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Summary

Two live, attenuated varicella zoster virus--containing vaccines are available in the United States for prevention of

varicella: 1) a single-antigen varicella vaccine

(VARIVAX,® Merck & Co., Inc., Whitehouse Station, New Jersey), which was licensed

in the United States in 1995 for use among healthy children aged

>12 months, adolescents, and adults; and 2) a

combination measles, mumps, rubella, and varicella vaccine

(ProQuad,® Merck & Co., Inc., Whitehouse Station, New Jersey), which

was licensed in the United States in 2005 for use among healthy children aged 12

months--12 years. Initial Advisory

Committee on Immunization Practices (ACIP) recommendations for prevention of

varicella issued in 1995 (CDC. Prevention

of varicella: recommendations of the Advisory Committee on Immunization Practices

[ACIP]. MMWR 1996;45[No.

RR-11]) included routine vaccination of children aged 12--18 months, catch-up

vaccination of susceptible children aged 19

months--12 years, and vaccination of susceptible persons who have close contact with

persons at high risk for serious complications

(e.g., health-care personnel and family contacts of immunocompromised persons). One

dose of vaccine was recommended

for children aged 12 months--12 years and 2 doses, 4--8 weeks apart, for persons aged

>13 years. In 1999, ACIP updated the recommendations (CDC. Prevention of varicella:

updated recommendations of the Advisory Committee on

Immunization Practices [ACIP]. MMWR 1999;48[No. RR-6]) to include establishing child

care and school entry requirements, use of

the vaccine following exposure and for outbreak control, use of the vaccine for certain

children infected with

human immunodeficiency virus, and vaccination of adolescents and adults at high risk

for exposure or transmission.

In June 2005 and June 2006, ACIP adopted new recommendations regarding the use of

live, attenuated varicella

vaccines for prevention of varicella. This report revises, updates, and replaces the 1996

and 1999 ACIP statements for prevention

of varicella. The new recommendations include 1) implementation of a routine 2-dose varicella vaccination program

for children, with the first dose administered at age 12--15 months and the second dose at age 4--6 years; 2) a second dose

catch-up varicella vaccination for children, adolescents, and adults who previously had received 1 dose; 3) routine vaccination of

all healthy persons aged >13 years without evidence of immunity; 4) prenatal assessment and postpartum vaccination;

5) expanding the use of the varicella vaccine for HIV-infected children with age-specific CD4+T lymphocyte percentages of

15%--24% and adolescents and adults with CD4+T lymphocyte counts

>200 cells/μL; and 6) establishing middle school,

high school, and college entry vaccination requirements. ACIP also approved criteria for evidence of immunity to varicella.

Introduction

Varicella is a highly infectious disease caused by the varicella-zoster virus (VZV). Secondary attack rates for this virus

might reach 90% for susceptible household contacts. VZV causes a systemic infection that results typically in lifetime immunity.

In otherwise healthy persons, clinical illness after reexposure is rare.

In 1995, a vaccine to prevent varicella

(VARIVAX,® Merck & Co., Inc., Whitehouse Station, New Jersey) was licensed

in the United States for use among healthy children aged

>12 months, adolescents, and adults; recommendations of the

Advisory Committee on Immunization Practices (ACIP)

regarding use of the varicella vaccine have been published previously

(1,2) This report revises, updates, and replaces earlier ACIP statements

(Table 1).

Methods

In response to increasing reports of varicella outbreaks among highly vaccinated

populations

(3--6), ACIP's measles-mumps-rubella and varicella (MMRV) workgroup first met in

February 2004 to review data related to varicella vaccine use in

the United States since implementation of the vaccination program in 1995 and to

consider recommendation options

for improving control of varicella disease. The workgroup held monthly conference calls

and met in person three times a year.

The workgroup reviewed data on the impact of the 1-dose varicella vaccination

program, including data on vaccination

coverage, changes in varicella epidemiology, transmission from vaccinated persons

with varicella, vaccine effectiveness,

immune response to vaccination, evidence of immunity, and potential risk factors for

vaccine failure. Published and

unpublished data related to correlates of protection, safety, immunogenicity, and

efficacy† of the new quadrivalent MMRV vaccine and

the immunogenicity and efficacy of a second dose of varicella vaccine also were

reviewed.

Cost-benefit and cost-effectiveness analyses were considered, including revised

cost-benefit analysis of both the 1- and 2-dose programs for children

compared with no vaccination program and the incremental benefit of a second dose.

Presentations were made to the full ACIP meetings in October 2004, February 2005, June 2005, and June 2006. Recommendation options were developed and discussed by the MMRV workgroup. When definitive research evidence was lacking, the recommendations incorporated expert opinion of the workgroup members. The workgroup sought input from partner organizations (i.e., the American Academy of Pediatrics [AAP], the American Academy of Family Physicians [AAFP], the American College of Obstetricians and Gynecologists, the Council of State and Territorial Epidemiologists, and the Association of Immunization Managers) and from state public health professionals and immunization program directors. Proposed recommendations and a draft statement were presented to the full ACIP in June 2005 and June 2006. After deliberations, final ACIP recommendations were approved in 2005 and 2006. Modifications to the draft statement were made following CDC and external review process to update and clarify wording in the document.

