

Chickenpox Party or Varicella Vaccine?

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1. Introduction

Chickenpox (varicella) is generally a much milder illness in children than in adults, with considerably lower rates of severe disease and death (Seward et al., 2000). Varicella is also virtually universal in many populations, meaning that very few individuals escape infection over a lifetime. Thus, a sound logic underlies the idea of chickenpox parties, at which susceptible children can acquire the contagious causative pathogen, varicella zoster virus (VZV), from their peers. However, chickenpox is not without risks, even for children of this age; severe, complicated, and occasionally fatal varicella occur in previously healthy children, as well as the immunocompromised (who are at very considerable risk) (Meyer et al., 2000; Galil et al., 2002a). There is an alternative in the form of a live attenuated vaccine that is both safe and effective in preventing varicella, particularly severe disease (Arvin and Gershon, 1996). In the United States, routine administration of this vaccine to young children has been advised since 1995 (Committee on Infectious Diseases, 1995; Centers for Disease Control, 1996). The European Working Group on Varicella recently advocated a similar strategy, provided a very high rate of coverage can be achieved (Rentier and Gershon, 2004). In the following article, we review the US experience of varicella vaccination, focusing on the consequent, profound changes in epidemiology and the challenges that may result over the coming years.

2. VZV Disease in Unvaccinated Populations

The human α -herpesviruses, herpes simplex viruses 1 and 2, VZV, and their precursors, have been coevolving with primates for over 70 million years, and represent supremely successful pathogens. The case of VZV illustrates the intriguing strategy of these viruses, since most individuals acquire lifelong VZV infection in childhood, with most viruses existing in latent form in the human population.

Latent infection of sensory neurons in the dorsal root and trigeminal ganglia is established during the course of the brief and highly contagious primary illness, varicella (chickenpox) (Kennedy, 2002). Reactivation from latency can produce zoster (shingles), with the reemergence of infectious virus in skin vesicles and attendant possibility of spread to new hosts (Hope-Simpson, 1965; Gnann and Whitley, 2002). Thus, despite the tendency of VZV epidemics to exhaust the supply of naïve hosts, a large pool of virus is maintained with the potential to reinitiate the cycle of infection.

Varicella has long been known as one of the six exanthemata of childhood and this characterization has been amply confirmed in epidemiologic studies of unvaccinated populations living in temperate climates (Wharton, 1996; Seward et al., 2000). In contrast to the other human herpesviruses, primary VZV infection is almost always symptomatic if the exposed susceptible child is examined carefully at the end of the incubation period. In the landmark work of Hope-Simpson, almost 90% of children were noted to have experienced varicella by the age of 10 (Hope-Simpson, 1952). More recent studies have pointed, if anything, to a lowering of the average age at acquisition of chickenpox into the pre-school years, postulated to reflect the greater participation of these younger children in group care in the Western industrialized societies (Brisson et al., 2001). Currently, only 1% of US-born adults are believed to be varicella-susceptible. In contrast, varicella in tropical countries shows a lower incidence in children, with the result that many more adults remain susceptible (Seward et al., 2000).

Varicella is generally thought of as a mild illness, with its main symptoms being the hallmark pruritic vesicular rash, fever, and malaise. However, serious and occasionally fatal complications occur with significant frequency, particularly in neonates, adults, and the immunocompromised (Guess et al., 1986; LaRussa, 2000). These include secondary bacterial infections of skin and lung together with pneumonia, encephalitis, and cerebellar ataxia. In the United States, these and other varicella-associated complications caused approximately 11,000 hospitalizations and 100 deaths annually prior to the introduction of varicella vaccination in 1995 (Meyer et al., 2000; Galil et al., 2002a). Despite the higher case-fatality in the above-mentioned risk groups, many deaths and severe complications occurred in previously healthy children due to their high incidence of varicella (Figure 2.1) (Peterson et al., 1996; Meyer et al., 2000).

