dorsal root ganglion, and this hypothesis was confirmed in 1861 by German physician Friedrich Wilhelm Felix von Barensprung.10

Herpes zoster was differentiated from erysipelas in the late 19th century.20 In 1900, Head and Campbell11 examined the pathologic mechanisms of herpes zoster and the bearing of these mechanisms on sensory location. In 1906, Hewlett12 analyzed the motor complications of herpes zoster, noting, “... herpes zoster is a far more serious disease in elderly people, for not only are the neuralgias more severe but motor complications are more liable to occur.”

In 1925, Cole and Kuttner21 evaluated the work of Kundratitz, who described the similarities between herpes zoster and varicella. The researchers wrote, “[Kundratitz’s] observations, aside from indicating a close immunological relationship between herpes zoster and varicella, are important in that they seem to show the presence of a transmissible virus in the vesicles of herpes zoster.”

Thomas H. Weller isolated VZV in 1949 by growing the virus in vitro in human tissue culture.10 Through this work, Weller proved a connection between varicella and herpes zoster. In 1952, Weller and Stoddard proved that the viruses causing chicken pox and shingles lesions were identical when they isolated VZV from both types of lesions.10

Weller was awarded the Nobel Prize in physiology or medicine in 1954 for his work in isolating VZV, as well as cytomegalovirus and the mumps, rubella, and poliomyelitis viruses, in human tissue cultures.13,15,22 In 1965, Hope-Simpson23 proposed that immunity to VZV plays a pivotal role in the pathogenesis of herpes zoster.

A milestone was achieved in 1986, when Andrew J. Davison and James E. Scott published the entire DNA sequence of VZV in the Journal of General Virology.1 Using M13-dideoxynucleotide technology, Davison and Scott1 discovered that the VZV genome consists of 124,884 base pairs, with a total of 70 genes spread out evenly between the two DNA strands. The researchers also compared the amino acid sequences of VZV to those of herpes simplex virus type 1, revealing a common ancestral origin of the two viruses.

The sequencing of the VZV genome opened the door to major developments in preventing VZV infection—including successful vaccines.1,4,9–11,14

Cost-effectiveness of vaccine

A primary impetus for the development of an anti-VZV vaccine was the alleviation of high costs associated with treatments, including hospitalizations, for herpes zoster and its most debilitating complication, PHN. Approximately 100,000 to 200,000 new cases of PHN are diagnosed in the United States every year.11 Postherpetic neuralgia can persist for many years and is often refractory to treatment. Although antiviral medications can limit the course of herpes zoster, they do little to ameliorate the severe pain associated with PHN.

The herpes zoster vaccine is likely to be cost-effective in the United States. Annual savings of $82 million to $103 million in health-care costs are projected to result from the vaccine, with cost-effectiveness ratios ranging from $14,877 to $34,852 per quality-adjusted life year gained.13,15

An analysis by the U.S. Centers for Disease Control and Prevention (CDC)13 estimated that approximately 17 patients would need to be vaccinated to prevent one case of herpes zoster, and approximately 31 patients would need to be vaccinated to prevent one case of PHN. With a cost of $150 for the single-shot vaccine, the cost per case of prevented herpes zoster is estimated to be $3,330, and the cost per case of prevented PHN is estimated to be $6,405.14–17

Pellissier et al14—using commonly cited thresholds for judging cost-effec-
tiveness—noted that the herpes zoster vaccine is likely to be cost-effective for a cohort of immunocompetent vaccine recipients aged 60 years and older in the United States. The researchers noted that savings were most substantial in terms of costs related to PHN.

Najafzadeh et al\textsuperscript{16} analyzed cost-effectiveness of the herpes zoster vaccine in Canada. Their analysis noted that herpes zoster vaccination reduced mean direct medical costs (excluding the cost of the vaccine itself) by $35 per person in Canada. They concluded that herpes zoster vaccination of adults—especially those aged 60 to 75 years—seems to be a cost-effective intervention that should be considered by Canadian decision makers.\textsuperscript{16} Adult Canadians will soon have the opportunity to protect themselves against shingles—a reactivation of the virus that causes chicken pox.