Epidemiology of Varicella

General

VZV is transmitted from person to person by direct contact, inhalation of aerosols from vesicular fluid of skin lesions of acute varicella or zoster, or infected respiratory tract secretions that also might be

aerosolized. The virus enters the

host through the upper-respiratory tract or the conjunctiva.

The average incubation period for varicella is 14--16

days§ after exposure to rash; however, this period can vary (range:

10--21 days). The period of contagiousness of infected persons is estimated to begin

1--2 days before the onset of rash and to

end when all lesions are crusted, typically 4--7 days after onset of rash

(7). Persons who have progressive varicella

(i.e., development of new lesions for >7 days) might be contagious longer, presumably

because their immune response is

depressed, which allows viral replication to persist. VZV

remains dormant in sensory-nerve ganglia and might be

reactivated at a later time, causing herpes zoster (HZ) (i.e., shingles), a painful

vesicular rash typically appearing in a dermatomal distribution

of one or two sensory-nerve roots.

Since implementation of a universal childhood varicella vaccination program in 1995,

the epidemiology and

clinical characteristics of varicella in the United States have changed, with substantial

declines in morbidity and mortality

attributable to varicella. No consistent changes in HZ epidemiology have been

documented.

Vaccinated persons might develop modified varicella disease with atypical

presentation. Varicella disease that develops

>42 days after vaccination (i.e., breakthrough varicella) typically is mild, with <50 skin

lesions, low or no fever, and shorter

(4--6 days) duration of illness. The rash is more likely to be predominantly

maculopapular rather than vesicular.

Nevertheless, breakthrough varicella is contagious.

Prevaccine Era

Before the introduction of varicella vaccine in 1995, varicella was a universal childhood disease in the United States,
with peak incidence in the spring and an average annual incidence of 15--16 cases per 1,000 population. On the basis of data
from the National Health Interview Survey (NHIS) for 1980--1990, an average of 4 million cases were estimated to have
occurred

annually (annual incidence rate: 15 cases per 1,000 population)
(8). Varicella was not a nationally notifiable disease
when vaccine was introduced in 1995, and surveillance data were limited. In 1994, only 28 states, the District of Columbia,
and New York City reported cases to CDC's National Notifiable Disease Surveillance System (NNDSS); reporting was
passive, with estimated completeness ranging from <0.1% to 20%
(9).
In multiple studies, age-specific incidence data were derived from NHIS and from state and local surveys
(8,10,11). During 1980--1990, an estimated 33% of cases occurred among preschool-aged children (i.e., children aged 12 months--4 years),
and 44% occurred among school-aged children (i.e., children aged 5--9 years) (annual incidence rates: 82.8 and 91.1 cases
per 1,000 children, respectively). Approximately 90%--92% of cases occurred among

persons aged <15 years, and cases

occurred rarely among persons aged >50 years. However, studies using data from state and local surveys conducted during

1990--1992 and during 1994--1995 indicated that the highest incidence of varicella occurred among preschool-aged rather than

school-aged children, indicating that the disease was being acquired at earlier ages (10,11). National seroprevalence data for

1988--1994 indicated that 95.5% of adults aged 20--29 years, 98.9% of adults aged 30--39 years, and >99.6% of adults aged

>40 years were immune to VZV (12). However, for reasons that are not well

understood, the epidemiology of varicella differs between countries with temperate and tropical climates

(13--18). In the majority of countries with temperate climates,

>90% of persons are infected by adolescence whereas in countries with tropical climates, a higher

proportion of infections are acquired at older ages, which results in higher susceptibility among adults

(19).

Estimates of the burden of varicella hospitalization varied according to the year(s) studied, the source of data, and

the definitions used for a varicella-related hospitalization (20--23). Estimates were higher if varicella was listed as either a

principal or a secondary cause of hospitalization, in which case some incidental varicella hospitalization might have been

included. During 1988--1995, an estimated 10,632 hospitalizations were attributable annually to varicella in the United States

(range: 8,198--16,586) (20). Another study demonstrated an annual average of 15,073

hospitalizations during 1993--1995, but this period might have included an epidemic year (22). Overall rates of hospitalization for varicella during 1988--1995 ranged from 2.3 to 6.0 cases per 100,000 population. If any varicella-related hospital discharge diagnostic code was included, rates varied between 5.0 and 7.0 cases per 100,000 population (20--23).

During 1988--1995, persons without severe immuno-compromising conditions or treatments comprised the largest proportion (89%) of annual varicella-related hospitalizations (20). Before vaccination, children aged <4 years accounted for 43%--44% of hospitalizations, and persons aged >20 years accounted for 32%--33% (20,22). The rate of complications from varicella was substantially higher for persons aged >20 years and for infants (i.e., children aged <1 year). Adults aged >20 years were 13 times more likely to be hospitalized when they had varicella than children aged 5--9 years, and infants aged <1 year were six times more likely to be hospitalized than children aged 5--9 years (20). The most common complications of varicella that resulted in hospitalizations were skin and soft tissue infections (especially invasive group A streptococcal infections), pneumonia, dehydration, and encephalitis. In 1980, an association was identified between Reye syndrome and the use of aspirin during varicella or influenza-like illness; since then, Reye syndrome, which was once considered a common complication resulting from varicella infection, has become rare

(24--26).

