Herpes Zoster Vaccination in People Aged 50–59 Years

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(See the Major Article by Schmader et al, on pages 922–8.)

Herpes zoster (or shingles), an infectious disease caused by reactivation of latent varicella-zoster virus (VZV) in the dorsal root or cranial nerve ganglia, typically manifests as unilateral acute pain accompanied by a vesicular rash. The acute pain and rash usually resolve within 2–4 weeks without treatment. Postherpetic neuralgia, commonly defined as pain that lasts >3 months after the onset of rash or cutaneous healing, is the most common and feared complication and can persist occasionally for years in some patients. In addition to postherpetic neuralgia, some patients may suffer from ocular, hearing, or other serious neurological complications [1, 2].

Age-related decline in cell-mediated immune responses is a major risk factor of herpes zoster as well as postherpetic neuralgia. The annualized incidence of herpes zoster was 4.6, 6.9, 9.5, and 10.9 per 1000 people aged 50–59, 60–69, 70–79, and ≥80 years, respectively [3]; the corresponding proportion of patients who had postherpetic neuralgia in each age group was approximately 5%, 10%, 17%, and 20%, respectively [4]. People with immunosuppressive illness or those receiving immunosuppressive therapy are more vulnerable to herpes zoster and more likely to develop postherpetic neuralgia. The annualized incidence of herpes zoster was 29.4 per 1000 men seropositive for human immunodeficiency virus (HIV) and 2.0 per 1000 HIV-seronegative men [5]. Diabetes mellitus, often accompanied by altered cell-mediated immunity, was associated with an increased risk of herpes zoster and prescriptions of opioids within a year of diagnosis of shingles [6].

Antiviral therapy can accelerate cutaneous healing and reduce severity and duration of pain. The treatment should be initiated in 72 hours after acute-symptom onset to maximize benefit [7], but such rapid treatment is often impractical due to delays in seeing a doctor or reaching a diagnosis. The treatment for postherpetic neuralgia is complex; sometimes treatment efficacy is unsatisfactory. Over half of patients require >1 prescription drug for relieving postherpetic neuralgia, but the pain can be relieved only in 50% of patients despite treatment [8]. These issues highlight a need to develop a vaccine that prevents herpes zoster and postherpetic neuralgia. In 2005, efficacy of a herpes zoster vaccine, Zostavax, was demonstrated among people aged ≥60 [9]. In 2006, the US Food and Drug Administration (FDA) approved Zostavax to prevent shingles in individuals aged ≥60 [10]. In 2008, the US Centers for Disease Control and Prevention (CDC) recommended routine vaccination among people aged ≥60 [11].

In the present issue of Clinical Infectious Diseases, Schmader et al [12] report the efficacy and safety profile of Zostavax in people aged 50–59. The event-driven trial was conducted among healthy subjects without immune compromise. The primary efficacy outcome was the relative reduction in the incidence of herpes zoster in the Zostavax versus placebo group. The secondary efficacy endpoint was the mean severity-by-duration score, a composite measure of herpes zoster incidence, severity, and duration of acute pain. Zostavax’s efficacy for postherpetic neuralgia was not evaluated in this study. The primary safety and tolerability endpoint was the incidence of serious adverse events. The study subjects were enrolled from people who reported a history of varicella or resided in a VZV endemic area for ≥30 years. The study defined “endemic area” as an area where varicella was a common childhood disease. In the United States, VZV infection in people aged >50 was >99% [13]; therefore, the restriction of “endemic area” may be less essential and the study findings might be generalized to other areas in study regions.
The trial accrued 129 herpes zoster cases. In total, 111 were diagnosed by polymerase chain reaction assay and 18 by a clinical evaluation committee consisting of 6 experts. Although the overall efficacy and safety result was less likely biased by the small proportion of cases (14%) without laboratory testing, diagnoses of these cases assisted by serologic testing might be more convincing when lesion swabs were unavailable. The incidence of serious adverse events was similar between groups. Zostavax significantly reduced the incidence of herpes zoster and the mean severity-by-duration score. Among herpes zoster cases, the mean severity-by-duration score was similar between groups, whereas the duration of both pain and rash that might also be clinically interested was not mentioned. On the basis of this trial’s results, the FDA approved Zostavax vaccine to prevent shingles in individuals aged 50–59 [14]. However, the CDC has not recommended routine use of this vaccine [15].

Several points need to be considered before a universal recommendation for people aged 50–59 can be given: (1) The reported injection-site adverse events in Schmader et al’s study [12] were more common among vaccine recipients (63.9%) than placebo recipients (14.4%). These adverse events were also more common among vaccine recipients (48.3%) than placebo controls (16.6%) in the trial conducted in people aged ≥60 [9]. The proportion of injection-site adverse events among vaccine recipients in Schmader’s study was about 1.3 times higher than that in the previous trial, suggesting that younger individuals might be more likely to experience Zostavax’s injection-site reaction. (2) The efficacy of Zostavax for postherpetic neuralgia in people aged 50–59 still needs evaluation, which can be achieved via postmarketing surveillance research. (3) Data on economic burden of herpes zoster have been available for people aged ≥60 [11] but not for people aged 50–59. People in their 50s are still working; thus, the loss of work time and productivity caused by herpes zoster is noteworthy. (4) The cost-effectiveness for universal vaccinations needs to be addressed because the incidences of herpes zoster and postherpetic neuralgia were relatively low in people aged 50–59 as compared with people aged ≥60, particularly among those who are immunocompetent.

The varicella vaccine, which used the same strain as Zostavax, was approved in the United States in 1995. The impact of varicella vaccination on population prevalence of shingles has been widely concerned [16], and the CDC has pointed out that Zostavax is not recommended for people of any age who have received varicella vaccine [11]. A very recent population-based study in Canada showed that the incidence of herpes zoster decreased moderately for children <9 years who have previously been targeted for varicella vaccination [17]. Assuming that the reduction in herpes zoster related to varicella vaccination could persist to adolescence or even adulthood, an eventual decline in the number of shingles should be present, leading to less need for herpes zoster vaccine. There is a need to investigate the long-term impacts of varicella vaccination on the incidence of herpes zoster among those who have received varicella vaccine. Moreover, Zostavax vaccination has currently been targeted toward immunocompetent older people. To develop a vaccine targeted toward immunocompromised individuals, who are more susceptible to the reactivation of VZV, should have much more practical significance.

Note

Potential conflicts of interest. All authors: No reported conflicts.

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References