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Positive implications of new data from recent varicella and zoster vaccines trials

A focus on the future was the theme of the 12th Annual Meeting of the IHMF[®] held from 28th to 30th October 2005 in Lisbon, Portugal.



Myron Levin ■

Aptly, the Martin Wood Memorial Lecture given by Professor Myron J Levin of the University of Colorado School of Medicine, USA, reviewed new information pertinent to childhood varicella zoster virus (VZV) vaccination to prevent varicella and the recent investigation of a vaccine to prevent herpes zoster in adults aged 60 and older. These data have exciting implications for the future management of VZV infections and their impact on healthcare utilization.



Associação de Turismo de Lisboa

Lisbon, Portugal – host city of the 12th Annual Meeting of the IHMF[®]

Varicella vaccination dramatically reduces varicella disease burden

The introduction of routine varicella vaccination in the USA has dramatically reduced the number of varicella cases. In fact, vaccination has had positive effects on all aspects of the epidemiology of varicella, with annual epidemics disappearing and herd immunity being observed.

Routine varicella vaccine coverage in the USA has increased steadily according to expectations. The National Immunization Survey conducted by the CDC documented that, between 1997 and 2003, coverage among children aged 19–35 months increased from 26% to 85%. Professor Levin said that, as a result, the number of varicella cases from 1995 to 2004 reported by the Varicella Active Surveillance Project declined by 83% in Antelope Valley, California, and by 93% in West Philadelphia, Pennsylvania (Figure 1). The greatest reduction in varicella incidence was mainly in 1–4- and 5–9-year olds targeted by the

vaccination programme. Importantly, this marked decline was observed not just in those vaccinated, but also in adults and children too young to be immunized, indicating the development of herd immunity.

Routine vaccination has also had a substantial impact on reducing the number of deaths due to varicella, continued Professor Levin. Compared with the average number of under 50-year-olds dying of varicella between 1990 and 1994, deaths from 2001 to 2002 declined by 87%. Furthermore, he said that hospitalization rates for varicella have decreased from about 3 per 100 000 population in 1995 to 0.6 per 100 000 in 2004 in the surveillance sites.

Summarizing the significant social gains achieved by universal immunization against varicella, Professor Levin said that, in the USA alone, the number of varicella cases has fallen by 3.4 million, decreasing hospitalizations by 9600 and saving 75 lives

Figure 1. Annual varicella cases reported by the Varicella Active Surveillance Project from Antelope Valley, California and West Philadelphia, Pennsylvania (Seward *et al.* *JAMA* 2002; **287**: 606).



compared with an unvaccinated population. This has resulted in considerable medical cost savings. In fact, since the introduction of varicella vaccination, Professor Levin cited a study indicating that the total estimated direct medical expenditure for varicella hospitalizations and ambulatory visits in the USA has declined by \$62.8 million.

Two doses for a more robust immune response

Professor Levin explained that although varicella vaccination has been a major success, there are two possible threats to confidence in the USA's national vaccination programme – breakthrough disease and the impact of VZV vaccination on the age-specific incidence of herpes zoster.

Breakthrough disease is an epidemiological consequence of a highly immunized paediatric population, said Professor Levin. It is usually mild with fewer than 50 lesions and of shorter duration than the 'wild-type' infection, although the rash may have an atypical appearance. Despite the fact that the vaccine has remained >95% effective in preventing typical varicella after exposure, he said that breakthrough disease affects about 15% of immuno-competent vaccinees when their immune response is in a range that makes them susceptible to VZV infection. This phenomenon is partly

due to a suboptimal response to the vaccine, but also raises the question of whether immunity to the VZV vaccine will wane over time.

Varicella outbreaks have been reported among school children despite a 96–100% vaccination coverage, highlighted Professor Levin. It therefore appears that one dose of vaccine does not necessarily provide sufficient herd-immunity

levels to prevent school outbreaks. In terms of the epidemiology of herpes zoster in adults, in the past, re-exposure to VZV in the community appeared to provide protection against shingles by boosting VZV-specific cellular immune responses. Indeed, a sex and practice-matched, case-controlled UK study has shown that re-exposure to VZV via social and occupational contact with children, or exposure to people with varicella, seems to protect against herpes zoster. Thus, explained Professor Levin, as VZV is removed from the general population by vaccination, the chances of VZV exposure to boost immune responses become fewer.

Studies using a second dose of varicella vaccine to overcome the potential problem of vaccine failure, whatever the underlying cause, have been encouraging, continued Professor Levin. They indicate that two doses produce a more robust immune response and, hence, are likely to provide better protection against VZV than one dose. ■

Vaccination prevents shingles and post-herpetic neuralgia

A large, landmark trial of a live, attenuated, Oka/Merck zoster vaccine has shown that vaccination of older adults can prevent both herpes zoster, the acute morbidity associated with it, and its debilitating complication, post-herpetic neuralgia (PHN). According to Professor Levin, this vaccine should help the 36.5 million people in the USA aged ≥60 years who currently have VZV latent in their sensory ganglia and are, thus, at risk of developing shingles.