During 1970--1994, the average annual number of deaths for which varicella was recorded as the underlying cause was

105; the overall average annual varicella mortality rate was 0.4 deaths per 1 million population. The age distribution of

varicella deaths has shifted during this period. During 1970--1974, persons aged <20 years accounted for 80% of varicella

deaths, compared with 46% during 1990--1994. During 1970--1994, the average case-fatality rate (CFR) for varicella for all

ages combined ranged from 2.0 to 3.6 per 100,000 cases, with higher rates among infants and adults aged

>20 years (27). Although CFRs declined substantially during this period, the risk for varicella-related death during 1990--1994 was still

25 times higher for adults than for children aged 12 months--4 years (CFR: 21.3 and 0.8 per 100,000 cases,

respectively). During the same period, 89% of varicella deaths among children and 75% of varicella deaths among adults occurred in

persons without severe underlying immunocompromising medical conditions. The most common complications among persons

who died of varicella were pneumonia, central nervous system complications (including encephalitis), secondary infection,

and hemorrhagic conditions. A recent reanalysis of varicella deaths also considered

varicella when listed as a contributing cause of death in addition to the underlying cause studied in the previous report

(28). During 1990--1994, a varicella diagnosis was

listed on an average of 145 death certificates per year (105 as an underlying cause and 40 as a contributing cause), with an

overall annual varicella mortality rate of 0.6 deaths per 1 million

population.

Varicella during pregnancy can have adverse consequences for the fetus and infant,

including congenital varicella

syndrome (see Prenatal and Perinatal Exposure). Reliable data on the number of cases

of congenital varicella syndrome are not

available. However, on the basis of age-specific varicella incidence (from NHIS), the

annual number of births, and the risk

for congenital varicella syndrome (1.1% overall risk in the first 20 weeks of pregnancy),

44 cases of congenital

varicella syndrome are estimated to have occurred each year in the United States

during the prevaccine era

(29).

Postvaccine Era

In 1995, a varicella vaccine

(VARIVAX,® Merck & Co., Inc., Whitehouse Station, New Jersey) was licensed in the

United States for use among healthy children aged

>12 months, adolescents, and adults. At that time, ACIP recommended

routine varicella vaccination of children aged 12--18 months, catch-up vaccination of

susceptible children aged 19 months--12

years, and vaccination of susceptible persons who have close contact with persons at

high risk for serious complications (e.g.,

health-care workers and family contacts of

immunocompromised persons) (1; Table 1). In 1999, ACIP updated the

recommendations

to include child care and school entry requirements, use of the vaccine after exposure and for outbreak control, use of the vaccine

for certain children infected with human immunodeficiency virus (HIV), and vaccination of adolescents and adults at high risk

for exposure or transmission (2; Table 1).

During 1997--2005, national varicella vaccination coverage among children aged 19--35 months increased from 27%

to 88%, with no statistically significant difference in coverage by race or ethnicity

(30). In 2005, state-specific varicella vaccination coverage ranged from 69% to 96%

(31). National surveillance data continue to be limited, but passive

surveillance data in certain states have documented a decline in

varicella incidence.

In four states (Illinois, Michigan, Texas, and West Virginia) with adequate

(>5% of expected cases during

1990--1994) reporting to NNDSS, varicella incidence for 2004 declined 53%--88% compared with the average incidence for

1990--1994, with vaccination coverage among children aged 19--35 months ranging from 82% to 88%

(32; CDC, unpublished data, 2006). During 2003--2005, the number of cases increased in Illinois and Texas; the biggest increase (56%) occurred in

Texas (Figure 1). The number of cases remained stable in Michigan (Figure 1) and declined minimally in West Virginia.

In 1995, along with implementation of the national vaccination program, CDC instituted active surveillance for varicella

in three communities (Antelope Valley, California; Travis County, Texas; and West Philadelphia, Pennsylvania) in

collaboration with state and local health departments to establish baseline data and to

monitor trends in varicella disease after

introduction of varicella vaccine. By 2000, vaccination coverage among children 19--35

months in these three communities had

reached 74%--84%, and reported total varicella cases had declined 71%--84%

(33). Although incidence declined to the greatest

extent (83%--90%) among children aged 12 months--4 years, incidence declined in all

age groups, including infants and

adults, indicating the herd immunity effects of the vaccination program. Since 2001,

only two sites were funded to

continue surveillance (Antelope Valley and West Philadelphia). By 2005, vaccination

coverage in these two sites had increased to

90%, and the reduction in incidence had reached 90% and 91%, respectively

(34). During 1996--2005, as vaccination

coverage continued to increase, the proportion of persons with varicella who had been

vaccinated increased from 2% to 56%.

During 1995--2004, peak incidence for varicella cases in active surveillance sites shifted

from age 3--6 years to age 9--11 years.

