Varicella zoster virus vaccines: effective, but concerns linger

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ABSTRACT • RÉSUMÉ

Both varicella and herpes zoster (HZ) can cause severe disease in certain age groups. The cell-mediated immune (CMI) response to the varicella zoster virus (VZV) is critical in preventing a recurrence of VZV. The varicella vaccine has markedly decreased the morbidity and mortality associated with varicella, but concerns linger about the cost and frequency of vaccine administration and the long-term effects on both adult varicella and HZ epidemiology in the individual and in the population. Therapy for HZ with an antiviral is only partially effective. A zoster vaccine is now available that boosts the CMI immune reaction to VZV in individuals and has proven safe and partially effective in preventing both HZ and post-herpetic neuralgia. Concerns about the zoster vaccine include the costs of administration, the overall health-care costs to society, and the acceptance and implementation of the vaccine in the elderly. Because of altered immune responses to VZV as a result of universal varicella vaccination it becomes even more compelling in the future to have a zoster vaccine ready to boost the CMI response to a sufficient level to prevent HZ. The 2 vaccines are intertwined in the future epidemiology of VZV disease.

La varicelle et le zona peuvent causer des maladies sévères à certains groupes d'âge. La réaction immunitaire à médiation cellulaire (IMC) à l'herpesvirus varicellæ (HVV) est déterminante pour prévenir la récurrence du virus. Le vaccin contre la varicelle a réduit de façon remarquable la morbidité et la mortalité associées à cette maladie, mais on se préoccupe toujours du coût, de la fréquence du vaccin et des effets à long terme sur la varicelle chez l'adulte et de l'épidémiologie du zona chez les individus et les populations. La thérapie antivirale du zona n'est que partiellement efficace, mais on dispose maintenant d'un vaccin contre la maladie qui renforce la réaction IMC individuelle et qui s'avère sûr et partiellement efficace pour prévenir le zona et la névralgie postherpétique. L'inquiétude face au vaccin contre le zona comprend le coût d'administration, le coût général des soins de santé à la société ainsi que l'acceptation et l'application du vaccin chez les personnes âgées. À cause de l'altération des réactions immunitaires au zona résultant de la vaccination universelle contre la varicelle, il devient encore plus contraignant pour l'avenir de disposer contre le HVV d'un vaccin qui portera la réaction IMC à un niveau suffisant pour prévenir le zona. Les 2 vaccins s'entrelacent dans la future épidémiologie de la maladie du zona.

Before the introduction of the varicella vaccine, almost every child in the United States had chickenpox (varicella), although the severity of disease varied. In some tropical countries, however, varicella zoster virus (VZV) exposure may only be 40%–50%.[1] In 1995, the United States became the first country to introduce a universal childhood vaccination program.[2] The vaccine (Varivax, Merck & Co, Inc, N.J.) received a high acceptance rate and has an excellent safety profile and high performance, resulting in a dramatically decreased rate of varicella morbidity and mortality.[3–6] About 2%–3% of healthy childhood vaccinees and 30%–40% of adult vaccinees experience breakthrough infection;[7] this form of varicella is less severe than primary varicella and frequently has an atypical presentation. In order to further prevent community transmission, however, the Advisory Committee on Immunization Practices since 2006 has recommended a 2-dose vaccination.[8]

Immune response and concerns about varicella vaccine

Although the live, attenuated Oka/Merck varicella vaccine was developed in Japan in 1974, approval in the United States took 20 years because of a continuing controversy regarding the costs of vaccination and revaccination, the duration of efficacy, and whether the vaccine could lead to an increase in both adult varicella and adult herpes zoster (HZ) in individuals, as well as in the population (herd immunity). Some countries have not implemented or have abandoned varicella vaccination programs, and other countries make it a choice.[9] In Canada, public health officials have recommended the varicella vaccine, but it is not mandatory, not offered for free in most provinces, and its acceptance has been low at about 21%.[10]

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A primary infection with either the wild-type or the vaccine-type VZV results in seeding into the ganglion during the viremia or through sensory nerves from the skin lesions, the identical virus recurring as zoster.[11] VZV-specific antibody levels provide an index of vaccine efficacy or confirm prior varicella disease,[12] but it is the VZV cell-mediated immunity (CMI) that provides protection of the individual against another episode of varicella and against a recurrence of its own latent VZV as HZ. Periodic exposures to persons with varicella, as well as periodic, sometimes asymptomatic, release of VZV from the ganglia, are both important mechanisms that provide a boost to CMI against VZV in individuals and the population. The vaccine virus can circulate in the community just as the wild-type virus to exogenously boost immunity of individuals, but the immunostimulatory potential of this vaccine virus is more modest.

