Published in final edited form as:

Adv Exp Med Biol. 2010 ; 659: 83–87. doi:10.1007/978-1-4419-0981-7_7.

Vaccination Against Varicella: What's the Point?

Anne A. Gershon

Department of Pediatrics, Columbia University College of Physicians and Surgeons, New York, NY 10032, USA

1 Introduction

Live attenuated varicella vaccine was developed in Japan in the early 1970s as a means to prevent varicella primary infection with varicella-zoster virus (VZV) in healthy and immunocompromised individuals (Takahashi et al., 1974). Takahashi had attenuated the virus by passage in various cell cultures using different propagation temperatures and produced a candidate vaccine virus that proved to be both safe and immunogenic. Initially, there was great controversy as to whether it was likely to be safe to develop a vaccine that had the potential to become latent after immunization and that might even be oncogenic (Brunell, 1977, 1978). It was also questioned as to whether varicella was a serious enough disease to be worth preventing.

Despite numerous objections, during the 1980s, a number of clinical trials in leukemic and healthy varicella-susceptible children and adults were undertaken, culminating in 1995, in the licensure of varicella vaccine and its recommendation as a routine childhood immunisation in the United States (Gershon et al., 2008). Clinical trials indicated that the Takahashi vaccine strain Oka was highly immunogenic, safe, and produced long-term immunity in healthy children and selected immunocompromised children. By the turn of the century, most of the published data on varicella vaccine had emanated from the United States, following commencement of routine administration (Centers for Disease Control, 1996). This manuscript discusses recent data on the saga of live attenuated varicella vaccine use in healthy children following its licensure in the United States.

By way of background, varicella is a generalized illness with a moderately long incubation period (2 weeks) and viremic phases as the rash develops. It represents primary infection with VZV. During varicella, latent infection with VZV develops in dorsal root ganglia (DRG) and cranial nerve ganglia (CNG). For the lifetime of most individuals the virus remains quiescent, but about 30% go on to manifest clinical zoster, usually in the 6th to the 8th decade of life when cell mediated immunity (CMI) to VZV wanes due to normal aging (Oxman et al., 2005). Zoster is a secondary infection with VZV, due to the same virus that was acquired during varicella (Breuer, 2003). Simply stated, varicella develops in persons with no humoral immunity to VZV; zoster develops in persons lacking CMI to VZV.

The Oka strain of live attenuated varicella virus was developed in the 1970s by Takahashi and his colleagues in Osaka, Japan (Takahashi et al., 1974). It was subjected to small studies there, and there seemed to be interest in bringing the vaccine to the west. In 1978, an international conference was held at NIH that included outstanding basic and clinical virologists of the era, to discuss whether varicella vaccine should be studied in the United States. A plethora of clinical trials in leukemic children and healthy adults and children soon followed, and, in 1995, as a result of their success regarding safety, immunogenicity, and protection, the vaccine was licensed in the United States (Gershon et al., 2008, 1984). One dose was recommended for children less than 13 years old, and two doses (at least 1 month apart) was recommended for older susceptible individuals. Routine immunisation was begun for children between the ages of 12 and 18 months.

At present, there is no question that this vaccine is highly effective. The incidence of varicella in the vaccinated and unvaccinated has decreased by about 80% as have hospitalizations for chickenpox and mortality from them (Gershon et al., 2008; Seward et al., 2002). A case control study indicated that not only was the vaccine about 85% protective from clinical varicella but also, with time over 8 years after vaccination, there was no loss of immunity. (Gershon et al., 2007; Vazquez et al., 2001; 2004). While an epidemiologic study suggested that there might be waning immunity after varicella vaccination, it did not consider the potential importance of primary vaccine failure that might be confused with secondary vaccine failure (Gershon et al., 2007; Chaves et al., 2007). A number of other studies also indicated that the vaccine was about 85% effective in preventing varicella (Gershon et al., 2008). However, it was disconcerting, that despite high rates of vaccine coverage, outbreaks of chickenpox still occurred in schools. When vaccine efficacy was calculated during these outbreaks, it was reported to vary from 44 to 100%, with an average of about 80%. The vaccine was not proving to be as effective as it had been projected from clinical trials (Gershon et al., 2008).

An additional potential concern about the vaccine was whether there would be an increase in the incidence of varicella in young adults who were not vaccinated, who had never achieved immunity after vaccination, or who had become only temporarily immune to varicella. Another concern was whether there would be a serious increase in the incidence of zoster in individuals who had experienced natural varicella in the past but lost CMI due to a decrease in re-exposure to VZV because vaccination resulted in decreased circulation of the virus.

