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Zoster Vaccine Recommendations: The Importance of Using a Clinically Valid Correlate of Protection

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The report by Tseng et al. [1] that the efficacy of live attenuated Oka/Merck zoster vaccine (ZOSTAVAX®; zoster vaccine) is comparable in persons 60 years of age vaccinated concomitantly and non-concomitantly with 23-valent pneumococcal polysaccharide vaccine (PNEUMOVAX®23; pneumovax) is particularly important and noteworthy. This is because the ZOSTAVAX® Prescribing Information was revised in December 2009 to advise that these two vaccines, both recommended for older adults [2], “should not be given concurrently because concomitant use resulted in reduced immunogenicity of ZOSTAVAX®” [3]. This prohibition, which increased the already challenging task of delivering the recommended vaccines to older adults [4–7], was based on the results of “a double-blind, controlled clinical trial in which 473 varicella history-positive, herpes zoster history-negative adults, 60 years of age or older, with no history of invasive pneumococcal disease were randomized to receive zoster vaccine and pneumovax concomitantly ($N = 237$), or pneumovax alone followed 4 weeks later by zoster vaccine alone ($N = 236$). At four weeks post-vaccination, the varicella-zoster virus (VZV) antibody levels following concomitant administration were significantly lower than the VZV antibody levels following non-concomitant administration (GMTs of 338 vs. 484 gpELISA units/mL, respectively; GMT ratio = 0.70 [95% CI: 0.61, 0.80])” [8,9]. Both groups were well matched for age, gender, underlying medical conditions and therapies, and >98% were Caucasian. However, the concomitant group had a substantially higher mean VZV antibody titer at baseline than the non-concomitant group (GMTs of 192.2 and 150.5 gpELISA units/mL, respectively). No cause for this imbalance was identified, and it was attributed to chance, but it does raise questions regarding the validity of the study. The authors suggested that to avoid a potential decrease in VZV immunogenicity, zoster vaccine and pneumovax should not be given concomitantly [9], and this advice was incorporated into the December 2009 revision of the

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ZOSTAVAX® Prescribing Information, despite the recognition that simultaneous administration of recommended vaccines can minimize missed opportunities to vaccinate adults [9,10].

In the study by Tseng et al. [1], vaccinations and incident cases of herpes zoster at Kaiser Permanente Southern California between January 1, 2007 and June 30, 2010 were identified by electronic health records in persons 60 years of age or older. The study demonstrated that the incidence of herpes zoster after vaccination with zoster vaccine in the population receiving both zoster vaccine and pneumovax on the same day (concomitant group, $N=7187$) was comparable to that in the population receiving pneumovax within one year to 30 days prior to zoster vaccine (non-concomitant group, $N=7179$). Follow-up time, from the date of zoster vaccination until the occurrence of herpes zoster or June 30, 2010, whichever was earlier, averaged 1.72 years and 1.79 years, respectively. There were 56 incident cases of herpes zoster in the concomitant vaccination cohort (with 12,339 person years of follow-up), and 58 in the non-concomitant vaccination cohort (with 12,869 person years of follow-up), yielding a herpes zoster incidence of 4.54 (95% CI: 3.43, 5.89) and 4.51 (95% CI: 3.42, 5.83) per 1,000 person-years, respectively. The concomitant group were younger (mean age 67.6 versus 68.8), less likely to be female or Caucasian, had a lower prevalence of chronic diseases and less healthcare utilization than the non-concomitant group. However, in a fully adjusted analysis, the hazard ratio comparing the incidence rate of herpes zoster in the concomitant and non-concomitant groups was 1.19 (95% CI: 0.81, 1.74) and the cumulative risk of herpes zoster in the two groups by the Kaplan-Meier method was comparable. As a further measure of comparability, the incidence of 13 acute indicator conditions unrelated to herpes zoster was also compared in the two groups, and yielded adjusted hazard ratios ranging from 0.87 to 1.46, with all 95% CIs overlapping 1.0. Thus the study by Tseng et al. [1] clearly found no evidence of an increased risk of herpes zoster in the population receiving zoster vaccine and pneumovax concomitantly.

