Changing Dynamics of Varicella-Zoster Virus Infections in the 21st Century: The Impact of Vaccination

Richard J. Whitley
Departments of Pediatrics, Microbiology, Medicine, and Neurosurgery, University of Alabama at Birmingham, Birmingham

(See the article by Jumaan et al., on pages 2002–7.)

In this issue of *The Journal of Infectious Diseases*, Jumaan et al., of the Centers for Disease Control and Prevention and the Group Health Cooperative in Seattle, report results of their probe of clinical codes for varicella-zoster virus (VZV) and herpes zoster (HZ), which used the Ninth Revision of the International Classification of Diseases [1]. They report the impact that VZV vaccination of children has on the incidence of herpes zoster in a managed-care population. Data were recorded for the years 1992–1995 and then for the years 1995–2002, which represented, respectively, pre- and post-licensure time periods for the varicella vaccine. The database consisted of 350,000 persons and accounted for 3.9 million person-years of observation during the 11-year period of the study. Jumaan et al. note that, for the age-adjusted population, the incidence of varicella decreased significantly after the introduction of varicella vaccine, from 2.63 cases/1000 person-years to 0.92 cases/1000 person-years, with the greatest impact being on children 1–4 years old, as would be expected. However, what is equally important—and, indeed, the focus of their report—is that the change in the incidence of herpes zoster, while fluctuating between the 2 spans of years, was not statistically significant, remaining at 4.05 cases/1000 person-years in 1992 and at 3.71 cases/1000 person-years in 2002.

Jumaan et al.’s study begins to address 1 of several major concerns that the academic and public-health communities had at the time of licensure of the VZV vaccine in 1995. When this vaccine was licensed, the 3 fundamental concerns were (1) the persistence (i.e., duration) of protective immune responses after vaccination, (2) the impact that vaccination would have on the incidence of chickenpox and/or its complications in the United States, and (3) the possibility that the incidence of herpes zoster would actually increase after the routine introduction of the vaccine into the pediatric-immunization schedule. With regard to the first concern, several studies have addressed the persistence of immune responses and the resultant protection, albeit while recognizing that the disease can occur in populations in which the frequency of vaccination apparently is high [2–6]. It is noteworthy that recent studies would suggest that, compared with later immunization, immunization of children who are <15 months old may be associated with an increased frequency of the disease [2–4]; this observation will require substantiation, because it will directly affect recommendations regarding the timing of the administration of vaccine to children. The second concern has begun to be addressed through recently reported studies performed in targeted communities by investigators at the Centers for Disease Control and Prevention [7], and these studies have shown that the incidence of chickenpox has progressively decreased in 3 of these targeted communities. Indeed, Jumaan et al.’s report also documents the impact that vaccination has on the decreasing incidence of chickenpox in yet another population; most important is that it fails to provide evidence for its real motivation—that is, to show an increase in the incidence of herpes zoster in this population.

Each of the 3 aforementioned concerns has an impact on the dynamic of VZV infections in the United States, because chickenpox and herpes zoster are inextricably linked. To state the matter simply,
exposure to varicella virus causes chickenpox—but not herpes zoster—in susceptible individuals. Similarly, exposure of a susceptible individual to a person with herpes zoster can result in chickenpox but will not lead to the reactivation of herpes zoster. For previously infected individuals exposed to a patient with VZV infection, boosting of virus-specific immune responses has been demonstrated [5, 8–10]. It must be remembered that, in the United States, neither chickenpox nor herpes zoster is a reportable disease; thus, the definitive disease burden can only be approximated for the population at large or on the basis of defined cohort studies. With the introduction of an immunization program, the overall incidence of chickenpox in the United States is decreasing. As an aside, it should be noted that only 38 states—soon 39 (with the addition of Missouri)—require immunization for school entry. Historically, experts have reported that the annual incidence of disease has approached the size of the birth cohort—that is, ~4 million; but such is no longer the case, because a decreased incidence of chickenpox correlates directly with fewer adults being exposed to children with this disease. As has been well documented, adult exposure to chickenpox has been associated with a lower incidence of herpes zoster in the exposed adult. As early as 1963, Hope-Simpson made the fundamental observation that the incidence of herpes zoster in pediatricians who routinely cared for children with chickenpox was lower than that in the population at large [11]. The fundamental premise is that there is a degree of senescence of the immune response to VZV, which results in the reactivation of virus to cause zoster. Thus, with repetitive exposure, enhancement of immune responses would be ongoing. Indeed, other studies have substantiated this observation and also have recognized the converse—namely, that adults who are not routinely exposed to children with chickenpox have a higher incidence of zoster [8–10, 12]. Therefore, as the impact of the VZV vaccine is documented, there has existed the real possibility that boosting of virus-specific immune responses in adults would decrease, resulting in an increase in the incidence of shingles. Fortunately, Jumaan et al.’s study does not, at least for the period of observation, support such concerns, because it has found that the incidence of zoster has remained constant.

As Jumaan et al. note, their study warrants one significant note of caution—namely, that it simply may be too soon after licensure of the varicella vaccine to be able to detect an increase in the incidence of zoster attributable to exposure to the vaccine. Even if use of the vaccine in children were to increase the incidence of zoster later in life, alternatives for the prevention of shingles may be on the horizon. A clinical trial worthy of note—namely, the Shingles Prevention Study, sponsored by the Veterans Administration Cooperative Trial Network, the National Institute of Allergy and Infectious Diseases, and Merck Sharp and Dome—has just been completed and awaits analysis of its data. In this clinical trial, nearly 40,000 individuals >60 years old either received an enhanced VZV vaccine or an unrelated vaccine. The endpoints for this clinical trial included both the reduced burden of pain and the incidence of herpes zoster, and it was grounded on the premise that immunological seroboosting that occurs with vaccination in older individuals will reduce zoster or its complications [13, 14]. Although the results of this trial have not yet been reported, if vaccination indeed decreases the incidence of shingles, this would provide support for the exposure of older individuals to live virus—even via an artificial route—as a way to decrease the incidence of shingles.

These clinical observations are not immediately applicable to much of the rest of the world. To this day, many developed countries do not recommend routine immunization to prevent chickenpox; thus, as noted above, while the dynamics of VZV infections are changing in the United States, other areas of the world will not experience such changes in the epidemiology of infection until varicella vaccine programs are implemented. The development and utilization of the varicella vaccine represents a significant advance in the prevention of disease in susceptible populations (both children and adults). A recent report of reduction in mortality after varicella vaccination adds further credence to public-health recommendations [15]. Public-health officials should be commended for their commitment to long-term follow-up studies to guarantee documentation of the impact that vaccination has on both chickenpox and herpes zoster.

References