Zoster is relatively uncommon in children but its incidence climbs steadily with age (Donahue et al., 1995); this is believed to reflect declining cell-mediated immunity (Berger et al., 1981; Levin et al., 2003b). Individuals with cellular, but not humoral, immunodeficiency are at increased risk for VZV reactivation and for dissemination (to skin beyond one or two contiguous dermatomes) and/or visceral disease (which is occasionally fatal) (Oxman, 2000; Gershon, 2001). Most zoster, however, consists of the classic vesicular rash in a unilateral dermatomal distribution and with accompanying pruritus and neuropathic pain (Gnann and Whitley, 2002). Children rarely experience troublesome pain, but the opposite is true in the elderly, many of whom go on to suffer debilitating postherpetic neuralgia (PHN) over the ensuing weeks and months (Gilden et al., 2000; Edmunds et al., 2001).

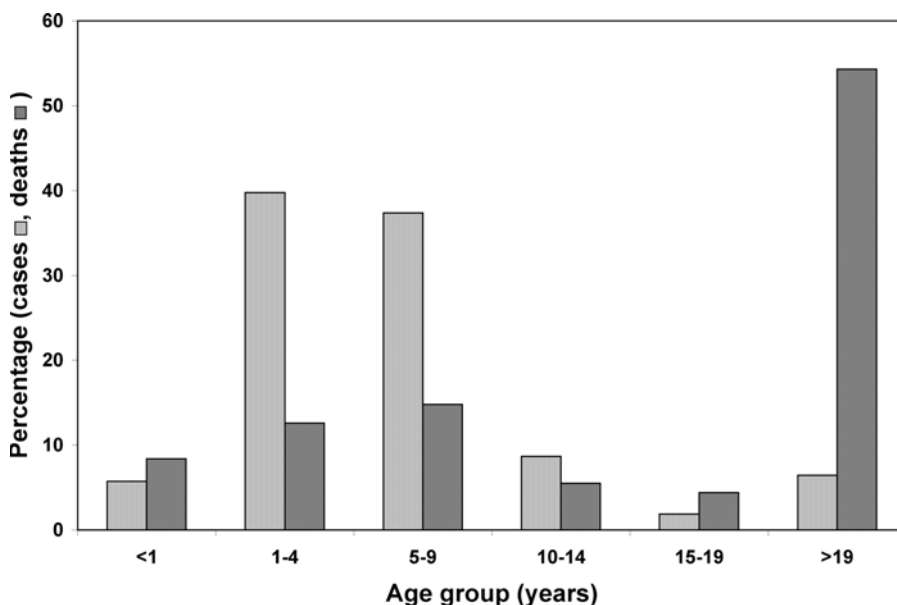


Figure 2.1. Proportions of varicella cases and deaths by age, 1990–1994 (pre-vaccine). Note that the majority of cases occurred in children, along with significant numbers of deaths despite a much lower case-fatality ratio than adults. Data are drawn from Meyer et al. (2000). *J. Infect. Dis.* 182, 383. (With permission from University of Chicago Press, © 2000 by the Infectious Diseases Society of America. All rights reserved.)

3. Varicella Vaccine

3.1. Safety, Immunogenicity, and Efficacy

Childhood deaths due to varicella were a major factor in stimulating the development of a live attenuated vaccine, which was accomplished in Japan in the 1970s. A clinical isolate (“Oka”) was passaged through human and non-human cells in tissue culture, resulting in the accumulation of numerous mutations (Gershon et al., 2004). Collectively, these confer an attenuated phenotype as reflected by reduced replicative capacity in the SCID-hu mouse model and, under certain conditions, in tissue culture (Moffat et al., 1998; Arvin, 2001).