The December 2009 change in the ZOSTAVAX® Prescribing Information suggests that antibody to VZV was not only being considered an indicator of the immunogenicity of zoster vaccine, but it was also being used as a surrogate for vaccine-induced protection against herpes zoster. This was almost certainly an inappropriate assumption, as demonstrated by the results of the study by Tseng et al. [1].

Antibody to VZV can protect susceptible immunocompetent and immunocompromised persons against varicella when administered prior to or shortly after VZV exposure, can identify persons immune to varicella as a result of prior VZV infection, and can serve as an indicator of the efficacy of varicella vaccination [11–18]. However, there is a large body of evidence that cell mediated immunity (CMI) to VZV is both necessary and sufficient to protect against herpes zoster, and that antibody to VZV does not play a significant role in preventing this manifestation of the reactivation of latent VZV, either in immunocompetent or in immunosuppressed persons (summarized in reference 19). When VZV-specific CMI declines, as it does with aging or in response to iatrogenic or disease-induced immunosuppression, the incidence and severity of herpes zoster and its complications increase significantly [19–24]. In contrast, levels of antibody are well maintained in older persons [19,25–27] and levels of antibody to VZV in immunosuppressed patients do not

correlate with levels of VZV CMI or with the risk of herpes zoster [19,28]. The Shingles Prevention Study (SPS) [29] and its Immunology Substudy demonstrated that the clinical efficacy of zoster vaccine was the result of its capacity to increase the waning levels of VZV CMI observed in older adults [27,29]. Placebo recipients in the SPS were not protected and demonstrated an age-related increase in the incidence and severity of herpes zoster and PHN that was correlated with an age-related decline in VZV CMI, whereas a comparable age-related decline in levels of antibody to VZV was not observed [19,27]. Furthermore, VZV antibody responses to zoster vaccine were not correlated with VZV CMI responses [27], and higher levels of VZV CMI shortly after herpes zoster onset were associated with reduced herpes zoster severity and reduced occurrence of postherpetic neuralgia [30]. In contrast, higher levels of antibody to VZV were associated with increased herpes zoster severity and increased occurrence of postherpetic neuralgia [30].

The change in ZOSTAVAX® Prescribing Information made in December 2009 advising that zoster vaccine and pneumovax, two vaccines recommended for older adults, “should not be given concurrently” was unfortunate because, as pointed out by Tseng et al. [1], that recommendation was based upon the faulty assumption that levels of antibody to VZV are relevant to protection against herpes zoster in older persons, and because it introduced an additional barrier to the administration of these two important vaccines to older adults. The admonition against concomitant administration of zoster vaccine was not echoed by other advisory bodies, leading to further confusion on the part of many healthcare providers. However, that unfortunate and inappropriate change in the ZOSTAVAX® Prescribing Information should also serve as an important wake-up call.

Advances in vaccinology are leading to the introduction of a large number of new vaccines, new vaccine platforms, adjuvants and combinations. This will make it impossible to base all advice and recommendations for vaccine usage, particularly for vaccines administered concomitantly versus separately, on the results of large randomized double-blind, placebo-controlled clinical trials. Consequently, it will be important to develop and/or select clinically valid and reliable correlates of protection to guide such advice and recommendations. Currently, efforts are underway to develop vaccines against diseases caused by viruses for which elements of CMI are the host defenses of primary importance, including VZV, herpes simplex viruses, cytomegalovirus, and other human Herpesviruses. This underscores the importance of developing and utilizing validated laboratory assays for virus-specific CMI that can provide reliable laboratory correlates of clinically significant immunity, namely, immunity to the disease targeted by the vaccine in question. This is especially true as we seek to develop improved versions of the currently licensed zoster vaccine [29] and other therapeutic vaccines.

The selection and evaluation of such clinically valid and reliable correlates of protection, and the design of suitable phase IV clinical studies, will need to be accomplished in advance of their deployment. Only this will ensure that recommendations on vaccine usage are evidence-based. Since this will often require more expertise than is likely to be found in a single federal agency or pharmaceutical company, it may require new paradigms to ensure that the expertise and experience of the dedicated personnel at the Food and Drug Administration (FDA) and industry are routinely augmented by appropriate external

expertise from other government agencies and academia. While there may be barriers, both legal and cultural, to introducing such a broad-based and integrated process, the potential benefits to the public health warrant its careful consideration and the effort required.

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