In this issue of the Journal, Shapiro and colleagues present data from a case-controlled study of the effectiveness of 2 doses of varicella vaccine during the first several years after implementation of a routine 2-dose recommended schedule. At 98.3%, the effectiveness of the 2-dose schedule is welcome news indeed. These data validate the calculations of experts from the Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) and the American Academy of Pediatrics (AAP) Committee on Infectious Diseases (COID), made in 2006 when both groups approved a recommendation for routine use of 2 doses of varicella vaccine during childhood. Shapiro and colleagues are to be commended for their forethought in establishing a broad surveillance network in Connecticut in the years after licensure of the varicella vaccine in 1995 and for their careful scientific and statistical evaluation of data generated from this important resource.

In understanding the context within which these new data should be viewed, it is important to reflect on the overall development and implementation of varicella vaccine. The strain that ultimately became the varicella vaccine in the United States and many other countries was first isolated by Takahashi et al in the early 1970s from a young Japanese boy whose name was Oka (hence the vaccine Oka strain) [1]. Takahashi et al successfully attenuated this isolate through serial passage in the laboratory, followed by 20 years of testing before approval as a monovalent vaccine (Varivax) in the United States in 1995. Its licensure reflected a milestone in vaccinology: as a herpesvirus, the Oka strain establishes latency in the human body, meaning that the vaccine remains in the recipient for the rest of his or her life. Careful scientific assessment then and subsequently has proved that reactivation of the vaccine strain, resulting in zoster or shingles, occurs much less frequently than with wild-type varicella-zoster virus [2]. Nevertheless, this was the first vaccine virus that persists even in a latent form.

Before licensure of the monovalent varicella vaccine (Varivax; Merck) in March 1995, ~4 million cases of varicella, 10,500–13,500 hospitalizations due to complications of varicella, and 100–150 deaths from varicella occurred annually [3–7]. The initial use of the vaccine was for the prevention of moderate or severe varicella disease, including hospitalization, long-term morbidity, and mortality. To accomplish this objective, the vaccine was recommended to be administered as a single dose given at 12–18 months of age [8, 9]. In the first 10 years after licensure, vaccination coverage increased to 88% among vaccine-eligible children 19–35 months of age [10]. Plummeting hospitalizations and deaths from varicella [7, 11, 12] were unequivocal testaments to the success of these initial goals of the varicella vaccination program.

With this success, however, came a new challenge, as breakthrough varicella disease received increasing attention from both public health officials and the general population. Prelicensure efficacy trials of a single dose of the vaccine had documented virtually 100% effectiveness in preventing moderate to severe varicella disease, and 80%–85% efficacy in the prevention of any varicella disease [13–16]. As severe varicella disease became increasingly rare because of the overwhelming success of the 1-dose schedule, and as mild disease decreased as well, those outbreaks of mild
breakthrough cases that did occur received increased visibility. In the late 1990s and early 2000s, hundreds of such outbreaks occurred annually [17–19]. Although this number of outbreaks unquestionably represented a significant improvement over the prevaccine era, the outbreaks still were costly to public health systems and created some confusion among parents who mistakenly thought that 1 dose of the vaccine was supposed to eliminate all risk of varicella disease.

It was against this backdrop that the CDC ACIP and AAP COID recommended in 2006 the incorporation of a second dose of varicella vaccine at 4–6 years of age in the US vaccination schedule [20, 21]. Data were limited at the time of the recommendation but suggested that 2 doses of varicella vaccine generate higher antibody titers and greater protection against breakthrough disease [22]. The study by Shapiro et al is the first to evaluate the effectiveness of 2 doses of varicella vaccine in a “real-world” setting following the AAP and CDC recommendations, and the high effectiveness of 98.3% found in this investigation supports the programmatic change instituted 4 years ago.

One issue that is left unresolved is whether the second dose of varicella vaccine is overcoming a primary vaccine failure in which a proportion of vaccine recipients fail to generate adequate protection after only 1 dose, or whether the second dose diminishes secondary vaccine failures by boosting varicella immunity that has waned since the first dose was given. Given the high effectiveness demonstrated in this trial, however, this distinction is more of an academic exercise than a clinical conundrum. What matters is that 2 doses work. A child receiving the recommended 2 doses of the vaccine is 95% less likely to develop breakthrough chickenpox than a child receiving only 1 vaccine dose. We are now in the second period of varicella control, and version 2.0 looks promising indeed.

References