Ample evidence has now accumulated to suggest that the vaccine is also highly attenuated with respect to human hosts, less than 2% of whom develop rash following subcutaneous inoculation (White et al., 1991). Extensive post-licensure surveillance in the United States has disclosed that other adverse symptoms are rare, and complications typical of varicella (encephalitis, cerebellar ataxia) have not been linked to the vaccine (Wise et al., 2000; Sharrar et al., 2001). Immunocompromised individuals are at higher risk (40%) for vaccine-associated rash and, when present, this was associated with secondary cases in early vaccine trials among children in remission from leukemia (Tsolia et al., 1990). Hence, vaccination of the immunocompromised is contraindicated in the United States (with the exception of minimally

symptomatic HIV infection and pure immunoglobulin deficiencies) (Centers for Disease Control, 1996, 1999). However, experience to date suggests that dissemination of vaccine strain varicella occurs only in the context of profound cellular immunodeficiency (unsuspected at the time of vaccination) (Ghaffar et al., 2000; Kramer et al., 2001; Sharrar et al., 2001; Gershon, 2003; Levy et al., 2003; Levin et al., 2003a).

Pre-licensure trials in several thousand susceptible individuals showed that a single dose of vaccine was around 70–90% efficacious against varicella in healthy children (somewhat less so in adolescents and adults), over follow-up periods of 1–10 years (Weibel et al., 1984; Gershon et al., 1988; Kuter et al., 1991; White et al., 1991; Johnson et al., 1997; Kuter et al., 2004). Rates of breakthrough varicella varied considerably between studies. Breakthrough varicella is caused by wild-type VZV but is usually considerably milder than disease in the unvaccinated, indicating partial vaccine-induced immunity. Vaccine immunogenicity, generally measured by antibody response to viral glycoproteins, is rather loosely related to protection against varicella (Li et al., 2002); cellular immune responses can also be demonstrated (Kumagai et al., 1980; Arvin, 1996; Smith et al., 2003). Higher antibody titers and cellular immune responses are achieved with the use of more potent vaccine formulations and two-dose schedules, which are associated with improved protection against varicella (Watson et al., 1995; Arvin and Gershon, 1996; Varis and Vesikari, 1996; Kuter et al., 2004;). However, the vast majority of children show seroconversion after a single dose of vaccine (Weibel et al., 1984; White, 1996), which is obviously the most attractive schedule in terms of cost and compliance.

3.2. The US Varicella Vaccination Program: Design and Coverage

In view of the safety, immunogenicity, and efficacy of Oka vaccine among the major risk group for varicella-related morbidity and mortality, the US program was centered upon the vaccination of healthy pre-school children (Centers for Disease Control, 1996). The primary aims of this program were (1) the direct prevention of varicella-related morbidity and mortality among vaccinated individuals and (2) reduction of disease burden among remaining varicella-susceptibles (of all ages) as a result of effects on VZV transmission (“herd immunity”). By offsetting the cost of vaccinating against the reduction of direct (medical) and indirect (lost productivity) costs of varicella, the program was expected to be highly cost-effective (Lieu et al., 1994). US recommendations were issued in 1995 for the universal immunization of (VZV-naïve) healthy children aged 12–18 months and catch-up vaccination of all older varicella-susceptibles (using two doses rather than one from adolescence onward) (Committee on Infectious Diseases, 1995; Centers for Disease Control, 1996). As mentioned above, avoidance of varicella vaccine is counseled in most cases of the immunocompromised; these individuals are considered to be best protected by the immunization of any varicella-susceptible family members. Varicella-susceptible women should be vaccinated before and not during pregnancy.

National immunization statistics are estimated in the United States through an extensive telephone survey (the National Immunization Survey), making it possible to track varicella vaccine uptake over time (Centers for Disease Control, 2004).

