Infection with varicella-zoster virus (VZV) causes considerable damage even before therapy can be initiated. Moreover, current therapeutic options are not completely effective. They do not reliably prevent postherpetic neuralgia (PHN), which, once established, is difficult to treat. Taken together, these observations strongly suggest that the most practical approach toward managing herpes zoster is prevention through vaccination.

In the 1960s, Hope-Simpson1 presented a hypothesis as to the biology and pathophysiology of zoster. During childhood varicella (chickenpox), viral latency is established in the dorsal root ganglia and persists for the individual’s lifetime. Both cellular and humoral immunity are also established.

This latent virus is constantly trying to reactivate, but the cell-mediated immunity maintains viral latency and prevents reactivation. However, cell-mediated immunity to VZV progressively declines with age, eventually falling below a threshold level necessary to prevent viral reactivation, leading to replication of the virus and subsequent zoster outbreak. Reduced immunity occurs despite periodic boosts from either exposure to chickenpox or an attempt of the latent virus to reactivate. These boosts prevent immunity from falling below the critical level and thus delay the reactivation of the virus.

This process explains why the risk of herpes zoster increases with advancing age and why there is an increased risk in immunosuppressed populations. Also, zoster itself results in a boost in the immunity to VZV—usually to a level higher than the boosts resulting from exposure to chickenpox or contained reversions. This could explain why recurrences of zoster are rare. However, as life expectancy is increasing, second and third cases of shingles are being observed more often.

A hypothesis was developed stating that if zoster vaccine live boosts cell-mediated immunity to the same level that is observed after shingles, then perhaps a subsequent zoster outbreak could be prevented or attenuated.2 This is a novel strategy in vaccine development.

Vaccines are usually given to individuals who have never been exposed to the targeted agent (eg, varicella vaccine). In the case of the zoster vaccine, however, immunization is targeting a virus that the individual has already been exposed to—in fact, a virus that is already present in the individual. The herpes zoster vaccine is also different from other vaccines in that its goal is not to induce new immunity, but to boost an already present cell-mediated immunity that prevents or at least reduces reactivation and multiplication of a latent virus dormant in the sensory ganglia.

The virus used to develop the zoster vaccine was the same as that used in the varicella vaccine: the Oka strain of attenuated VZV, originally developed by Takahashi in the early 1970s.

For zoster vaccination, the production method was modified to yield a more potent, higher titer vaccine, as pilot studies3-5 demonstrated that more vaccine was needed to produce sufficient cell-mediated immunity in older individuals with preexisting immunity who are less responsive immunologically than younger vaccine recipients.

The Shingles Prevention Study

The Shingles Prevention Study was a Cooperative Studies Program conducted through the US Department of Veterans Affairs, are summarized. Also provided are general recommendations and contraindications for the use of zoster vaccine live among patients aged 60 years or older.

However, when examining the incidence of zoster in different age cohorts, a 63.9% reduction was observed among the youngest group studied (ie, ages 60 to 69 years). In the sample population aged 70 years or older, a 37.6% reduction in incidence rates was recorded. Among the study’s oldest cohort, those aged 80 years or older, an 18% reduction was measured.

Thus, it appears that the vaccine is most effective in preventing zoster infection for individuals aged between 60 and 69 years. It prevents zoster infection approximately two thirds of the time in this age group, and only one third of the time for older individuals (ie, aged 70 years or older) (Figure 1). These results suggest that for maximum effectiveness in disease prevention, zoster vaccination is best implemented at age 60 years.

Burden of Illness—Among subjects in whom herpes zoster was diagnosed during the Shingles Prevention Study, the burden of illness (BOI) was measured using a subjective pain questionnaire intended to determine disease severity. Subjects with a suspect rash were asked to rate the amount of pain they experienced in the previous 24 hours. The questionnaire was used from rash onset and during follow-up for at least 6 months, allowing researchers to collect enough data to generate a pain-duration score (ie, area under the curve), a primary endpoint of the study.

Questionnaire results demonstrated a 61% BOI reduction with the experimental vaccine as compared to placebo, a statistically significant difference (Figure 2).

