A Review of Varicella Vaccine

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The Food and Drug Administration licensed varicella vaccine in March 1995. Data are now available from 6 years of its use representing approximately 24 million vaccinations. The impact of universal varicella immunization recommendations has made it clear that the prevention of varicella is as important as the prevention of the other routine childhood diseases.¹

Although vaccine coverage rates have improved, the National Health Interview Survey shows considerable variation throughout the United States—from 16% in Idaho to 78% in states with child care and school regulations requiring this vaccine (e.g., Maryland).² What is behind this discrepancy?

Physicians who routinely administer varicella vaccine with the other childhood vaccines find that most parents (70% to 90%) agree to vaccination.³ Physicians who do not vaccinate against varicella help to maintain a large pool of susceptible hosts. These susceptible hosts will have less chance of being exposed to varicella during childhood because the varicella vaccination program has reduced the incidence of this disease during childhood by more than 80%.⁴ Unfortunately, the susceptible hosts will become more difficult to reach for preventive care services as they become older, but varicella virus—a highly contagious virus spread primarily in respiratory secretions—will probably eventually reach them. Of course, older susceptible hosts are at greatly increased risk for complications of varicella compared with children.

COMMON QUESTIONS

Reviewing the answers to the following common questions from parents may help pediatricians increase varicella vaccination as part of standard care.

Is Varicella Worth Preventing?

Approximately 100 deaths are attributable to complications of varicella annually in the United States. For example, when varicella vaccine first became available to the private sector in 1995–1996, there were 76 wild varicella–related deaths, 52 of which occurred in children 1 to 9 years old.¹ Eighty percent of these were previously healthy children. There are currently more pediatric deaths due to varicella than to any other disease for which a vaccine is routinely recommended (except pneumococcus).⁵

Although the severity of varicella is extremely variable, the average number of lesions (an index of severity) ranges from 250 to 500. The most common complications are secondary bacterial infections of the skin and soft tissues. The

EDUCATIONAL OBJECTIVES

1. Provide answers to the most common questions asked by parents of their pediatricians regarding varicella vaccination.
2. Review the latest recommendations of the Advisory Committee on Immunization Practices and the American Academy of Pediatrics regarding immunization of children with the varicella vaccine.

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most dreaded of these is necrotizing fasciitis caused by group A β-hemolytic streptococci. Other complications include pneumonia, central nervous system dysfunction, and gastrointestinal complaints. The risk of complications increases with age such that morbidity and mortality rates are 10 to 20 times greater in adolescents and adults than in children.6 Nonetheless, approximately 11,000 previously healthy individuals in the United States (46% of them children) are hospitalized each year secondary to complications of varicella. This number may still be an underestimate because not all states report varicella hospitalizations.

How Effective Is the Vaccine?
The protective efficacy of varicella vaccine has been evaluated by three different methods (historical-control, placebo-control, and household exposure studies) during clinical trials, and 5 field studies of the currently licensed varicella vaccine have been published. Pre-licensure studies indicated that varicella vaccine was approximately 95% effective for the prevention of severe disease and 70% to 91% effective for the prevention of all clinical varicella.3 Post-licensure studies are reassuring in that the vaccine’s effectiveness, measured during community outbreaks and in community settings, is similar to that described in pre-licensure studies.7

Can Children Acquire Varicella if They Have Had the Vaccine?
In clinical trials, the seroconversion rate of children who received one dose of vaccine was approximately 97% within 4 to 6 weeks of vaccination.8-11 Seroconversion rates in adults and adolescents who received two doses reached 99% within 4 to 6 weeks of the second dose. Individuals who seroconverted either were completely protected or had a mild case of varicella (fewer than 50 vesicles and none of the complications expected with natural varicella).12