**Development of vaccine**
Michiaki Takahashi\textsuperscript{23} developed a vaccine for VZV in 1974 after he obtained blood samples from a Japanese boy who was afflicted with chicken pox. Takahashi attenuated the virus by growing it in human cell samples. In the 1980s, Merck Sharp & Dohme Corp, a subsidiary of Merck & Co, Inc, of Whitehouse Station, NJ, developed the vaccine as Varivax, which the U.S. Food and Drug Administration (FDA) approved in 1995.\textsuperscript{24} Varivax is nationally recommended for children aged as young as 12 months as a way to prevent infection with VZV. The vaccine contains live, attenuated virus based on the Oka strain of varicella.\textsuperscript{24}

ProQuad (Merck & Co Inc, Whitehouse Station, NJ) was subsequently formulated for inoculation against measles, mumps, rubella, and VZV.\textsuperscript{25} ProQuad contains 10 times more live, attenuated VZV than does Varivax.

In 1997, a live, attenuated vaccine was developed as a form of concentrated Varivax to prevent shingles in adults. Levin\textsuperscript{17} noted that initial studies of the vaccine suggested that a higher titer of live, attenuated virus would be required to elicit a significant, durable increase in CMI against VZV in older adults. In 2006, the FDA licensed Zostavax (Merck & Co Inc, Whitehouse Station, NJ),\textsuperscript{26} or zoster vaccine live, for the prevention of herpes zoster in individuals aged 60 years and older.\textsuperscript{13,16,17,26-28} Guidelines for the use of Zostavax, by the CDC’s Advisory Committee on Immunization Practices (ACIP), are shown in Figure 1.

Many authors have debated the effectiveness of VZV vaccine, including whether the vaccine is more advantageous to the patient than natural exposure.\textsuperscript{29} In October 2009, Weinberg et al\textsuperscript{30} noted that higher CMI at the onset of herpes zoster was associated with reduced severity of both herpes zoster and PHN. Weinberg et al\textsuperscript{30} also noted that herpes zoster and the zoster vaccine generated comparable CMI.\textsuperscript{26,30}

**Safety of vaccine**
Possible adverse effects of the zoster vaccine range from fever and mild rash to seizure, low blood cell counts, and pneumonia. According to the CDC\textsuperscript{2} and the World Health Organization, severe adverse effects from the vaccine are rare, and the benefits of immunity outweigh the risks of getting the vaccine.

In the Shingles Prevention Study (SPS), Oxman et al\textsuperscript{27} compared vaccinated individuals with a placebo group.
for adverse effects occurring within the first 42 days after vaccination. Minor adverse effects occurred more often in the vaccinated group than in the placebo group, included varicella like rashes or erythema at the injection site, localized pain or tenderness, and swelling pruritus ($P<.05$ for all comparisons). The numbers and types of serious adverse events in the first 42 days were similar between the two groups. However, cardiac events occurred more often among vaccine recipients than among placebo recipients—0.6% vs 0.4%, respectively.2,26,27

Serious adverse events occurred at a similar rate (1.4%) in vaccine and placebo recipients.27 Among reported serious adverse events in the SPS (Days 0 to 42 postvaccination), serious cardiovascular events occurred more frequently in subjects who received Zostavax (20 [0.6%]) than in subjects who received placebo (12 [0.4%]) in the AE Monitoring Substudy. The frequencies of serious cardiovascular events were similar in subjects who received Zostavax (81 [0.4%]) and in subjects who received placebo (72 [0.4%]) in the entire study cohort (Days 0 to 42 postvaccination).

**Why vaccination is important**

The importance of vaccination is highlighted by the fact that the incidence and severity of herpes zoster and PHN increase with age in association with a progressive decline in CMI to VZV.3,4,8,13,22,27-30 In the SPS,27 38,546 adults older than age 60 years were given an investigational live, attenuated Oka/Merck VZV vaccine (ie, zoster vaccine). Two endpoints were assessed. The primary endpoint was pain and discomfort associated with herpes zoster, as measured by the incidence, severity, and duration of the pain and discomfort. The secondary endpoint was the incidence of PHN.

Oxman et al27 reported that use of the zoster vaccine, compared with placebo, reduced the burden of illness resulting from herpes zoster by 61.1% ($P<.001$), reduced the incidence of herpes zoster by 51.3% ($P<.001$), and reduced the incidence of PHN by 66.5% ($P<.001$). The SPS27 was a pivotal study, demonstrating that vaccination reduced morbidity from herpes zoster and PHN among older adults. The SPS27 also suggested that—with an aging population and lengthening life expectancy—preventing herpes zoster would offer important medical and economic benefits in the United States.