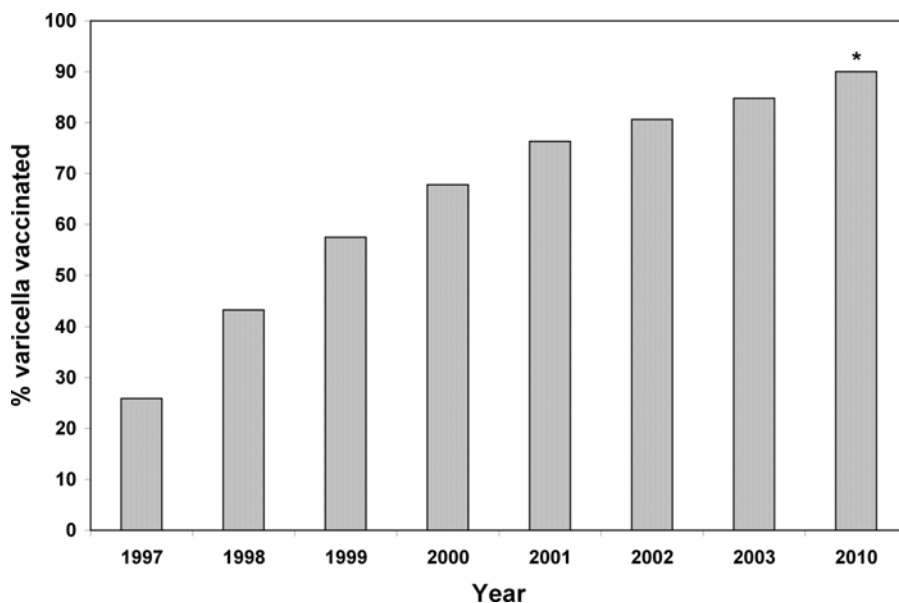


Figure 2.2. US national varicella vaccination coverage among children of ages 19–35 months. Data are drawn from the National Immunization Survey (NIS) (Centers for Disease Control, 2004). Asterisk indicates projected coverage level.

Latterly, many states have introduced a requirement for varicella vaccination (or positive disease history) among children entering daycare and/or elementary school. Such requirements, which are already commonplace in relation to other vaccines in the United States, have undoubtedly contributed to the increasing uptake of varicella vaccination. This is believed to have reached approximately 85% of 19–35-month olds across the United States by 2003 with a continuing upward trend (Centers for Disease Control, 2004) (Figure 2.2).

3.3. Impact of the US Varicella Vaccination Program

Within less than a decade, the epidemiology of varicella in the United States has been transformed from that of an almost universal childhood illness to a relative rarity. In the near future, we may expect varicella to become a notifiable disease nationwide, but clearly this would until recently have been difficult to achieve, considering the estimated 4 million cases of varicella every year. Therefore, documentation of the changing epidemiology of varicella has had to derive from other sources, detailed below. Collectively, these give a clear picture of declining varicella incidence and falling rates of varicella-related hospital admissions and deaths. Benefit extends from vaccinated to unvaccinated-susceptible groups (e.g., infants), confirming the existence of herd immunity.

3.3.1. Cases

Varicella incidence has been followed prospectively by the CDC since 1995 in sentinel counties of the United States (Figure 2.3). Following vaccine licensure in

