

Varicella Zoster Virus Redux

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IN MAY 2008, the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention in the USA recommended the routine administration of a live-attenuated high-potency varicella zoster vaccine to all adults over 60 years of age without specific contraindications, for the prevention and attenuation of herpes zoster (HZ).¹ Nevertheless, many physicians still consider this vaccine to be of marginal value. This is not a reasonable conclusion. This short article reviews available data.

ACUTE HZ (SHINGLES) is a common and miserable disease, particularly in people over 50 years of age. It produces 3–4 weeks of pain, pruritus and generalized malaise which negatively impact quality of life (QoL) significantly, despite antiviral and analgesic use.² Chronic complications of zoster, such as post-herpetic neuralgia (PHN), which are increasingly common when zoster occurs in people of advancing age, are often refractory to treatment and complicated by side-effects (especially in a geriatric population with other medical problems). PHN has an even bigger impact on QoL than acute zoster, and can last for years, if not decades.³ It is therefore logical to try and prevent this disease or reduce suffering for affected patients.

How effective is the recently licensed vaccine? Most of the data available come from the Shingles Prevention Study (SPS).⁴ This was a multicentre, randomized, double-blind trial that compared the effect of a zoster vaccine with placebo in adults >60 years of age on the incidence and severity of HZ and PHN, over an average of 3.1 years. Diagnosis of HZ was made primarily by polymerase chain reaction testing. The experimental vaccine reduced the burden of illness (using a composite end-point that is sensitive to both HZ severity and incidence) by 61%. HZ severity was determined by a pain questionnaire, administered repeatedly over 6 months from the onset of a suspect rash. In vaccinated patients, the overall decrease in HZ incidence was 51%, a figure that was even lower in the older cohort, which suggested that a good deal of the efficacy of this vaccine was achieved by attenuating of HZ rather than preventing it entirely. These data are presented in the original manuscript⁴ but are absent from the package insert (PI)⁵ which lists just the decrease in incidence of HZ following vaccination.

The dramatic effect of the vaccine on pain scores following HZ is illustrated by looking at those individuals with scores >600 (equivalent to 2 months of 'the worst pain imaginable') in the SPS. Only 22% of these patients had received the experimental vaccine.⁶ Similarly, there were 27 subjects who received the vaccine whose HZ pain subsequently met the definition of PHN compared with 80 patients in the placebo group – a reduction of about two-thirds.⁴ Again, these data are not reflected in the PI, which mentions only the reduction in PHN among subjects who actually had HZ. Follow-up in the SPS approached 5 years (though with decreasing numbers in the later years of follow-up). Vaccine efficacy for burden of illness as well as incidence of both HZ and PHN was essentially maintained in Years 2–4.⁷ Vaccine efficacy for all end-points decreases as a function of age at

vaccination, but remains >40% for all but the actual incidence of HZ in vaccinees over 79 years of age in the SPS.⁸ Long-term persistence studies suggest that protection against HZ continues at least through Year 7.⁹

Safety evaluation in the SPS showed little difference in the two subject groups.⁴ Deaths were virtually identical, at 4.1% from the day of vaccination to the end of study and 0.1% in the first 6 weeks following vaccination. Serious adverse events (SAEs) occurring in the first 6 weeks were also essentially identical in the two study groups at 1.4%. Exhaustive re-examination of these SAEs by both body systems and diagnosis groups showed no significant differences.¹⁰ Local reactions, similar to those produced by other vaccines, did occur significantly more often in the vaccine recipients. A statistically significant increase in SAEs and some cardiovascular events in the vaccine group, which was seen in a small non-randomized safety substudy, were not confirmed in the study as a whole.⁴