After introduction of vaccine in 1995, the number and rate of annual varicella-related

hospitalizations declined. In

one study of a nationally representative sample that was conducted during 1993--2001,

varicella hospitalizations declined

75% (22). In another study, the annual varicella-related hospitalization rate declined

88% during 1994--2002

(23) (Figure 2). Hospitalization rates declined 100% among

infants, and substantial declines also were recorded in all other age groups (up

to age 50 years); hospitalization rates declined 91% among children aged <10 years,

92% among children and adolescents

aged 10--19 years, and 78% among adults aged 20--49 years. The greater decline in

hospitalizations among children led to

an increase in the proportion of varicella-related

hospitalizations among adults (40% of hospitalizations in 2002 occurred

among persons aged >20 years) (23). In the

combined active surveillance area, varicella-related hospitalizations declined from

2.4--4.2 hospitalizations per 100,000 population during 1995--1998 to 1.5 per 100,000

population in 2000

(33) and to 0.8 per 100,000 population in 2005

(34).

During 1995--2001, the number of deaths for which varicella was listed as the

underlying cause decreased from 115 to

26 (28) (Figure 3). Since then, the number of deaths declined further; 16 deaths were

reported in 2003. Age-adjusted

mortality rates decreased 66%, from an average of 0.41 deaths per 1 million population

during 1990--1994 to 0.14 during

1999--2001. The decline was observed in all age groups <50 years, with the greatest

reduction (92%) occurring among children aged

12

months--4 years (0.09 deaths per 1 million population), followed by an 88% reduction

among children aged 5--9 years

(0.10 deaths per 1 million population). Deaths among persons aged

>50 years did not decline to the same extent; however,

the validity of reported varicella deaths in this age group is low

(35), and the majority of these deaths are not considered to

be caused by varicella. During 1999--2001, the average rate of mortality attributed to

varicella among all racial and

ethnic populations was <0.15 deaths per 1 million persons. Persons without high-risk

conditions (e.g.,

malignancies, HIV/acquired immunodeficiency syndrome [AIDS], and other

immune deficiencies) accounted for 92% of deaths attributable

to varicella. The average rates of deaths for which varicella was listed as a contributing

cause of death also

declined during 1999--2001, compared with 1990--1994.

Despite high 1-dose vaccination coverage and the success of the vaccination program

in reducing varicella morbidity

and mortality, reports to CDC from active surveillance sites and from states with

well-implemented vaccination programs and surveillance indicate that in certain states

and in one

active surveillance site, the number of reported varicella cases

has remained constant or declined minimally, and outbreaks have continued to occur.

During 2001--2005, outbreaks

were reported in schools with high varicella vaccination coverage (range 96%--100%)

(3,4). The outbreaks were similar in

certain respects: 1) all occurred in elementary schools, 2) vaccine effectiveness was

similar (range: 72%--85%), 3) the highest

attack rates occurred among the younger students, 4) each outbreak lasted

approximately

2 months, and 5) index cases occurred among vaccinated students (although their

disease was mild). Overall attack rates among vaccinated children varied

(range: 11%--17%), with attack rates in certain classrooms as high as 40%. These data

indicate that even in settings in

which vaccination coverage was nearly universal and vaccine performed as expected,

the 1-dose vaccination program could

not prevent varicella outbreaks completely.

Prenatal and Perinatal Exposure

In the prevaccine era, prenatal infection was uncommon because the majority of women of childbearing age

were immune to VZV (12,36). Varicella in pregnant women is

associated with a risk for VZV transmission to the fetus or

newborn. Intrauterine VZV infection might result in congenital varicella syndrome, neonatal varicella, or HZ during

infancy or early childhood (37--46). Infants who are

exposed prenatally to VZV, even if asymptomatic, might have measurable

varicella-specific IgM antibody during the newborn period, have persistent varicella-specific IgG immunity after age 1 year without

a history of postnatal varicella, or demonstrate positive lymphocyte transformation in response to VZV antigen

(37).

Congenital varicella syndrome was first recognized in 1947

(40). Congenital varicella syndrome can occur among

infants born to mothers infected during the first half of pregnancy and might be manifested by low birthweight, cutaneous

scarring, limb hypoplasia, microcephaly, cortical atrophy, chorioretinitis, cataracts, and other anomalies. In one study, incidence

of congenital varicella syndrome was calculated using aggregate data from nine cohort studies carried out during

1986--2002 (47). Rates were 0.6% (4 of 725) for 2--12 weeks' gestation, 1.4% (9 of 642)

for 13--28 weeks, and 0 (0 of 385) after

28 weeks.

In a prospective study of 1,373 mothers with varicella during pregnancy conducted in

the United Kingdom and

West Germany during 1980--1993, the highest risk (2%) for congenital varicella

syndrome was observed when maternal

infection occurred during 13--20 weeks' gestation

(43). The risk was 0.4% after maternal infection during 0--12 weeks' gestation.

No cases of congenital varicella syndrome occurred among the infants of 366 mothers

with HZ during pregnancy. Nine

isolated cases involving birth defects consistent with congenital varicella syndrome

have been reported after maternal varicella

beyond 20 weeks' gestation (with the latest occurring at 28 weeks)

(47,48). In a prospective study, HZ occurred

during infancy or early childhood in four (0.8%) of 477 infants who were exposed to VZV

during 13--24 weeks' gestation and in six (1.7%)

of 345 infants who were exposed during 25--36 weeks' gestation

(43).