After over a decade of use, there is no evidence that the pediatric varicella vaccination program is increasing varicella disease rates among older children and adults, the ones at greater risk of higher morbidity and mortality from varicella.[13] Because skin lesions develop in response to varicella vaccination in only 5%–7% of patients, the vaccines may result in a lower degree of ganglion population by the vaccine virus; thus, the frequency of zoster is anticipated and has been found in the early years after introduction of the vaccine to be lower among vaccinees than among persons who have had chickenpox.[14–17] As vaccine recipients age, the risk for and manifestation of Oka/Merck strain zoster in older persons at greater risk of zoster complications can be better determined.

The concern lingers, however, that varicella disease may be ameliorated in the young population at the expense of causing later onset of HZ in the elderly, at an age when there is higher risk of more severe complications, such as post-herpetic neuralgia (PHN). With fewer children currently having wild-type varicella, the lower incidence of periodic exogenous exposures of adults to wild-type varicella is expected to lead to decreasing CMI against VZV, resulting in an increase in HZ incidence especially among individuals under age 50. In elderly individuals, this decreased exposure, combined with natural decline in CMI to VZV, is expected further to increase the risk of HZ in this age group in future years.[18–22] The zoster vaccine is anticipated to become a substitute for this boosting effect. Ironically, the more effective the varicella vaccine is in reducing varicella, the more imperative is the need for an effective zoster vaccine as a means of boosting VZV-specific CMI responses.

At this stage, data are inconclusive regarding an effect of the varicella vaccination program on HZ epidemiology. Some studies show an increase and some show no increase, whereas other studies show a rising trend in HZ incidence even in the absence of a vaccination program.[16,23–28] The savings from reduced rates of hospitalization for varicella might be overshadowed by the increases in HZ hospitalization costs.[25] Mathematical models predict that by decreasing varicella exposures, the varicella vaccination program might increase the risk of HZ in the short and medium term (during the first 30–50 years of the vaccination program).[18,20,23,29] In the long term, as vaccinated cohorts age into older adulthood, the incidence of HZ is expected to decline to levels lower than in the prevaccine era because of the reduced tendency of vaccine virus strain, compared with wild-type virus, to reactivate.[14,30] But the United States is part of a global community that has not broadly accepted varicella vaccination; the future epidemiology of varicella and zoster, therefore, is somewhat muddled.

Recurrence of VZV as HZ disease

The lifetime risk of having HZ is estimated to be 30%; approximately 1 million cases occur annually in the United States.[24,27,31–34] The likelihood of infection with zoster is inversely proportional to the host's CMI to VZV, and the incidence may be increasing even in areas where the VZV vaccines have not been introduced. Zoster lesions contain high concentrations of VZV that can be spread by the airborne route and cause primary varicella in exposed susceptible persons, but zoster is far less contagious than varicella. Immunosuppression increases the risk of zoster, but the majority of cases still occur in the immunocompetent older population.[24,35–37] Zoster is frequently a mild disease, but there are increased risks with ophthalmic zoster and in the elderly because of the burden of PHN. The risks of both HZ and PHN increase with increasing age. Approximately 10%–18% of persons with HZ also have PHN, a HZ-associated pain syndrome that can last months or even years and has no consistently effective treatment.[27] Most of the burden of HZ and PHN is borne by the older individual in terms of pain and reduced quality of life, as patients exhibit reduced health status measures, increased health resource use, and impairment of physical, psychological, social, and functional performance.[38]

HZ treatment

Three drugs (acyclovir, famciclovir, and valacyclovir) are approved by the Food and Drug Administration for treatment of zoster in immunocompetent patients. Taken orally, the drugs reduce the duration of viral shedding and lesion formation, reduce the time to rash healing, and decrease the severity and duration of acute pain from zoster. All 3 drugs are exceptionally well tolerated and have minimal contraindications, although dose adjustments must be made in renal insufficiency. Valacyclovir and famciclovir show superior pharmacokinetic characteristics and simpler dosing regimens than acyclovir, but they are more expensive. As antiviral drugs are most effective when started within 72 hours of rash onset, early presentation is encouraged;[39] existing data suggest that a benefit might extend beyond this time period, and antivirals should be considered if pain is severe or lesions are progressive.[40,41] Although systemic

antivirals may lessen some of the complications of ocular zoster, there does not appear to be convincing or consistent evidence of the benefit of the systemic antiviral in preventing or treating the most severe complications of herpes zoster ophthalmicus, and major ocular complications still occur in many individuals given the recommended doses of systemic antiviral.