Herpes zoster causes considerable morbidity, which greatly impacts an individual's quality of life, explained Professor Levin. The most debilitating and common complication of

shingles is the associated pain, he said, which may be both acute and chronic and can persist for months or even years. As established herpes-zoster-associated pain is notoriously difficult to manage effectively, prevention of shingles should be a fundamental objective.

Shingles prevention study tests immunization hypothesis

Details of this major study, known as the Shingles Prevention Study (SPS), were described by Professor Levin. The study, led by the Department of Veterans' Affairs, supported by the National Institute of Allergy and Infectious Diseases (part of the National Institutes of Health) and Merck & Co. Inc., was conducted to

test the hypothesis that immunization of older persons with an investigational zoster vaccine would boost the age-related decline in cell-mediated immunity to VZV, thereby providing protection against herpes zoster and PHN.

The SPS was a controlled trial of the zoster vaccine conducted at 22 sites in the USA. With a median dose of 24 600 pfu (18 700–60 000 plaque-forming units [pfu]/dose) the zoster vaccine administered contained at least 14 times more VZV antigen than the minimum potency of the childhood varicella vaccine.

Endpoints

The pre-specified endpoints of the study were the burden of illness (BOI) and the incidence of PHN. The burden of illness due to herpes zoster represented the summation of the pain experience of all subjects in the trial who developed herpes zoster and reflects frequency of shingles, pain severity and pain duration. The severity of illness for each individual case of zoster, a component of the BOI, was determined by the Zoster Brief Pain Inventory (ZBPI). This is a validated measure that captures herpes zoster pain and discomfort, the latter being unique noxious skin sensations characteristic of herpes zoster that are not always considered as pain by patients with shingles.

The incidence of PHN was defined as pain associated with herpes zoster that was rated as 3 or more on a scale ranging from 1 ('no pain') to 10 ('pain as bad as you can imagine') and persisted or appeared >90 days after the onset of the rash.

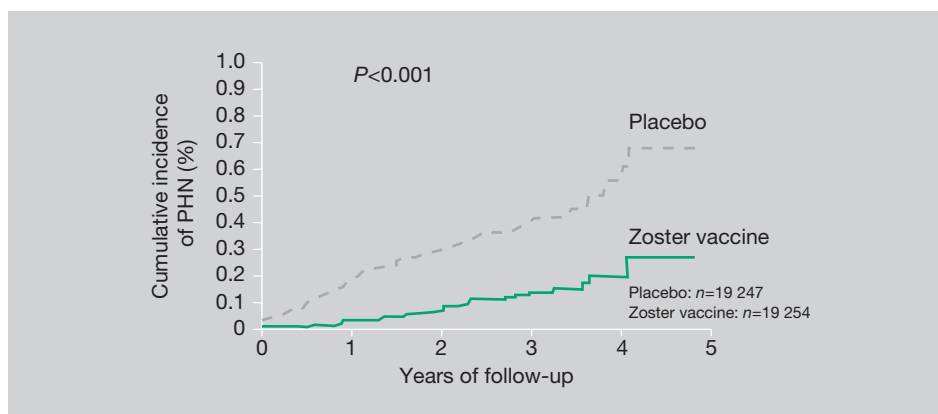
Results show efficacy of zoster vaccine

The median age of the subjects was 69 years; about 40% were ≥70 years of age and nearly 7% were ≥80 years old. More than 95% of the subjects were successfully followed up; <1% were lost to follow up. A total of 1308 suspected cases of herpes zoster were evaluated. Of these, 957 cases were confirmed to be shingles (315 among vaccine and 642 among placebo recipients) and 107 cases of PHN were confirmed (27 among vaccine and 80 among placebo recipients).

According to Oxman *et al.* (Oxman MN *et al.* *N Engl J Med* 2005;**352**: 2271) the vaccine significantly reduced the burden of illness due to herpes zoster by 61.1% and the incidence of PHN by 66.5% compared with placebo ($P<0.001$) (Figure 2). The incidence of herpes zoster was reduced by 51.3% compared with placebo ($P<0.001$) (Figure 3). The overall incidence of herpes zoster per 1000 person years fell from 11.1 in the placebo group to 5.4 in the vaccine group.

Figure 2.

Zoster vaccination reduces the incidence of post-herpetic neuralgia (PHN). Reproduced with permission from Oxman MN *et al.* *N Engl J Med* 2005; **352**: 2271. © 2005 Massachusetts Medical Society.

