EDITORIAL

Preventing Shingles and Its Complications in Older Persons

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In the United States each year, herpes zoster, or shingles, develops in half a million people 60 years of age or older. Although the symptoms are often mild in younger persons, the risk for serious complications of herpes zoster, including postherpetic neuralgia, ocular involvement, and central nervous system disease, increases with advancing age.[1] The rising age-specific incidence of shingles and the aging population in the United States are likely to contribute to additional shingles-associated morbidity in coming years.[2] The prevention of herpes zoster and its complications in older persons will improve quality of life and should be a public health priority.

Since 2008, the U.S. Advisory Committee on Immunization Practices has recommended that all immunocompetent persons 60 years of age or older receive a single dose of a live attenuated herpes zoster vaccine (Zostavax).[1] In a large, placebo-controlled trial, the efficacy of this vaccine against herpes zoster was 51.3%, and the efficacy against postherpetic neuralgia was 66.5%.[3] Further follow-up of participants and postmarketing studies have confirmed the effectiveness of the vaccine and have documented declines in the efficacy of the vaccine over time.[4] Among 176,078 members of Kaiser Permanente who were 60 years of age or older and matched controls, the effectiveness of the live attenuated vaccine against herpes zoster decreased from 68.7% (95% confidence interval [CI], 66.3 to 70.9) in the first year after vaccination to 4.2% (95% CI, –24.0 to 25.9) in the eighth year.[5] These data, coupled with information on the immunogenicity of booster doses of the vaccine, will inform recommendations regarding the need for a subsequent dose or doses.[6]

In this issue of the *Journal*, Cunningham et al. report on the efficacy of two doses of an investigational, adjuvanted herpes zoster subunit vaccine (HZ/su) in immunocompetent persons 70 years of age or older.[7] This trial, involving 13,900 persons, was conducted concurrently with a previously reported trial involving persons 50 years or age or older in which the same vaccine and schedule were used.[8] The vaccine contains a recombinant varicella–zoster virus (VZV) glycoprotein E with a novel adjuvant ($AS01_B$) designed to improve CD4+ T-cell–mediated immune responses, which are thought to be important in preventing the reactivation of latent VZV. A lower dose of this adjuvant is used in a malaria vaccine that was approved in 2015 by the European Medicines Agency for children living in areas in which malaria is endemic.

In 2015, the efficacy of HZ/su against herpes zoster was reported as 97.2% (95% CI, 93.7 to 99.0) among participants 50 years of age or older and as 97.9% (95% CI, 87.9 to 100.0) among participants 70 years of age or older during a mean follow-up period of 3.2 years.[8] In the current trial, during a mean follow-up period of 3.7 years, the efficacy against herpes zoster was 89.8% (95% CI, 84.2 to 93.7) in persons 70 years of age or older. Efficacy was similar among participants who were 70 to 79 years of age and those who were 80 years of age or older, and it was maintained for the duration of the trial. For the outcome of postherpetic neuralgia, the investigators included the participants who were 70 years of age or older from both trials, and they report an efficacy of 88.8% (95% CI, 68.7 to 97.1).

Given the limited efficacy and duration of Zostavax, newer vaccine formulations with improved efficacy are welcome. Although the higher point estimates of efficacy with the HZ/su vaccine

are encouraging, the direct comparison of results from different trials is problematic. For example, in the pivotal trial evaluating Zostavax, the incidence of postherpetic neuralgia in the control group was higher than that in the control group in the HZ/su trial, which may indicate that the Zostavax efficacy trial included a more frail population, more active surveillance, or the use of a more sensitive case definition. A major benefit of the HZ/su vaccine as compared with Zostavax appears to be retention of high efficacy against herpes zoster and postherpetic neuralgia in the oldest age groups and over time. Continued follow-up of the vaccinated cohorts is warranted.

Although the safety profile regarding serious adverse events reported in the trials of HZ/su was reassuring, a full understanding of less common serious side effects will be known only as larger and more diverse populations are vaccinated. This is particularly pertinent given the new adjuvant included in this vaccine. It is worth noting that the short-term reactogenicity with this adjuvanted vaccine is higher than with other adult vaccines. In the first 7 days after vaccination, 79.0% of vaccine recipients, versus 29.5% of placebo recipients, reported local or systemic reactions, and 11.9% of vaccine recipients, versus 2.0% of placebo recipients, reported that their reactions were severe enough to prevent normal activity. It is remarkable that few participants declined the second injection, but whether adherence would be similar in a different population, especially one that included more frail older adults, is unknown.

Policy deliberations regarding the HZ/su vaccine will need to include consideration of how these trial data will translate into routine conditions of use. The HZ/su trials reported data on participants who received two doses of vaccine — therefore, the efficacy of a single dose, or of two doses given on a different schedule, is not known. Persons with a history of herpes zoster or of herpes zoster vaccination were excluded from these trials, so the benefit of the vaccine in those populations is uncertain. Ultimately, HZ/su may provide an option for immunocompromised persons who are at high risk for herpes zoster and its complications and are unable to receive the live attenuated vaccine. This would be a major advance in efforts to prevent herpes zoster.

Despite the 2008 recommendations for the zoster vaccine, by 2014 only 27.9% of adults 60 years of age or older reported being vaccinated.[9] In the early years after vaccine approval, supply constraints limited uptake. In more recent years, the supply has been sufficient, and the reasons for the continued poor uptake include provider challenges (e.g., cost, storage of the frozen formulation, and complex Medicare reimbursement), limited public awareness of the disease and vaccine, a lack of requirements for adult vaccination, and the focus on acute medical care over prevention among practitioners caring for adult patients.[10] Although HZ/su may address some of these issues, such as easier storage requirements for a nonreplicating product, it will have its own challenges, including the two-dose schedule and the higher reactogenicity. Thus, the full public health value of herpes zoster vaccines will not be realized unless we identify and address barriers to delivery and uptake.

Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

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DOI: 10.1056/NEJMe1610652