Understanding basic aspects of the natural history of VZV infection is helpful in understanding the pathogenesis of both varicella and zoster. VZV is a highly cell-associated virus when propagated in cell culture. It does not emerge in infectious form from the cells in which it grows, and therefore its only means of spread is from one cell to another (Chen et al., 2004). In the human body, VZV spreads by the same means, slowly from one cell to another. This slow spread from cell to cell explains why the humoral antibody response has little impact on recovery from varicella; cell free virions, which can be neutralized by specific antibodies, do not develop in the body as VZV spreads. In order to defend against VZV that is spreading in the body, CMI is required. However, there is one place in the body where cell-free virus is released from infected cells, and this is in the superficial epidermis, where one of the receptors of VZV that confines it to cells is not synthesized; as a result,

VZV is able to escape from the cell in infectious form. VZV in vesicle fluid is cell free, well formed, and highly infectious; it is also capable of causing latent infection. Because latent virus can remain safe for decades in a host and later emerge and infect a whole new population of younger individuals who have never previously seen this virus and are therefore susceptible to it, this has enormous significance for the biology and survival of VZV. In turn, these younger individuals, develop chickenpox followed by latency, and the virus survives for another generation.

There is evidence that preventing VZV from infecting the skin can decrease the incidence of zoster. Children with underlying leukemia have a high incidence of zoster during their chemotherapeutic treatment if they have had varicella. In contrast, vaccinated leukemic children have a lower incidence of development of zoster, although those with a history of a vaccine associated VZV rash are more likely to develop zoster than vaccinees with no rash (Hardy et al., 1991). Hypothesis exist that there is less zoster because most vaccinated children do not develop VZV rashes. In vitro studies of the Oka strain of VZV indicate that it is quite capable of causing latent infection with VZV (Chen et al., 2003). It seems likely that varicella vaccine is not only effective in preventing varicella but also in preventing zoster. The lower incidence of zoster in vaccinees as compared to those with previous natural infection has been found in leukemic children following renal transplantation and in children with HIV infection (Gershon et al., 2008). Whether this will also be true for healthy children will not be known for certain for decades when these children, vaccinated in the mid-1990s, become older adults.

How can we explain the failure of 15% of vaccinated children to develop protective immunity to varicella after vaccination? This level of protection is lower than that seen after measles and rubella immunization. Could it be due to the fact that VZV causes latent infection? Is there another factor that is involved, and what might this be?

At one time, it was thought that the dose of virus in a live vaccine was unimportant as long as the virus could multiply in the host in order to stimulate the immune system. However, studies with measles vaccine failed to confirm this hypothesis (Aaby et al., 1996). We now know that generally speaking for varicella vaccine, the higher the immunizing dose the stronger the immune response (Krause and Klinman, 1995). Nevertheless, when varicella vaccine was being developed, it was common to determine the lowest dose that would stimulate an antibody response. Possibly the dose of virus in the licensed vaccine in the US is on the low side for stimulation of immunity to VZV. Although clinical trials suggested that this dose stimulated humoral immunity in about 95% of children, the test that was used yielded false positive results when low levels of immunity were being assessed (Provost et al., 1989, 1991). In contrast, a group of 138 children in New York, Tennessee, and California were tested for seroconversion after receiving 1 dose of the vaccine licensed in the United States, using the fluorescent antibody to membrane antigen (FAMA) assay, which is the "gold standard" (Williams et al., 1974); only 76% of these children seroconverted (Michalik et al., 2008). These results were one of the reasons that a second dose of varicella vaccine was mandated in 2006 by the Centers for Disease Control and Prevention (CDC) for all children. At present, studies in the US are underway to determine whether the second dose confers more protection than only 1 dose.

It is projected that 2 doses will provide more protection than 1 dose, and that use of 2 doses of measles-mumps-rubella-varicella vaccine will be even more effective against varicella than two doses of the monovalent vaccine (Kuter et al., 2004; Shinefield et al., 2006). The goal is to decrease circulation of VZV to the lowest possible levels and to have a highly immunized population in order to decrease both varicella and zoster. Judicious use of the zoster vaccine may also help to achieve this goal (Oxman et al., 2005).