These mild cases of varicella, which develop 42 days or more after vaccination of an individual who responded to the vaccine initially, are referred to as breakthrough cases. Current follow-up of the post-licensure lots has demonstrated a breakthrough rate of 1% per year and this has not changed in 7 years (Merck & Co., Inc., personal communication, November 2000). During the pre-licensure clinical trials, children received varying doses of vaccine. These children have been observed for 5 to 10 years and their breakthrough rates have varied from 2% to 4% per year.13,14 Breakthrough disease does not appear to increase in severity with increasing time since immunization, emphasizing the role of the anamnestic immune response in long-term protection. Data from the Philadelphia active surveillance sites show that, when viewed cumulatively, the proportion of breakthrough varicella cases reported increased from 0.1% in 1995 to 25% in 2000. Data from Los Angeles are similar.15

Parents should be told that the vaccine is 95% to 100% effective in preventing severe varicella and approximately 90% effective in preventing all clinical varicella. Approximately 10% of those who are vaccinated will have mild varicella following a close exposure to wild varicella.1

Should Children With Breakthrough Varicella Be Excluded From School or Child Care?
Further studies of transmission in community settings and households are needed to answer this question. It is likely that transmission from breakthrough cases is less than that from natural varicella, given the few lesions (and thus low virus load) in the former (Fig. 1).

Often, other rashes (eg, scabies and coxsackievirus) are presumed to be varicella. This author believes that physicians should obtain a culture (when possible) from any vaccinated child who has a suspicious vesicular rash. Laboratory confirmation of such vesicular rashes is now free through Merck’s varicella-zoster identification service (212-305-1556) and the Centers for Disease Control and Prevention’s (CDC’s) National Varicella Laboratory (404-639-0066). Both laboratories use polymerase chain reaction techniques to identify viral strains so as to differentiate between “wild” and “vaccine” strains. The results depend on adequate specimen collection (ie, one needs plenty of epithelial cells, similar to collecting a sample for direct fluorescent antigen studies). Instructions and specimen collection kits can be obtained from the CDC.
How Safe Is the Varicella Vaccine?

Local reactions around the injection site are the most common complaints, but these are typically mild. Fever within 42 days of vaccination also has been recorded as an adverse vaccine effect.\(^16\)

Before licensure of the vaccine in 1995, approximately 11,000 individuals in study groups were vaccinated with varicella vaccine. This provided the initial information regarding the safety and effectiveness of the vaccine. Since licensure, a far larger number of children have received the vaccine and the Vaccine Adverse Event Reporting System (VAERS)\(^17\) has demonstrated additional possible adverse effects. The most common VAERS report involved rashes following varicella vaccine. Others include thrombocytopenia, secondary transmission, secondary bacterial skin infections (eg, cellulitis), and various neurologic syndromes, including Guillain–Barré syndrome. Although VAERS reports do not prove a causal association with vaccination, they are important as a way to generate hypotheses that can then be explored through active, prospective studies.

Can Vaccinated Children Spread Varicella Virus?

Initial evidence for transmission of the vaccine virus came from children with leukemia who were vaccinated. They frequently had rashes associated with varicella vaccine. They also had more lesions than did children with competent immune systems who had rashes associated with varicella vaccine. This is why varicella vaccine is used only under protocol for patients with cellular immunosuppression. However, in this setting, a transmission rate of 17% occurred.\(^18\)

Since marketing of the vaccine began in 1995, only three healthy vaccinated children have had documented transmission of vaccine virus.\(^3\) All of them had a vesicular rash. A 1-year-old boy receiving topical steroids for eczema had 30 generalized vesicular lesions. He transmitted varicella to his seronegative pregnant mother, who chose to abort the fetus, from which no varicella DNA was identified. Another 1-year-old child had two vesicular lesions 14 days after varicella vaccination. A 4.5-month-old sibling had varicella 19 days later. A 1-year-old boy had 12 lesions 17 days postvaccination. His 35-year-old father had a varicella-like rash 17 days later.

Not all varicella-like rashes following vaccination are from vaccine virus. In fact, based on polymerase chain reaction analysis, virus isolated from rashes 2 weeks after vaccination is usually a “wild” strain (ie, the individual was, unfortunately, incubating the disease when vaccinated). When virus is isolated from rashes between 2 and 4 weeks after varicella vaccination, the vaccine strain is usually recovered. When virus is isolated from breakthrough cases more than 4 weeks after vaccination, the wild strain is most common.