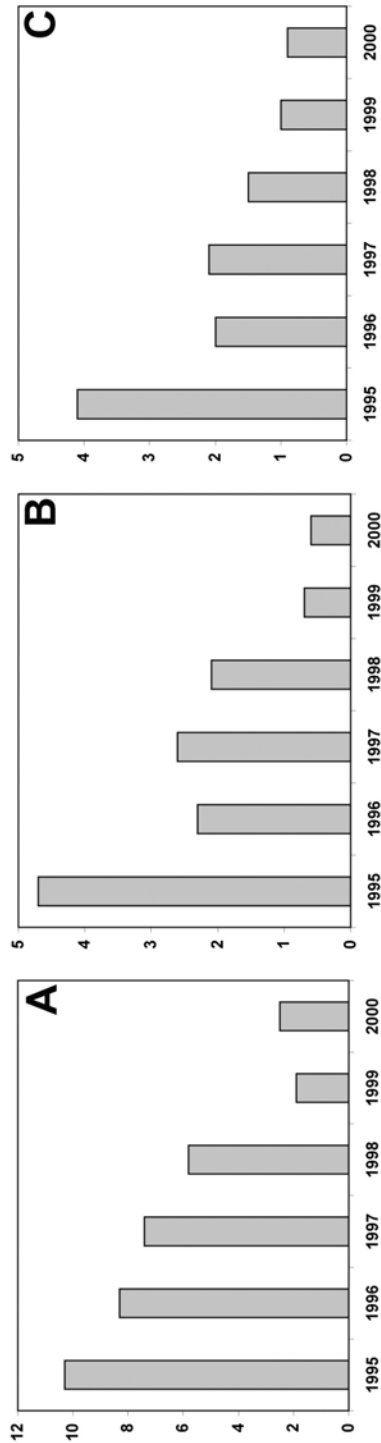


Figure 2.3. Varicella incidence in three sentinel counties of the United States following vaccine introduction in 1995. Data are drawn from Seward et al. (2002). *J. Am. Med. Assoc.* 287, 606 and represent annual rates of reported cases per 1,000 population in each county. (A) Antelope Valley, California; (B) Travis County, Texas; (C) West Philadelphia, Pennsylvania. (With permission, Copyright © 2002, American Medical Association. All rights reserved.)

1995, the proportion of immunized children rose steadily in these counties, while varicella incidence declined by between 71% and 84% by 2000 (Seward et al., 2002). An independent prospective cohort study elsewhere in the United States showed a similar trend as vaccine coverage within the study population rose to 63% over the period 1995–1999 (Clements et al., 2001). In both studies, varicella incidence declined markedly among both vaccinated and unvaccinated groups, strongly suggesting a herd immune effect despite only partial vaccine coverage. Further confirmation of the fall in varicella incidence comes from those few states that have had consistent (if incomplete) reporting of varicella over the last several years. Each of these four states has shown a steady decline in varicella incidence, with a 67–82% reduction by 2001 compared with the pre-vaccination period 1990–1994 (Centers for Disease Control, 2003).

3.3.2. Hospitalizations

Accompanying the falling incidence of varicella, one would expect a decline in related hospital admissions. Data are beginning to accrue that show this effect. A trend toward reduced hospital admissions was reported in the “sentinel counties” over the period 1995–2000 (Seward et al., 2002). Statistics from the National Hospital Discharge Survey, collated for the period 1988–1999, likewise showed a trend toward decreased hospitalizations which is anticipated will be confirmed over subsequent years (Galil et al., 2002a). A large health insurance claims database has been interrogated to disclose consultation and hospitalization rates for varicella and showed reductions of 59% and 80%, respectively, over the period 1994–2001 (as vaccination coverage rose to some 60%) (Jane Seward, CDC, personal communication). Of note, this was associated with a reduction of 75% in direct medical costs. Declining hospitalizations for varicella among military recruits have also been noted since the mid-nineties, part of which may be attributable to programs aimed specifically at the identification and vaccination of varicella-susceptibles in the armed forces (Ryan et al., 2003).

3.3.3. Deaths

Deaths from varicella are rare and fluctuated from year to year prior to the introduction of varicella vaccination (Meyer et al., 2000), so hasty conclusions could not be drawn regarding mortality rates. A recent statewide study, in California, is suggestive of the expected decline in varicella-associated mortality over the period 1988–2000 (McCoy et al., 2004). An analysis of varicella deaths nationally in the United States has yet to be published at the time of writing but is keenly awaited.*

4. Issues of Concern in the Varicella Vaccine Era

Following the introduction of new vaccines, it is naturally important to monitor disease activity particularly carefully as is the case for varicella. A number of problems need to be addressed.

*An analysis of national death records, 1990–2001, has now been published and confirms a sharp decline in varicella-related deaths. See: Nguyen, H.Q., Jumaan, A.O., and Seward, J.F. (2005). Decline in mortality due to varicella after implementation of varicella vaccination in the United States. *N. Engl. J. Med.* 352, 450–458.