The onset of varicella in pregnant women from 5 days

before to 2 days after delivery results in severe varicella infection in

an estimated 17%--30% of their newborn infants. These infants are exposed to VZV

without sufficient maternal

antibody to lessen the severity of disease. The risk for neonatal death has been

estimated to be 31% among infants whose mothers

had onset of rash <4 days before giving birth

(45). This estimate was made on the basis of a limited number of infant deaths

and might be higher than the actual risk because the study was performed before

neonatal intensive care was available. In

addition, certain cases were not part of prospective studies but were reported

retrospectively, making the results subject to selection

bias. When these cases were reevaluated subsequently by another investigator, certain

infants were demonstrated to have been at

higher risk for death because of low birthweight; in at least one case, another cause of

death was probable

(46). Varicella-zoster immune globulin (VZIG) has been reported to reduce incidence of

severe neonatal varicella disease

(49) and therefore is indicated in such situations. Nevertheless, the risk for death

among neonates who do not receive postexposure

prophylaxis with VZIG is likely to be substantially lower than was estimated previously.

Herpes Zoster Surveillance

After primary infection, VZV persists as a latent infection in sensory-nerve ganglia. The

virus can reactivate, causing

HZ. Mechanisms controlling VZV latency are not well understood. Risk factors for HZ

include aging, immunosuppression,

and initial infection with varicella in utero or during early childhood (i.e., age <18

months). An estimated 15%--30% of

the general population experience HZ during their lifetimes

(50,51); this proportion is likely to increase

as life expectancy increases. The most common complication of HZ, particularly in older

persons, is postherpetic neuralgia (PHN),

the persistence of sometimes debilitating pain weeks to months after resolution of HZ.

Life-threatening complications of HZ also can occur; these include herpes ophthalmicus, which can lead to blindness. Another severe manifestation is

dissemination, which might involve generalized skin eruptions, and central nervous system, pulmonary, hepatic, and

pancreatic complications. Dissemination, pneumonia, and

visceral involvement typically are restricted to immunocompromised

persons. VZV can be transmitted from the lesions of patients who have HZ to susceptible contacts. Although few data are available

to assess this risk, one household contact study reported

that the risk for VZV transmission from HZ was approximately

20% of the risk for transmission from varicella

(52).

Varicella vaccination might alter the risk for HZ at the level of both the individual and the population (i.e., herd

immunity). Just as wild-type VZV can cause wild-type HZ, attenuated vaccine virus has the potential to become latent and later reactivate

to cause vaccine virus strain (also called Oka-strain) HZ

(53). Multiple studies have evaluated the risk for Oka-strain HZ

after vaccination of immunocompromised or healthy children

(54--58). In a study of leukemic children, the rate of HZ after a

mean 4.1 years of follow-up (range: 6 months--10 years) was 2% in vaccine recipients and 15% in controls with a history of

varicella (54). A subset of 96 of these vaccine recipients was matched prospectively according to chemotherapeutic protocol with

96 leukemic children who had experienced natural varicella. Analysis indicated that the incidence of HZ was

approximately three times lower in vaccine recipients (0.80 per 100 person-years) than in the matched leukemic children who had experienced

natural varicella (2.46 per 100 person-years) (p = 0.01). Data for healthy children are more limited, and findings might be influenced

by multiple factors (e.g., incomplete ascertainment, limited duration of follow up or no follow up of subjects of older ages,

no comprehensive screening for wild-type varicella infection before or after vaccination, or lack of testing all cases to distinguish

Oka- from wild-type HZ). Nonetheless, these studies suggest that the risk for Oka-strain HZ after a single dose of varicella vaccine

is lower than that after wild-type varicella infection

(56--58). Over time, the risk for and manifestation of Oka-strain HZ should

be examined in older persons who are at greater risk for HZ complications. Persons who experience varicella infection

before vaccination (i.e., as a result of in utero or unapparent infection) or after vaccination (i.e., as a result of breakthrough

infection) presumably are latently infected with two strains of VZV. The risk for HZ in these persons is unknown. No long-term

studies have been conducted that compare the risk for Oka-strain HZ in persons who receive 1 dose of varicella vaccine with the risk

for those who receive 2 doses.

Varicella vaccination also might change the risk for HZ at the population level. With the development of herd

immunity and reduction in the likelihood of exposure, the varicella vaccination program prevents wild-type VZV infection

among vaccine recipients and nonvaccine recipients, eliminating the risk for wild-type HZ in these persons. Reduction in

the likelihood of wild-type varicella infection also increases the

median age for acquiring varicella (although age-specific

incidence rates themselves are lower). This reduces the risk for varicella infection

during early childhood (i.e., age <18 months),

thereby reducing a risk factor for childhood HZ.

