

Second Dose of Varicella Vaccine for Children: Are We Giving It Too Late?

Eugene D. Shapiro

Departments of Pediatrics, Epidemiology and Public Health, and Investigative Medicine and the Yale Center for Clinical Investigation, Yale University School of Medicine, New Haven, Connecticut

(See the article by Michalik et al., on pages 944–9.)

Live attenuated varicella vaccine was approved by the Food and Drug Administration (FDA) in 1995 for administration to healthy susceptible persons ≥ 12 months of age. A single dose of the vaccine for children ≤ 12 years of age (ideally administered at 12–15 months of age) and 2 doses of the vaccine administered at least 1 month apart for persons ≥ 13 years of age were recommended. Since routine immunization of children began, there have been substantial declines (among both children and adults) in the incidence of varicella, in hospitalizations and ambulatory visits for varicella, in mortality due to varicella, and in overall expenditures for varicella-related illnesses [1–5]. In sentinel areas in which the Centers for Disease Control and Prevention (CDC) has established active surveillance (Ante-

lope Valley, California; Travis County, Texas; and West Philadelphia, Pennsylvania), the incidence of varicella declined by 75%–83% from 1995 to 1999, and the seasonal pattern of increased incidence in the spring was attenuated [1]. Indeed, the decrease in the incidence of varicella was out of proportion to the percentage of children who had been vaccinated, indicating that there was apparent herd immunity that affected even unvaccinated children < 1 year of age [6].

A large case-control study indicated that the vaccine's overall effectiveness up to 8 years after immunization was 87% [7]. Thus, although the vaccination program certainly was effective, "breakthrough" varicella (varicella in persons who had previously received varicella vaccine) occurred with some frequency. Since most breakthrough disease is mild, why does this matter? In the first place, children with breakthrough disease are able to transmit the virus to others, which has resulted in numerous disruptive outbreaks of varicella in day-care centers and in schools despite high rates of immunization at many of these sites [8–9]. Moreover, approximately one-third of children with breakthrough varicella have moderate or severe disease, and there has been at least one death in an immunized child. In addition, those who have had breakthrough varicella may be at higher risk of

subsequently developing zoster than are immunized persons.

In preclicensure studies it had been reported that the seroconversion rate against varicella-zoster virus after 1 dose of varicella vaccine was $> 95\%$ [10], so a vaccine effectiveness of only 87% was surprising. The case-control study indicated that the vaccine's effectiveness in the first year after vaccination was 97%, but there was a statistically significant decrease to an effectiveness of 86% in the second year after vaccination; the vaccine's effectiveness diminished only slightly during the subsequent 6 years [7]. This pattern of breakthrough disease is most consistent with primary vaccine failure, which occurs as a result of either failure to seroconvert or rapid loss of antibodies soon after immunization due to insufficient stimulation of memory T cells. On the other hand, a report from CDC investigators indicated that, in Antelope Valley, California, the incidence of varicella stopped declining from 2002 to 2004, an event that the investigators attributed to waning of vaccine-induced immunity over time (i.e., secondary vaccine failure) [11]. Either of these types of vaccine failure might be overcome by a second dose of the vaccine, but appropriate timing of a second dose could differ, depending on which type of vaccine failure is the problem.

In this issue of the *Journal*, Michalik et al. [12] report the results of a study in

Received 20 December 2007; accepted 20 December 2007; electronically published 4 March 2008.

Potential conflicts of interest: E.D.S. has received honoraria for talks from Merck & Co., manufacturer of the varicella vaccine.

Financial support: National Center for Research Resources, a component of the National Institutes of Health (NIH), and NIH Roadmap for Medical Research (Clinical and Translational Science Award UL1 RR024139 and grant K24-RR022477).

Reprints or correspondence: Dr. Eugene D. Shapiro, Dept. of Pediatrics, Yale School of Medicine, 333 Cedar St., PO Box 208064, New Haven, CT 06520-8064 (Eugene.Shapiro@Yale.edu).

The Journal of Infectious Diseases 2008; 197:935–7
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0022-1899/2008/19707-0001\$15.00
DOI: 10.1086/529044

which they measured antibody concentrations, using the fluorescent antibody to membrane antigen (FAMA) assay, in 148 healthy susceptible children an average of 4 months after being immunized with a single dose of monovalent varicella vaccine. The percentage of children who seroconverted (titer of $\geq 1:4$)—only 76% (95% confidence interval, 66%–85%)—was substantially lower than the >95% of children reported to have seroconverted by the glycoprotein ELISA (gpELISA) in prelicensure studies.