4.1. Identification and Vaccination of Varicella-Susceptibles

In the new era of low VZV circulation, there is a concern that significantly higher numbers of people may reach adulthood without developing immunity because they have neither encountered wild-type VZV nor received vaccine (or have responded poorly to vaccination, see next section). Disease modeling suggests that numerically, cases among adults (along with hospitalizations and deaths) will decline overall provided herd immunity is achieved by high rates of childhood vaccination (Halloran et al., 1994). However, should pockets of susceptibility occur there would be potential for nasty outbreaks of varicella in adults.

The US vaccination policy already calls for the immunization of varicella-susceptible adults (Centers for Disease Control, 1996, 1999), but there are difficulties in meeting this objective, first and foremost of which is the identification of such individuals. In the absence of specific outreach programs, this is very much an opportunistic affair, yet the groups at highest risk of being susceptible to varicella (e.g., immigrant workers) (Centers for Disease Control, 2000) are also among the least likely to participate in regular healthcare. As the first vaccinated cohorts reach adulthood, this problem may well be compounded by a number of factors. Firstly, the reliability of vaccination history is likely to be poor; secondly, there is no good laboratory correlate of immunity following vaccination (Gershon et al., 2004); thirdly, varicella is likely to be sufficiently rare so that public awareness of its risks will be limited. It will be important in public health terms to address each of these points, in order to avoid an excess of adult varicella cases (that will be attributed to failures of the vaccine program). Part of this preparedness should involve a strategy for the containment of outbreaks that would include screening (by history, vaccination records, and serology) and vaccination (including true post-exposure prophylaxis of history-negative individuals).

4.2. Breakthrough Varicella

As discussed above, both primary and secondary vaccine failures were demonstrated during pre-licensure trials. Since the introduction of routine varicella vaccination, active surveillance and studies during outbreaks have confirmed the occurrence of vaccine failure in the field, and offered the opportunity to assess risk factors for this (Table 2.1). At least two outbreaks appear to have been initiated by a case of breakthrough varicella, possibly reflecting primary vaccine failure in those children (Galil et al., 2002c; Lee et al., 2004). A recent study showed that, although in general breakthrough varicella is less transmissible than wild-type disease, this is not the case for those few children who develop more than 50 spots (Seward et al., 2004). It appears that children aged less than 15 months at the time of vaccination are more prone to breakthrough disease (Galil et al., 2002b). Some studies have suggested that individuals with asthma are at increased risk, particularly those requiring systemic steroid therapy (Izuriet al., 1997; Verstraeten et al., 2003); further studies of this effect are ongoing. Administration of VZV vaccine within 28 days of MMR is also associated with vaccine failure.

All of the above-mentioned risk factors can be explained in terms of inadequate induction of adaptive immunity at the time of vaccination. However, the

Table 2.1. Representative Post-licensure Studies of Varicella Vaccine Effectiveness

| Study | Vaccine effectiveness* | | Study setting |
|-------------------------|------------------------|-------------------------|-------------------------------------|
| | All disease | Moderate/severe disease | |
| Clements et al. (1999) | 83% (67–90%) | 100% | Prospective cohort |
| Galil et al. (2002c) | 44% (–6–67%) | 86% | Child care center outbreak |
| Izurietta et al. (1997) | 86% (73–92%) | 100% | Child care center outbreak |
| Lee et al. (2004) | 56% | 90% | School outbreak |
| Seward et al. (2004) | 79% (70–85%) | 92% (84–97%) | Secondary attack rate in households |
| Vazquez et al. (2004) | 87% (81–91%) | 98% (93–99%) | Case control, clinical practice |

* 95% confidence intervals, where available, are shown in parentheses.

majority of individuals experiencing breakthrough varicella do not display these risk factors. Some primary vaccine failures may reflect problems in the preparation and storage of the vaccine, which is heat-labile. In addition, there are indications that the protection afforded by vaccination may wane over time, likely reflecting attrition of the immune response (so-called secondary vaccine failure). One study showed vaccine effectiveness declining after the first year before reaching a plateau (Vazquez et al., 2004), while other studies have suggested a slower effect (risk of breakthrough disease rising at 5 or more years after vaccination) (Lee et al., 2004). These findings at first appear to conflict with earlier data, in which immune responses appeared exceptionally robust (even showing a secondary rise some years after vaccination) (Johnson et al., 1997; Zerboni et al., 1998; Kuter et al., 2004).