Two clinical trials have assessed the role of oral corticosteroids in combination with acyclovir for treatment of zoster and prevention of subsequent PHN.[42,43] A 3-week tapering course of corticosteroids, in combination with an oral antiviral agent, led to diminished acute zoster pain and decreased time to cutaneous healing, cessation of analgesic therapy, and return of uninterrupted sleep and normal daily activities. However, corticosteroids did not prevent the development of PHN. Corticosteroids are recommended for patients over the age of 50 if not contraindicated, and should be used with caution in patients with comorbid conditions such as diabetes

Immune status relation to HZ infection

Protection from HZ is maintained by boosts in CMI resulting from either periodic exposure to persons with varicella or by periodic release of VZV from the ganglia into the bloodstream. Before the introduction of childhood varicella immunization, adults who lived or worked with children were at lower risk of HZ than those adults with infrequent exposure to children.[21] After the introduction of the varicella vaccine, the immune boosts will be decreased, since exposure to the vaccine virus results in lower CMI boosts than exposure to wild-type virus, both as exogenous and endogenous exposures. Among the varicella vaccinees, however, the incidence of HZ is expected to be lower because there may be a lower degree of ganglion population by the virus (skin lesions only develop in a small number of vaccine recipients). On the other hand, the immune response to varicella vaccine may not be as long lasting as that to wild-type varicella infection.

HZ vaccine

Boosting VZV CMI through immunization has a strong biological rationale.[35,44,45] The United States Shingles Prevention Study was a large, randomized, double-blind, placebo-controlled study performed using a new live attenuated Oka/Merck vaccine (Zostavax, Merck & Co, Inc)[46,47] with a potency estimated to be 14 times that of the varicella vaccine. In this study, 38 546 subjects 60 years or older who had a history of varicella but no history of HZ were enrolled at 22 sites, and 95% of them completed the study with a mean follow-up of over 3 years. Subjects were randomly assigned to receive 1 subcutaneous dose of the vaccine or placebo. Overall, the vaccine reduced the burden of illness from HZ by 61.1% ($p < 0.001$) and reduced its incidence by 51.3% ($p < 0.001$). The duration of pain and discomfort among participants with confirmed HZ was significantly shorter in the vaccine group (21 days vs 24 days; $p = 0.03$), and the incidence of PHN was reduced by 66.5% ($p < 0.001$).

Table1—Queries about the herpes zoster vaccine (Zostrix)

Indications and advantages of vaccine For prevention of herpes zoster (HZ) in individuals 60 years of age and older. Lowers risk of HZ by 50%; for those who have HZ, prevents post-herpetic neuralgia (PHN) in 66%.
Vaccine use in patients under age 60 years The Shingle Prevention Trial[46,47] did not study this age group, but there is no reason to believe that the vaccine would be less safe or less efficacious in this group.
Contraindications to vaccine This live zoster vaccine is currently contraindicated in immunocompromised patients, children, and pregnant women, although studies are underway to answer questions about vaccination in these groups more specifically.
Duration of vaccine protection from herpes zoster Unknown, but no revaccination currently recommended.
Vaccine used to treat HZ No, zoster vaccination is not indicated to treat acute HZ, to prevent persons with acute HZ from acquiring PHN, or to treat ongoing PHN.
Vaccine in patients who have had HZ Yes. Although patients with recent HZ receive a cell-mediated immune boost, it is recommended that they receive the vaccine. This eliminates the need to sort through medical histories that may not be all that reliable.
Vaccine in patients who have not had varicella (varicella zoster virus [VZV]) Yes. It is likely that administration of the zoster vaccine to a VZV-seronegative adult will provide at least partial protection against varicella. No adverse events have occurred in those who have not had varicella.
Getting herpes zoster from the vaccine No. The vaccine was not found to induce cases of HZ. Approximately 0.3% demonstrate either a zoster-like or chickenpox-like rash after receiving the vaccine; polymerase chain reaction technique suggests that most reported episodes are from the wild-type recurrence, occurring by chance alone.
Zoster vaccine given concurrently with other vaccines Yes. Vaccination at age 60–65 years as part of a national program with influenza and pneumococcal vaccines would be convenient. Zoster vaccine, however, only needs to be administered once.
Ongoing research on zoster vaccine that may alter future recommendations Duration of zoster vaccine effect, use in immunosuppressed individuals, use in younger age groups, necessity for booster, the effect of varicella vaccine on HZ epidemiology, and the effect of the zoster vaccine on varicella epidemiology.

The zoster vaccine is now recommended for all persons aged >60 years who have no contraindications, including persons who report a previous episode of zoster or who have chronic medical conditions (Table 1). The vaccine should be offered at the patient's first clinical encounter with his or her health-care provider. It is administered as a single dose subcutaneously in the deltoid region of the arm.[48,49]

Live vaccines are usually contraindicated in immunosuppressed people. The safety and efficacy of the zoster vaccine has not yet been established in adults with HIV, with or without evidence of immunosuppression. However, there remains a large "gray zone" of mildly to moderately immunocompromised patients in whom the risk–benefit ratio for vaccination is not well defined. If a patient is going to be immunosuppressed in the future or is currently in remission, they might be considered candidates for the zoster vaccine.