Exposure of persons with latent wild-type VZV infection to persons with varicella is

thought to boost specific

immunity, which might contribute to controlling reactivation of VZV and the

development of HZ

(50). Concern has been expressed that by providing fewer opportunities for varicella

exposure among persons with previous wild-type varicella

infection, reduction in the likelihood of exposure might

increase the risk for HZ, possibly within as few as 5 years after introduction of

varicella vaccination (59) and reaching a vaccination

coverage of >90%.

Herpes zoster is not a nationally notifiable disease in the United States, and HZ

surveillance has been conducted

using multiple methods, study sites, or data sources. For certain studies, baseline data

were available before the start of the

varicella vaccination program. One study that included baseline data was a

retrospective analysis of electronic medical records from

a health maintenance organization (HMO) during 1992--2002

(60). This HMO study indicated that age-adjusted incidence

of HZ remained stable during 1992--2002 as incidence of

varicella decreased (60). Age-adjusted and -specific

annual incidence rates of HZ fluctuated slightly over time; the age-adjusted rate was

highest in 1992, at 4.1 cases per 1,000

person-years, and was 3.7 cases per 1,000 person-years in 2002. For other studies

initiated in the postvaccine era, baseline data are

not available (61--63). An analysis of national incidence data from the Medstat

database (available at

http://www.medstat.com/Products/view/?id=71) demonstrated

an overall incidence of HZ in 2000 and 2001 of 3.2 (95% confidence interval [CI]

= 3.1--3.2) per 1,000 person-years (61), representing no increase in age-adjusted HZ in

the past 20 years in the United

States compared with earlier published data

(64). Data from two HMOs in Oregon and Washington for 1997--2003 indicated

no statistically significant increase in HZ incidence rates except among

children aged 10--17 years (relative risk [RR] = 1.12, CI

= 1.05--1.18); these increases were attributed to increased use of oral steroids

(62). Another study of data gathered from a statewide telephone survey during

1999--2003 in Massachusetts demonstrated an increase in HZ

(63). Age groups particularly affected included persons aged 25--44 years and those

aged >65 years. Finally, in the two active varicella surveillance

sites (Antelope Valley, California, and West Philadelphia, Pennsylvania), active

surveillance for HZ in children aged <20 years

has been ongoing since 2000. During 2000--2004, incidence of HZ in children aged <10

years declined significantly

(p<0.05) from 0.75 to 0.23 cases per 1,000 children

(65; CDC unpublished data, 2006). In summary, multiple studies and

surveillance data demonstrate no consistent trends in HZ incidence in the United States

since implementation of the varicella

vaccination program in 1995.

Use of Acyclovir to Treat and Prevent Varicella

Acyclovir is a synthetic nucleoside analog that inhibits replication of human herpes viruses, including VZV. Since the
early 1980s, intravenous acyclovir has been available to treat immunocompromised persons who have varicella.
When administered within 24 hours of onset of rash, acyclovir has been demonstrated to be effective in reducing
varicella-associated morbidity and mortality in this population
(66--68).
In 1992, the Food and Drug Administration (FDA)
approved the use of oral acyclovir for the treatment of varicella
in otherwise healthy children. This approval was made on the basis of
placebo-controlled, double-blind studies
(69,70) that demonstrated the beneficial clinical effects (i.e., a decrease in the number of days in which new lesions appeared, the
duration of fever, and the severity of cutaneous and systemic signs and symptoms) that occurred when acyclovir was
administered within 24 hours of rash onset. No serious adverse events occurred during the period of drug
administration. Administration of acyclovir did not decrease transmission of varicella or reduce the duration of absence from school. Because few
complications occurred (1%--2%), these studies could not determine whether acyclovir had a statistically significant effect on disease
severity among healthy children. In these studies, antibody titers after infection in children receiving acyclovir did not
differ substantially from titers of children in the control group

(69,70). Clinical trials among adolescents and adults have

indicated that acyclovir is well-tolerated and effective in

reducing the duration and severity of clinical illness if the drug is

administered within 24 hours of rash onset

(71--73).

In 1993, AAP's Committee on Infectious Diseases published a statement

regarding the use of acyclovir (74). AAP did

not consider administration of acyclovir to healthy children to have clinical benefit

sufficient to justify its routine

administration; however, AAP stated that certain circumstances might justify its use.

AAP recommended that oral acyclovir should

be considered for otherwise healthy persons at increased risk for moderate to severe

varicella (e.g., persons aged >12 years,

persons with chronic cutaneous or pulmonary disorders, persons

receiving long-term salicylate therapy, and persons receiving

short, intermittent, or aerosolized courses of corticosteroids). Certain experts also

recommend use of oral acyclovir

for secondary case-patients who live in the same households as infected children

(74).

Acyclovir is classified as a Category B drug in the FDA

use-in-pregnancy rating. Although studies involving animals

have not indicated teratogenic effects, adequate, well-controlled studies in pregnant

women have not been conducted.

However, a prospective registry of acyclovir use during pregnancy that collected data

on outcomes of 596 infants whose mothers

were exposed to systemic acyclovir during the first trimester of pregnancy indicated

that the rate and types of birth

defects

approximated those in the general population

(75). AAP has not recommended routine use of oral acyclovir for

pregnant women because the risks and benefits to the fetus and mother were unknown. However, in instances of serious,

viral-mediated complications (e.g., pneumonia), AAP has recommended that intravenous acyclovir should be considered

(74).