**Concerns about vaccine administration**

Kimerlin et al13 outlined five areas of concern regarding routine administration of the zoster vaccine—vaccine cost; off-label uses of the vaccine for younger patients; decreasing exposure to natural immunity; whether immunocompromised patients should be candidates for vaccination; and whether patients with previous herpes zoster exposure should be vaccinated.

As previously mentioned, the estimated cost per case of prevented herpes zoster is $3,330, and the estimated cost per case of prevented PHN is $6,405.4,14-17 These cost savings are likely to influence the use of herpes zoster immunization for patients aged 60 years or older. Regarding the second concern, it is unclear if off-label use of the zoster vaccine for patients aged 50 to 59 years is warranted. The incidence of herpes zoster increases after 50 years of age, and the burden of herpes zoster for patients aged 60 years is substantial. Studies show that the efficacy of the zoster vaccine is greater among individuals 60 to 69 years of age than among individuals aged 70 years or older.13,27,30 Thus, it is logical to presume that
the vaccine may be even more immunogenic in individuals between 50 and 59 years of age. However, available immunogenicity data for this age group are based only on small sample sizes, and no efficacy data exist for this group.

In regard to the third concern, wild-type VZV infections (ie, natural immunizations from varicella exposure) are declining as a result of universal vaccination against chicken pox in childhood. As a consequence, the likelihood that the immune systems of older people will be “boosted” by exposure to a child with chicken pox is declining.

Will adults in the future need to receive vaccination earlier than is currently recommended? As previously noted, higher VZV CMI at the onset of herpes zoster has been associated with reduced severity of herpes zoster and PHN, and herpes zoster and the zoster vaccine were found to generate similar CMI25. The effects of vaccination vs natural exposure in eliciting CMI will require careful postlicensure monitoring over many years. Patients who received Varivax or ProQuad may be candidates for herpes zoster vaccination as they age.13,20

Regarding the fourth concern, the zoster vaccine is not currently licensed for use in immunocompromised patients. However, safety and efficacy of the vaccine need to be evaluated more thoroughly in immunocompetent people for whom immunosuppressive therapy would be anticipated, such as individuals awaiting organ transplantation, asymptomatic patients with early-stage HIV infection, patients who will be receiving chemotherapy for cancer, and patients who will be receiving immunosuppressive therapy for rheumatoid arthritis, lupus or other autoimmune diseases.

In terms of the fifth concern, it is unknown whether the zoster vaccine will be efficacious in patients who have had previous episodes of herpes zoster. This population was excluded from the SPS.27 These five concerns can serve as focal points for future research that will have great implications for prevention of herpes zoster.11,21,26

Role of physicians in patient education
Paek et al28 addressed questions of patient awareness, knowledge, symptoms and treatment in the Herpes Zoster Global Awareness Survey. In this study, 8,688 adults aged 50 years and older in 22 countries were surveyed in December 2006 and January 2007. The survey results showed wide variation in patient awareness of herpes zoster, but universally poor knowledge of the causes and symptoms of herpes zoster, with only 3% of respondents mentioning chicken pox as the cause. In addition, 71% of respondents were unaware of their own risks of herpes zoster, believing that they were unlikely or very unlikely to get the disease.

The pivotal point of the study by Paek et al28 is that physicians must embrace misconceptions of zoster-related morbidity among individuals who have no first-hand experience of the disease. The study by Paek et al28 highlighted the global educational need to raise public awareness of the seriousness of herpes zoster and its potential long-term complications.13,27,28 In Figure 2, Web sites featuring information on herpes zoster, varicella and vaccinations are listed.

Final notes
With continued advances in medical care and preventative services, the median age of the U.S. population is increasing. Physicians are likely to encounter more morbidity arising from medical conditions that affect older adults, including herpes zoster. Vaccination of older adults against herpes zoster is likely to decrease the incidence of this condition, as well as alleviate costs associated with treatments and hospitalizations. Vaccination is also likely to decrease new cases of PHN, which severely affects quality of life.

Because the success of any vaccine initiative depends on public awareness of
the disease, physicians should try to increase public awareness of herpes zoster. However, risks and benefits regarding vaccine use must be addressed on a case-by-case basis following ACIP guidelines.

As a result of mandated varicella vaccinations for children, natural immunity from varicella has decreased. Future research into vaccination for prevention of herpes zoster will be of paramount importance in eradication of morbidity from VZV.

References