What has changed between studies is the level of circulating VZV. There is good evidence of boosting of anti-VZV immune responses by both exposure to wild-type varicella and a second dose of vaccine (Arvin et al., 1983; Watson et al., 1995). Now that varicella is becoming rare, vaccinees may be exposed insufficiently to boost declining immunity to varicella, instead succumbing to breakthrough infection when an exposure eventually occurs (Figure 2.4). If this concept of an immune “threshold” is accurate, then it may be appropriate to consider giving booster doses of varicella vaccine later, as well as measures to maximize initial vaccine responses (e.g., a two-dose schedule or a higher titer vaccine).

4.3. Herpes Zoster

Little is yet known about zoster in vaccinees; in the immunocompromised, vaccine is significantly protective (Hardy et al., 1991) and it is reasonably assumed that zoster incidence will be reduced generally among vaccinated individuals. The mechanisms by which VZV immunity is maintained in the naturally infected host are not clear. Subclinical or abortive reactivations of the latent virus that do not result

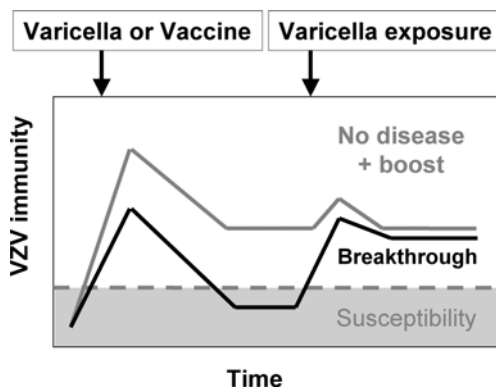


Figure 2.4. A model of VZV-specific immunity. Following vaccination or primary exposure to VZV, specific immunity (antibodies and T-cells) is generated. This wanes slowly over time. On re-exposure to VZV, subjects in whom immunity has fallen below a protective threshold become re-infected and experience breakthrough varicella (or, in the case of the unvaccinated, a second episode of chickenpox). Those with protective immune responses instead experience a boost to their immunity.

in the symptoms of herpes zoster have been demonstrated in the healthy and immunocompromised patients and have been shown to be associated with recovery of cellular immunity to VZV (Hata et al., 2002). Immunity to zoster may also be enhanced by periodic reexposure to VZV (Arvin, 1996; Thomas et al., 2002). There is thus a concern that, following the introduction of universal childhood vaccination, zoster may become more common among adults because of the loss of boosting exposures to varicella (Brisson et al., 2002). Active surveillance of zoster cases (among both vaccinated and unvaccinated) is underway in sentinel counties of the United States and will be important to guide future public health policy. While VZV IgG titers do not decrease with age, VZV-specific T cell responses decline. One possibility that is being pursued is to immunize aging individuals against zoster, using a higher potency, live attenuated VZV vaccine (Levin et al., 1998, 2003b); the results of a large trial are expected soon. Although current evidence suggests that the live attenuated varicella virus is less likely to reactivate than the wild-type viruses that circulate in the population, trends in zoster incidence over time may indicate that individuals who have been vaccinated against varicella would benefit from later immunization against zoster. An alternative strategy that might be particularly useful to protect immunocompromised individuals against zoster would be an inactivated VZV vaccine (Hata et al., 2002).

5. Summary

The most compelling rationale for introducing universal vaccination against varicella was the predicted benefits to healthy children. Current evidence from the US experience indicates that these benefits are being realized. As is true for any new vaccine, implementation of such a program necessitates disease surveillance and

modifications of the vaccine regimen as needed. In the case of VZV, the epidemiology of herpes zoster must be tracked as well as varicella disease trends. The prevention of herpes zoster may be another use of live attenuated or inactivated varicella vaccines.

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