Worldwide epidemiological data suggest that the ideal age for HZ vaccination might be at 50–55 years, the time at which the incidence of HZ begins to increase exponentially and a time when the individuals would mount a greater immune response to the vaccine.[32] The potential loss of environmental boosting of VZV CMI after the introduction of universal varicella vaccination may also become an impetus to shift the zoster vaccine to a younger age group.[50] On the other hand, since the duration of the zoster vaccine's effect is not yet known, early vaccination may increase the likelihood that a booster dose is required in later years.

Concerns and cost-effectiveness of zoster vaccine

Given that the zoster vaccine is currently only approved for adults aged 60 and over, in the next several decades the incidence of HZ may increase among those under 50, who will be less exposed to wild-type virus to boost their immunity. The economic burden of zoster in the elderly is substantial and includes direct costs attributed to health-care use and indirect costs attributed to losses in productivity from temporary or more permanent disability. In addition, much of the economic burden of zoster is borne by individual patients as reduced quality of life related to pain and suffering.

Health policy analysts have a different viewpoint to patients and individual physicians, since they must weigh many different variables in their recommendations, and there are many unknowns in the VZV vaccine programs.[51,52] Two key areas of uncertainty are the burden of disease associated with PHN, and whether the vaccine offers additional protection over and above the protection resulting from a reduced incidence of HZ. Cost-effectiveness depends heavily on the cost of the vaccine and on the age of those vaccinated. The long-term impact of vaccination in the general population remains unclear, and vaccination against HZ needs to be compared with other possible uses of health-care resources.

Several, but not all, studies have shown that the vaccine is likely to be cost effective.[51–54] A Markov cohort model to estimate whether routine vaccination of the elderly (60+) would be cost effective, when compared with other uses of health-care resources, suggests that vaccination of 65-year-olds is likely to be cost effective with a single-dose schedule but not with a double-dose schedule. The savings, in fact, would not be in the cost (because of the high cost of the vaccine) but, rather, in the reduction of the burden of illness.[55] Other cost-effectiveness studies suggest that it is more cost effective to vaccinate at a younger age, because the higher incidence of HZ among the elderly is offset by lower vaccine efficacy as age increases.[52,53] Others suggest that only at age 70 years do base-case cost-effectiveness ratios become satisfactory.[54]

The introduction of childhood varicella vaccination, however, could increase the incidence of HZ to such an extent that HZ vaccination would become more cost effective in the future.[18,21,56,57] Moreover, the introduction of a zoster vaccination could have an effect on the evaluation of the varicella program. The combined varicella and zoster vaccination programs need to be evaluated using a comprehensive cost-effectiveness model.

Zoster vaccine acceptance and uptake

For individuals, insurance coverage is variable in the U.S. Medicare Part B, which covers flu shots and pneumococcal vaccine, does not cover the shingles vaccine, but it is partially covered under the more complex and costly Part D. Pricing varies, but the total bill, including the doctor's fee, can come to several hundred dollars.

The zoster vaccine has not been incorporated well into preventive strategies in the United States. In a report published in 2009,[58] evaluating the year 2007, only 2% of those over age 60 years had received the zoster vaccine in the United States,[58] and 73% of respondents were unaware of the zoster vaccine. Only 78% stated that they would accept zoster vaccination if their doctor recommended it. So there are many barriers to acceptance, including patient awareness and physician recommendations, some of the latter having to do with storage and administration issues associated with this vaccine. For the possible benefits of the zoster vaccine to be realized, the vaccine must be widely used. Low uptake of other adult vaccinations suggests that this will not be easily achieved.

Varicella and zoster vaccine strategies for the future

Most analyses of the cost-effectiveness of the varicella vaccine have been modelled on the assumption that varicella vaccination would have no adverse effect on the epidemiology of the closely related disease HZ; this assumption, however, seems incorrect. Health officials need to devise a cost-effective universal varicella vaccination program in coordination with a zoster booster vaccine intervention strategy that exceeds the level of natural boosting

once occurring when wild-type varicella circulated in the community. International travel and immigration to the United States makes the situation even more complex as both wild-type and vaccine-type VZV continue to circulate or fail to circulate in the population. Because of the aging of the population, the fact that the zoster vaccine has not been recommended for administration to those under 60, and the demonstrated lack of adherence by older individuals to any vaccination program, the burden of HZ disease may not improve substantially for the population except by more education, acceptance, universal mandates, and effective implementation strategies.

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