Although we are concerned about the exposure of susceptible pregnant women to vaccine recipients who have a rash, there are data suggesting that this concern is overemphasized.\(^3\) There have been susceptible pregnant women who have been inadvertently vaccinated and some women who have become pregnant shortly after vaccination despite having been advised against allowing this to happen. Excluding those
who elected to have a therapeutic abortion, pregnancy outcomes and rates of spontaneous abortion among these women were no different from those of the general population. Data from before and after licensure reinforce this. Women who are immunized during pregnancy should be reported to the Varicella Pregnancy Registry at 1-800-986-8999.

**Will the Varicella Vaccine Increase the Incidence of Zoster?**

This question arises because varicella is a herpes virus with both a primary disease (varicella or chickenpox) and a reactivated disease (zoster or shingles). Currently, cases of zoster in vaccinated individuals have been mild and without complications. Actually, the information gathered thus far suggests that the vaccine reduces the incidence of zoster.\(^{19}\)

Among children, the expected incidence of zoster is 77 per 100,000 person-years. Only 8 cases of zoster have been reported thus far among the 45,000 person-years in clinical vaccine trials. This represents an incidence of 18 cases per 100,000 person-years. The incidence of natural zoster in adults is approximately 131 per 100,000 person-years. There has been only 1 case of zoster reported in vaccinated adults, for a calculated incidence of 12.8 per 100,000 person-years.\(^{20}\) Hardy and Gershon found a fivefold reduction of zoster when they compared individuals with leukemia who had natural varicella with individuals with leukemia who had received varicella vaccine.\(^{18}\)

Some zoster in vaccinated individuals results from prior natural varicella infections. This was demonstrated when the viruses cultured from the skin vesicles of one vaccinated child and one vaccinated adult were identified as wild zoster by using restriction endonuclease analysis.\(^{21}\) Levin et al. have used an experimental varicella vaccine in individuals older than 40 years to determine whether zoster and post-herpetic neuralgia can be prevented by boosting the cell-mediated immune responses.\(^{19}\) The initial findings are promising.

**How Long Does Immunity Persist?**

Measles, mumps, rubella, and polio are all more serious in adults than in children, so this concern about persistent immunity was posed for them in the 1970s. Systemic viral vaccines induce cellular immunity and, with it, anamnestic immune responses. So it is reasonable to assume that immunity from varicella vaccine will last a lifetime. However, we do not have final data to show that immunity will not wane during a lifetime or that reexposure will result in an anamnestic immune response within 5 to 7 days (ie, before the end of the natural incubation phase of this pathogen).\(^{6}\) We do have information that demonstrates long-term persistence of antibody from varicella vaccination in Japan for 20 years and in the United States for 10 years\(^{13,14}\) and 16 years (B. Watson, MD, unpublished data, December 2000). Ongoing studies continue to confirm this.\(^{3}\)

**What Are the Requirements for Storing and Handling Varicella Vaccine?**

Varicella vaccine has special storage issues because of its sensitivity to temperature. Shipment and storage in a frozen state is essential to maintain potency. It is critical to follow the manufacturer’s recommendations regarding handling, both before and after reconstitution, to guarantee vaccine efficacy. Temporary storage at refrigerated temperatures is allowed for up to 3 consecutive days. If storage and handling requirements have not been followed, vaccination of susceptible individuals will result in reduced or no protection.\(^{20}\) We will receive more reports of varicella in vaccinated individuals, which, in turn, will reflect badly on varicella vaccine in general. Vaccines that are stable in the refrigerator are being investigated.

**NEW RECOMMENDATIONS FROM THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES (ACIP) AND THE AMERICAN ACADEMY OF PEDIATRICS POSTEXPOSURE VACCINATION AND OUTBREAK CONTROL**

Outbreaks in child care centers may last 3 to 5 months, with cumulative attack rates of 88% among unvaccinated children. Similarly, outbreaks in closed institutions (eg, homeless shelters for families) may last 6 months. Varicella vaccination within 3 to 5 days of exposure was not studied using the licensed vaccine, but several published studies of various pre-licensure lots
demonstrated their efficacy.\textsuperscript{7} It is possible that timely vaccination following exposure to varicella could curtail an outbreak.