Two nucleoside analogs, acyclovir and famciclovir, have been approved by FDA for treating HZ. If administered within

72 hours of rash onset, acyclovir has accelerated the rate of cutaneous healing and reduced the severity of acute pain in adults

who have HZ (76). Oral famciclovir, when administered

during the same period, has similar efficacy

(77).

Acyclovir is not indicated for prophylactic use among

otherwise healthy children, adolescents, or adults without evidence

of immunity after exposure to varicella. Vaccination is the method of choice in these situations. No studies have been

conducted regarding prophylactic use of acyclovir among immunocompromised persons; therefore, VZIG is recommended in

these situations.

Vaccines for Prevention of Varicella

Two live attenuated varicella virus vaccines are licensed in the United States for

prevention of varicella:

single-antigen varicella vaccine

(VARIVAX,® Merck & Co., Inc., Whitehouse Station, New Jersey) and combination MMRV

vaccine (ProQuad,® Merck & Co., Inc., Whitehouse, New Jersey). Both vaccines are derived from the Oka strain of live,

attenuated VZV. The Oka strain was isolated in Japan

(78) in the early 1970s from vesicular fluid in a healthy child who had

natural varicella and was attenuated through sequential propagation in cultures of human embryonic lung cells,

embryonic guinea-pig cells, and human diploid cells (WI-38). The virus in the Oka/Merck vaccine has undergone further passage through

human diploid-cell cultures (MRC-5) for a total of 31 passages.

In 1995, the single-antigen varicella vaccine was licensed in the United States for use among healthy persons aged

>12 months. This vaccine is lyophilized; when reconstituted as directed in the package insert and stored at room temperature for

a maximum of 30 minutes, it contains a minimum of 1,350 plaque forming units (PFUs) of Oka/Merck VZV in each 0.5

mL dose (79). Each dose also contains 12.5 mg of hydrolyzed gelatin, trace amounts of neomycin and fetal bovine serum, 25

mg of sucrose, and trace residual components of MRC-5 cells (including DNA and protein). The vaccine does

not contain preservatives. Since 1995, >55 million doses have been distributed in the United States. Reporting of serious

adverse events has been rare (see Vaccine-Associated Adverse Events).

In 2005, the combination MMRV vaccine was licensed in the United States for use

among healthy children aged

12 months--12 years. The attenuated measles, mumps, and rubella vaccine viruses in

ProQuad® are identical and of equal titer

to those in the measles, mumps, and rubella (MMR) vaccine,

MMRII® (80). The titer of Oka/Merck VZV is higher in

MMRV than in single-antigen varicella vaccine, a minimum of 3.99

log10 PFUs compared with 1,350 PFUs (approximately

3.13 log10) in each 0.5 mL dose. The other constituents are similar to those in the

single-antigen varicella vaccine.

Immune Response to Vaccination

In clinical trials of the single-antigen varicella vaccine conducted before licensure,

seroconversion was assessed using lots

of vaccine with different amounts of PFUs and laboratory

assays with different levels of sensitivity and specificity. Using

a specially developed, sensitive gp-enzyme-linked immunosorbent assay (ELISA) test

that is not available

commercially, seroconversion (defined by the acquisition of any detectable varicella

antibodies >0.3 gpELISA units) was

observed at approximately 4--6 weeks after vaccination with

1 dose of varicella vaccine in approximately 97% of 6,889

susceptible children aged 1--12 years (79). The seroconversion rate was 98% for

children aged 12--15 months and 95% among those

aged 5--12 years (81). Adolescents aged 13--17 years had a lower seroconversion rate

(79%) after a single dose of vaccine. A

study performed postlicensure used fluorescent antibody

to membrane antigen (FAMA) titers 16 weeks after vaccination to
assess serologic response and demonstrated that 61 (76%) of 80 healthy child vaccine
recipients seroconverted (FAMA titers
>1:4) after 1 dose of single-antigen varicella
vaccine (82).
Primary antibody response to the vaccine at 6 weeks postvaccination is correlated with
protection against disease
(83,84). In clinical trials, rates of breakthrough disease were lower among children with
varicella antibody titers of
>5 gpELISA units than among those with titers of <5 units
(84); children with a 6-week postvaccination antibody titer of <5 gpELISA units were
3.5 times more likely to have breakthrough varicella than those with a titer of
>5 gpELISA units. Later studies of
immunogenicity

(85) have reported the proportion of vaccinated children who achieved this antibody
level
instead of seroconversion. After 1 dose of the
single-antigen varicella vaccine, 86% of children had gpELISA levels of
>5 units/mL (85). Studies performed
using FAMA indicated that a titer >1:4 at 16 weeks postvaccination is correlated with
protection against disease
(82). Of healthy persons with a titer of >1:4 at 16 weeks post vaccination, <1% have
had varicella after a household exposure (n = 130).
In contrast, the attack rate among those with a titer of <1:4 was 55% (n = 60).
Persistence of antibody in children after 1 dose of single-antigen varicella vaccine was
demonstrated in both short- and

long-term follow-up studies. In a clinical study, the rate of antibody persistence detected by gpELISA was nearly 100% after 9

years of follow-up for 277 children (85). Another study demonstrated that although antibody titers (detected by FAMA)

might decline 12--24 months after vaccination, the median titer did not change after 1--4 years and even rose after 10 years