References

- Aaby P, Samb B, Simondon F, et al. A comparison of vaccine efficacy and mortality during routine use of high-titre Edmonston-Zagreb and Schwarz standard measles vaccines in rural Senegal. *Trans R Soc Trop Med Hyg.* 1996; (90):326–330. [PubMed: 8758096]
- Breuer J. Monitoring virus strain variation following infection with VZV: is there a need and what are the implications of introducing the Oka vaccine? *Commun Dis Public Health.* 2003; (6):59–62. [PubMed: 12736975]
- Brunell PA. Commentary: protection against varicella. *Pediatrics.* 1977; (59):1–2.
- Brunell PA. Varicella vaccine: the crossroads is where we are not! *Pediatrics.* 1978; (62):858–859.
- Centers-for-Disease-Control. Prevention of varicella: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *Morb Mort Wkly Rep.* 1996; (45):1–36.
- Chaves SS, Gargiullo P, Zhang JX, et al. Loss of vaccine-induced immunity to varicella over time. *N Engl J Med.* 2007; (356):1121–1129.
- Chen J, Gershon A, Silverstein SJ, Li ZS, Lungu O, Gershon MD. Latent and lytic infection of isolated guinea pig enteric and dorsal root ganglia by varicella zoster virus. *J Med Virol.* 2003; (70):S71–S78. [PubMed: 12627492]
- Chen JJ, Zhu Z, Gershon AA, Gershon MD. Mannose 6-phosphate receptor dependence of varicella zoster virus infection in vitro and in the epidermis during varicella and zoster. *Cell.* 2004; (119):915–926.
- Gershon AA, Arvin AM, Shapiro E. Varicella vaccine. *N Engl J Med.* 2007; (356):2648–2649.
- Gershon AA, Steinberg S, Gelb L. NIAID-Collaborative-Varicella-Vaccine-Study-Group. Live attenuated varicella vaccine: efficacy for children with leukemia in remission. *JAMA.* 1984; (252):355–362. [PubMed: 6330386]
- Gershon, A., Takahashi, M., Seward, J. Live attenuated varicella vaccine. In: Plotkin, S. Orenstein, W., Offit, P., editors. *Vaccines*. Philadelphia: WB Saunders; 2008. p. 915-958.
- Hardy IB, Gershon A, Steinberg S, LaRussa P, et al. The incidence of zoster after immunization with live attenuated varicella vaccine. A study in children with leukemia. *N Engl J Med.* 1991; (325):1545–1550. [PubMed: 1658650]
- Krause P, Klinman DM. Efficacy, immunogenicity, safety, and use of live attenuated chickenpox vaccine. *J Pediatr.* 1995; (127):518–525. [PubMed: 7562270]
- Kuter B, Matthews H, Shinefield H, et al. Ten year follow-up of healthy children who received one or two injections of varicella vaccine. *Pediatr Infect Dis J.* 2004; (23):132–137. [PubMed: 14872179]
- Michalik DE, Steinberg SP, LaRussa PS, et al. Primary vaccine failure after 1 dose of varicella vaccine in healthy children. *J Infect Dis.* 2008; (197):944–949. [PubMed: 18419532]
- Oxman MN, Levin MJ, Johnson GR, et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *N Engl J Med.* 2005; (352):2271–2284.
- Provost PJ, Krah DL, Kuter BJ, et al. Antibody assays suitable for assessing immune responses to live varicella vaccine. *Vaccine.* 1991; (9):111–116. [PubMed: 1647574]
- Provost P, Krah D, Miller W, et al. Comparative sensitivities of assays for antibodies induced by live varicella vaccine. *Interscience Conference on Antimicrobial Agents and Chemotherapy.* 1989
- Seward JF, Watson BM, Peterson CL, et al. Varicella disease after introduction of varicella vaccine in the United States, 1995–2000. *JAMA.* 2002; (287):606–611. [PubMed: 11829699]
- Shinefield H, Black S, Thear M, et al. Safety and immunogenicity of a measles, mumps, rubella and varicella vaccine given with combined Haemophilus influenzae type b conjugate/hepatitis B

vaccines and combined diphtheria-tetanus-acellular pertussis vaccines. *Pediatr Infect Dis J*. 2006; (25):287–292. [PubMed: 16567978]

Takahashi M, Otsuka T, Okuno Y, Asano Y, Yazaki T, Isomura S. Live vaccine used to prevent the spread of varicella in children in hospital. *Lancet*. 1974; (2):1288–1290.

Vazquez M, LaRussa P, Gershon A, Steinberg S, Freudigman K, Shapiro E. The effectiveness of the varicella vaccine in clinical practice. *N Engl J Med*. 2001; (344):955–960. [PubMed: 11274621]

Vazquez M, LaRussa PS, Gershon AA, et al. Effectiveness over time of varicella vaccine. *JAMA*. 2004; (291):851–855. [PubMed: 14970064]

Williams V, Gershon A, Brunell P. Serologic response to varicella-zoster membrane antigens measured by indirect immunofluorescence. *J Infect Dis*. 1974; (130):669–672.