The Philadelphia Department of Health used the vaccine in this way in 1998 after notification of 2 varicella cases within 36 hours of diagnosis of varicella. Data in this setting demonstrated the efficacy of the vaccine for prevention of all disease (95%) and severe disease (100%). Specifically, the outbreak consisted of just 5 cases and lasted only 3 weeks. The shelter was closed to new admissions for 6 weeks.

In comparison, a varicella outbreak occurred in another homeless shelter with 450 families, but reporting was delayed and no vaccine intervention was undertaken.\textsuperscript{16} Cases were isolated and several individuals were treated with acyclovir. This outbreak included 63 cases and the shelter was closed for 6 months.

Thus, varicella vaccine may shorten outbreaks by preventing or modifying disease among a proportion of individuals already exposed and by preventing cases among individuals not yet exposed. Local and state health departments should consider the use of varicella vaccine for controlling outbreaks by either advising susceptible individuals who have been exposed to contact their regular health care provider for vaccination or offering vaccination themselves.\textsuperscript{16}

\textbf{Use}

\textit{Children Infected With Human Immunodeficiency Virus (HIV).} Varicella vaccine may be administered to children infected with HIV with age-specific CD4+ T-lymphocytes greater than 25%. Varicella vaccine may be administered to children infected with HIV who do not have symptoms of acquired immunodeficiency syndrome (AIDS).

\textit{Child Care and School Entry.} The ACIP encourages the establishment of state-based varicella vaccine requirements for child care and school entry.

\textit{Susceptible Older Individuals.} The CDC continues to be notified of deaths due to wild varicella among healthy adults, usually the parents of young children. The ACIP voted in February 1999 to recommend varicella vaccine for all susceptible individuals, regardless of age, who are at high risk for varicella exposure.

\textbf{U.S. Military Populations.} Military populations experienced marked increases in the rates of varicella in the 1980s. In the U.S. Army, the hospital admission rate for varicella was 1.3 per 1,000 person-years in 1988, which represented a 4-fold rise from the 1980 rate.\textsuperscript{22} Enlisted personnel in the U.S. Navy experienced an 18-fold rise in varicella-related admission rates, from fewer than 0.2 per 1,000 person-years in 1975 to 2.7 per 1,000 person-years in 1988.\textsuperscript{22} In 1989, an outbreak on a large military ship produced 109 cases (11% attack rate). At Great Lakes, Illinois, in 1987, 758 hospital admissions (19.7 per 1,000 person-years) occurred among military recruits and students because of varicella.

The high rate of varicella may have occurred because approximately 7% of recruits entering military service in 1989 were susceptible to varicella.\textsuperscript{23,24} This higher than expected incidence of susceptibility to varicella may reflect an increase in the proportion of recruits who were raised in tropical areas (e.g., Puerto Rico) where varicella is not as common.

Currently, all enlisted personnel in the U.S. Navy (approximately 45,000 per year) begin their career at the training center in Great Lakes, Illinois. A varicella prevention program was started there in December 1996. All recruits are screened, and seronegative recruits receive two doses of varicella vaccine, as well as all other required vaccines (e.g., measles–mumps–rubella). Hospitalization rates for Navy and Marine Corps members had already begun to drop between 1987 and 1994,\textsuperscript{24} probably because prompt treatment with acyclovir limited spread. However, more recent inpatient discharge data demonstrate that the downward trend has continued for all military services. In 1997, the hospital admission rate was only 0.24 per 1,000 person-years.\textsuperscript{6}

Varicella is a preventable threat to military readiness. The ACIP recommends varicella vaccination for all susceptible individuals, including adults.\textsuperscript{7}

\textbf{CONCLUSION}

The impact of universal varicella immunization recommendations is exciting. Herd immunity has led to decreases in disease in all varicella active surveillance sites.\textsuperscript{1} In recent years, the incidence of varicella in Philadelphia has dropped
REFERENCES