When the vaccine effectiveness was compared among the age-defined

cohort, there was very little difference in disease severity ratings assigned by members of the youngest group. Among the cohort older than 70 years, disease severity increases progressively with age in both study groups—but most dramatically in the placebo group. Thus, while the vaccine becomes less effective in disease prevention as patient age increases, it becomes more effective in reducing disease severity.2

**Postherpetic Neuralgia**—The effect of zoster vaccine live on the incidence of PHN was also examined in this study.2 Postherpetic neuralgia was defined as pain continuing or starting 90 days after rash onset that is rated at 3 or higher on a self-reported subjective scale of 0 to 10.

Results from the Shingles Prevention Study2 demonstrated that, compared to placebo, the vaccine reduced PHN incidence by 66.5% overall, 65.7% in subjects aged 60 to 69 years, and 66.8% in those aged 70 years and older. Thus the vaccine reduced the occurrence of PHN by about two thirds regardless of age (Figure 3).2

**Vaccine Safety Profile**—In a comparison of the placebo and vaccine groups, there was no difference in any of the serious adverse events reported, whether examined by diagnosis or by body system. Likewise, mortality rates were essentially identical between study groups during the Shingles Prevention Study.2 Moreover, there were no statistically significant differences between groups with regard to vaccine-related severe events. Two such cases occurred in the vaccine group, three in the placebo group.2 However, local reactions, generally minor, were common enough among vaccine recipients to result in a statistically significant difference.

**Zoster Vaccine Live Recommendations and Guidelines**

As a result of promising results reported in the Shingles Prevention Study,2 zoster vaccine live was approved by the US Food and Drug Administration in May 2006 for the prevention of herpes zoster in immunocompetent individuals aged at least 60 years. Soon thereafter, the Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention (CDC) recommended that this vaccine be administered routinely to all individuals aged at least 60 years. One year later, the CDC included the herpes zoster vaccine in the adult immunization schedule. Most recently, in May 2008, the CDC followed up their recommendations with a definitive release that confirmed zoster vaccine should be given routinely to all patients older than 60 years who do not...
have specific contraindications—including patients with chronic medical conditions and those who have already had herpes zoster infection.

Contraindications to zoster vaccine live include a history of anaphylactic reaction to any of the components of the vaccine, immunodeficient states, the use of immunosuppressive therapies, active untreated tuberculosis, known or suspected pregnancy, and any current serious illness (Figure 4). Although human immunodeficiency virus infection per se is not a contraindication for vaccination, AIDS with a CD4 count below 200 or with active opportunistic infections is.

In addition, vaccinations may need to be delayed as a result of illness or modifications to pharmacotherapeutic regimens may be required prior to administration of the herpes zoster vaccine. For example, it is recommended that individuals be vaccinated before beginning immunosuppressive chemotherapy. In addition, the long-term use of antiviral agents for herpes-simplex virus should be stopped before vaccination with the zoster vaccine, as they will interfere with viral replication.

In summary, according to the Shingles Prevention Study, zoster vaccine live leads to a 51% reduction in the incidence of herpes zoster infection and a 61% reduction in BOI. The vaccine was most effective in disease prevention among the youngest study cohort (60–69 y). It was most effective in reducing disease severity in the older cohort (≥70 y). Overall, zoster vaccine live was determined to be relatively safe, and it effectively reduced the incidence of PHN by about two thirds in all age groups.

Figure 4. Contraindications and patients for whom the zoster (shingles) vaccine is not recommended. (See http://www.cdc.gov/vaccines/pubs/vis/downloads/vis-shingles.pdf and http://www.cdc.gov/mmwr/PDF/rr/rr5705.pdf for more information.) *Zoster vaccine live is not indicated for women of child-bearing age. †Individuals with a minor illness (eg, common cold) may be vaccinated. Zoster vaccine live should not be provided to patients with a moderate or severe illness (ie, body temperature, 101.3°F); these patients should be encouraged to wait until full recovery before vaccination.

References