The ACIP now includes the HZ vaccine in the recommended adult immunization schedule at 60 years of age.¹¹ An SPS immunology substudy demonstrated that cell-mediated immunity (CMI) response to the vaccine decreases as a function of the recipient's age, and suggests that vaccine efficacy might be greater in 50–59-year-old patients.¹² Vaccination of these individuals is approved in Europe (EPAR HC-674). Studies in 50–59-year-old patients designed to expand the age criteria of vaccination are now under way in the US (ClinicalTrials.gov number, NCT00534248). Vaccination is recommended even if the recipient has already had shingles, primarily on pragmatic grounds:¹ about 20% of the diagnoses of prior HZ are probably incorrect¹³ and vaccination of individuals with previous HZ does not appear harmful.⁷ Recent studies also suggest that second attacks of HZ are more frequent than the 2–5% figure derived from older literature indicates, perhaps due to longer life expectancy.^{14,15} Since the SPS immunology substudy suggests that varicella zoster virus-specific CMI response following HZ is comparable with that following vaccination¹² and the effective inoculum is much greater, it seems reasonable to wait at least several years following HZ before vaccinating.

The ACIP has recently released extensive recommendations for using the zoster vaccine.¹ Specific guidelines are given for the degree of immunosuppression beyond which vaccination is not advised. These are based on information discussed by expert panels, since immunocompromised individuals were specifically excluded from participation in the SPS.⁴ For example, vaccination of HIV-infected individuals is permissible as long as they do not meet the criteria for AIDS, and specific dosages are also given for corticosteroids and drugs such as methotrexate. No recommendations are given for recombinant immunomodulators or mediators. Guidelines are presented for malignancies, chemotherapy, antivirals and transplants. These may be conservative since potential vaccinees have pre-existing antibody, vaccine virus is quite attenuated and it is still sensitive to antivirals. Susceptible children with leukaemia in remission can be safely vaccinated against varicella as

long as chemotherapy and steroids were stopped 1 week before to 1 week after administration.¹⁶

The ACIP release summarizes several studies of the cost-effectiveness of this vaccine. The US\$ figure for Quality Life Years gained is quite variable depending on the assumptions for vaccine efficacy, cost, duration of protection and disease incidence. None of these models considers the pain and suffering of HZ and its complications. Nevertheless, the numbers are comparable with accepted clinical interventions.¹

The HZ vaccine is not perfect. It does not prevent shingles in all recipients, particularly older individuals; it does reliably reduce the severity of the zoster-related disease in this cohort, however, and reduces the incidence of PHN by two-thirds in everyone.⁴ HZ is a painful disease and its complications are life-altering and difficult to treat.

The recently licensed HZ vaccine is a good pre-emptive measure that should be used whenever possible.

Conflicts of Interest

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Key Paper

Measurement of varicella-zoster virus (VZV)-specific cell-mediated immunity: comparison between VZV skin test and interferon-gamma enzyme-linked immunospot assay.

Sadaoka K, Okamoto S, Gomi Y, Tanimoto T, Ishikawa T, Yoshikawa T *et al*. *J Infect Dis* 2008;**198**:1327–1333.

Cell-mediated immunity (CMI) is critical for the prevention and control of varicella-zoster virus (VZV)-related disease. To assess CMI to VZV, varicella skin tests and interferon-gamma enzyme-linked immunospot (ELISPOT™) assays were performed in healthy volunteers and the results were compared. In total, 151 subjects were examined: 16 aged 20–29 years; 26 aged 30–39 years; 18 aged 40–49 years; 73 aged 50–59 years; and 18 aged 60–69 years. All were seropositive by a glycoprotein antigen-based enzyme-

linked immunosorbent assay (gpELISA). Skin test reactivity was significantly correlated with the ELISPOT™ count, and both decreased with increasing age, indicating an age-dependent decline in CMI to VZV. In contrast, the antibody titre obtained by the gpELISA did not correlate with skin test reactivity. The results suggest that the skin test and ELISPOT™ assay are both reliable for assessing CMI to VZV and can easily be applied to screen individuals susceptible to the development of herpes zoster.