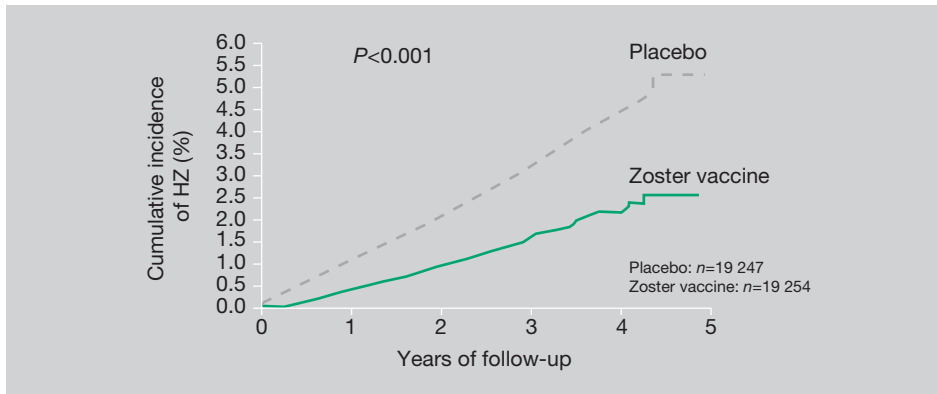


SPS design and methods

- Randomized, double-blind, placebo-controlled trial
- Enrolled 38 546 individuals aged ≥60 years
- Subjects received an injection of either the live, attenuated Oka/Merck strain-containing zoster vaccine or placebo
- Individuals were educated about the signs and symptoms of herpes zoster at enrolment
- Those who had a new rash or new unilateral pain suspected to be herpes zoster were urged to contact their study site immediately
- To identify and evaluate the severity of all cases of shingles that occurred in the study population as soon as possible after rash onset; subjects were actively followed-up for a median of 3.1 years after vaccination by calling the study's Automated Telephone Response System (ATRS) every month
- Cases of suspected herpes zoster were evaluated by clinical assessment by laboratory tests and an expert committee, and with the PCR assay of skin lesions having priority.
- Antivirals and pain control were provided as standard care.

Figure 3.

Zoster vaccination reduces the incidence of herpes zoster (HZ). Reproduced with permission from Oxman MN et al. *N Engl J Med* 2005; **352**: 2271. © 2005 Massachusetts Medical Society.



The zoster vaccine was efficacious in all age groups included in the study. When the results were stratified by age, the vaccine effect on the incidence of herpes zoster showed a tendency to be greater in younger subjects (60–69 years) (Figure 4). In this ‘younger’ group, the vaccine efficacy against herpes zoster was 63.9% and its efficacy against BOI was 65.5%, whereas, in the ‘older’ group (≥70 years), the vaccine efficacy against herpes zoster was 37.6% and its efficacy against BOI was 55.4%. These results suggest that the vaccine effect in ‘younger’ subjects is mediated mostly by preventing herpes zoster, whereas the effect in ‘older’ subjects is due to a combination of preventing and attenuating shingles.

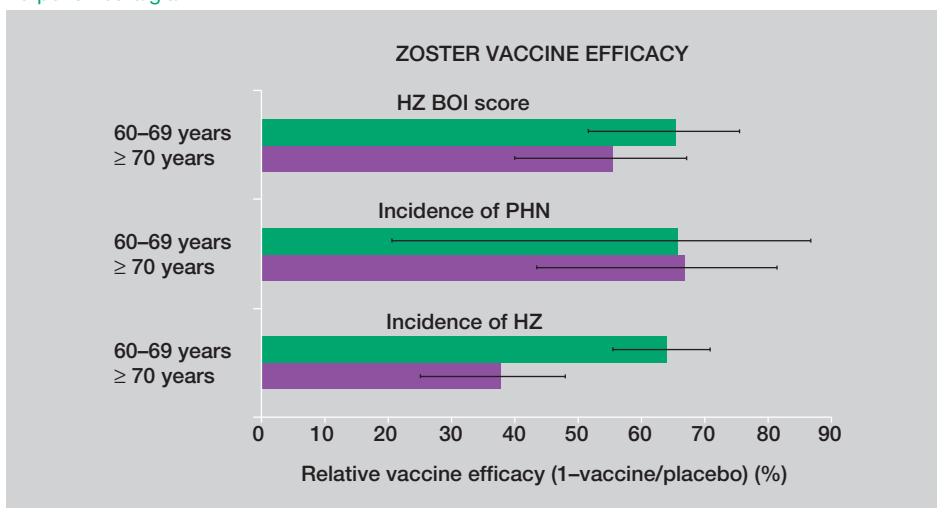
Importantly, the effect of the vaccine has persisted through the 3.1 years of follow-up, and 7500 of the original cohort are now being followed up for an additional period.

Positive implications of the SPS

According to Professor Levin, the SPS has shown that a vaccine exists that will safely prevent or attenuate herpes zoster in large numbers of older people, substantially reducing the morbidity associated with the condition. Furthermore, the zoster vaccine may be able to address any change in epidemiology of herpes zoster that results from universal vaccination to prevent varicella in children. ■

Figure 4.

Zoster vaccine efficacy stratified by age. HZ, herpes zoster; BOI, burden of illness; PHN, post-herpetic neuralgia.



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