Antibodies to varicella-zoster virus after vaccination have been measured by different methods. For studies in healthy children before the vaccine was approved, the gpELISA developed by the US manufacturer of varicella vaccine (Merck & Co.) was most often used [10, 13]. The FAMA assay was used extensively in prelicensure studies of varicella vaccine in children with underlying leukemia [14]. The FAMA assay is considered to be the gold standard for judging immunity to varicella, but it requires live (unfixed and wet-mounted) cells infected with varicella-zoster virus (VZV) and cannot be automated; consequently, it is not widely available [15, 16]. FAMA titers are highly correlated with neutralization antibody titers to VZV [17]. In 1995, the FDA established a gpELISA titer of ≥ 5 units/mL as an *approximate* correlate of protection [18], but this estimate has not been validated by clinical studies.

In contrast, a FAMA titer of $\geq 1:4$ at the time of exposure (and as long as a year before exposure in healthy individuals) is highly correlated with protection against chickenpox both after vaccination and after natural infection [19, 20]. FAMA titers have correlated well with resistance or susceptibility to infection in clinical settings [15, 19–23]. In 131 individuals with a household exposure to varicella and a FAMA titer of $\geq 1:4$, the attack rate of varicella was <2%. By contrast, of 68 exposed individuals with FAMA titers of <1:4, 59% developed clinical cases of varicella. Of these 68, among persons with natural immunity to VZV (history of dis-

ease and no vaccine), the attack rate was 74% (23/31). Among vaccinees, the attack rate was 46% (17/37) after household exposure. This suggests that approximately one-third of vaccinees with FAMA titers of <1:4 may not actually be susceptible to varicella. However, having a FAMA titer of $\geq 1:4$ clearly indicates immunity to varicella.

In June 2006, the Advisory Committee on Immunization Practices recommended that a second dose of varicella vaccine be administered routinely to children [24]. Although the vaccine can be given as soon as 3 months after the first dose, it is recommended that it be administered between 4 and 6 years of age. This is largely because a combined measles-mumps-rubella-varicella (MMR-V) vaccine was approved in October, 2005 [25, 26]. As a result, both the first and second doses of varicella vaccine are easily given at the same time as MMR vaccine via this combined vaccine at 12–15 months and 4–6 years of age, respectively. This allows the second dose of the vaccine to be administered without requiring an additional injection in the already crowded schedule for childhood immunizations. However, if the substantial number of cases of breakthrough varicella is due to primary, rather than secondary, vaccine failure, this timing for the second dose risks leaving a substantial number of children susceptible for several years until they receive the second dose and may diminish its impact on the epidemiology of the disease.

To further complicate matters, the amount of varicella virus in monovalent varicella vaccine and in MMR-V vaccine differs substantially, because varicella vaccine is less immunogenic when combined with MMR vaccine in the same preparation. Monovalent varicella vaccine contains a minimum of 1350 pfu per dose, whereas MMR-V vaccine contains a minimum of 9700 pfu of varicella vaccine per dose (according to the package insert labeling) [27]. The few data available have indicated that, after 2 doses of monovalent vaccine, titers of antibody to VZV, as

measured by gpELISA, increase by a factor of 12 but that, after 2 doses of MMR-V vaccine, titers may increase up to 40-fold [16, 28, 29]. However, immunogenicity of MMR-V vaccine has not been assessed using the clinically validated FAMA assay. Moreover, because of problems with production at Merck [30], MMR-V vaccine is either not available at this time or is in short supply, and most children are receiving monovalent vaccine. There is uncertainty about if and when MMR-V vaccine will again become available.

Because of the limited and conflicting data on which to base recommendations for policy, it is important to obtain additional data to try to clarify whether most breakthrough cases of varicella are due to primary or secondary vaccine failure. Continued direct assessment of the vaccine's effectiveness over time is essential. Because breakthrough varicella is often such a mild illness (and the skin lesions may be primarily papular), it is often difficult to distinguish the rash of breakthrough varicella from other causes of papulovesicular rashes. Consequently, in studies of the vaccine's effectiveness, laboratory confirmation of cases of breakthrough varicella is important. Indeed, lack of laboratory confirmation of cases is one of several shortcomings of the CDC's report that suggested that many cases of breakthrough varicella were due to secondary vaccine failure (waning immunity) [31]. The immunogenicity of both monovalent varicella vaccine and of MMR-V vaccine (if it again becomes available) should be assessed by directly comparing the results of gpELISA and FAMA assays in the same samples.

There was controversy about the benefits of universal vaccination against varicella when the vaccine program was introduced [32]. It has now been demonstrated that varicella vaccine has already had a huge positive impact on the morbidity, mortality, and economic consequences of varicella in the United States. However, more questions remain to be

answered before we can determine the optimal use of this effective vaccine.

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