(86). In Japan, VZV antibodies were present in 37 (97%) of 38 children who received varicella vaccine 7--10 years earlier (with

titers comparable to those of 29 children who had had natural varicella infection within the previous 10 years)

(87) and in 100% of 25 children when followed for as long as 20 years (i.e., antibody levels were higher than those observed 10 years earlier)

(88). Interpretation of long-term studies is complicated by at least two factors. First, asymptomatic boosting of

vaccine-induced immunity by exposure to wild-type VZV is likely. Because varicella vaccine is not routinely recommended in Japan,

coverage of children was estimated to be low (approximately 20%) during 1991--1993. Second, sample sizes were limited as a result

of the decrease in the number of children followed-up with increasing time since vaccination.

The second dose of varicella vaccine in children produced an improved immunologic response that is correlated

with improved protection. A comparative study of healthy children who received 1 or 2 doses of single-antigen varicella

vaccine administered 3 months apart indicated that a second dose provided higher antibody levels as measured by the proportion

of subjects with titers of >5 gpELISA units and by

geometric mean titers (GMTs) and higher efficacy (85; Tables 2--4). The proportion of subjects with antibody titers of >5 gpELISA units in the 2-dose recipients was higher 6 weeks after the second dose than after the first dose (99.6% and 85.7%, respectively) and remained high at the end of the 9-year follow-up period, although the difference between the two regimens narrowed (97% and 95%, respectively). GMT 6 weeks after the second dose was substantially higher than that after a single dose (142 and 12, respectively). The difference in GMTs between the two regimens did not persist over 9 years of follow-up among subjects who seroconverted after vaccination, although GMTs in both regimens remained high by the end of the study period. However, receipt of a second dose decreased the rate of breakthrough varicella significantly (3.3-fold) and increased vaccine efficacy (p<0.001). Another study that assessed the immunogenicity of a second dose received 4--6 years after the first dose demonstrated a substantial increase in antibody levels in the first 7--10 days in the majority of those tested, indicating an anamnestic response. On the day of the second dose, GMT was 25.7, compared with 143.6 GMT 7--10 days after the second dose; 60% of recipients had at least a fourfold increase in antibody titers, and an additional 17% had at least a twofold increase (89). Three months after the second dose, GMT remained higher than on the day of second dose (119.0 and 25.7, respectively). Among children, VZV antibody levels and GMTs after 2 doses administered 4--6 years apart were comparable to those obtained when the 2 doses were administered 3 months apart.

The combination MMRV vaccine was licensed on the basis of noninferiority of immunogenicity of the

antigenic components compared with MMR and varicella vaccines administered concomitantly at separate inspection sites rather

than on clinical efficacy (80). Clinical studies of healthy children aged 12--23 months indicated that those who received 1 dose

of MMRV vaccine had levels of antibody to measles, mumps, rubella, and varicella similar to levels of children who received

1 dose of MMR and 1 dose of varicella vaccines concomitantly at separate injection sites. For the varicella component

in MMRV, 91.2% (CI = 87.0%--94.4%) of children achieved antibody titers of

>5 gpELISA units/mL 6 weeks after

vaccination (90). A subgroup of children received a second dose of MMRV vaccine approximately 3 months after the first dose.

The serologic response (>5 gpELISA units/mL) after 2 doses was 99.2% (CI = 97.0%--99.9%) (Table 2). Also, GMT for

varicella after the second dose of MMRV vaccine increased approximately

forty-onefold (90). Administration of combination

MMRV vaccine to healthy children aged 4--6 years who had been vaccinated previously with MMR and single-antigen

varicella vaccines resulted in similar antibody levels and a

twenty-fivefold increase in GMT levels (91).

Among persons aged >13 years, multiple studies have

described seroconversion rates after receipt of the

single-antigen varicella vaccine (range: 72%--94% after 1 dose and 94%--99% after a second dose administered 4--8 weeks

later) (79,92,93). In clinical studies, detectable antibody levels have persisted for at

least 5 years in 97% of adolescents and

adults who were administered 2 doses of vaccine 4--8 weeks apart

(79). However, other studies demonstrated that 25%--31%

of

adult vaccine recipients who seroconverted lost detectable antibodies (by FAMA) at

multiple intervals (range: 1--11

years) after vaccination (93,94). For persons who had breakthrough disease after

exposure to varicella, the severity of illness or

the attack rates did not increase over time

(95).

Innate (i.e., nonspecific) and adaptive (i.e., humoral and cellular) immunity are

important in the control of primary

varicella infection. The capacity to elicit cell-mediated immunity is important for viral

clearance, providing

long-term protection against disease and preventing symptomatic VZV reactivation.

Studies among children and adults have

indicated that breakthrough varicella typically is mild, even among vaccine recipients

without seroconversion or vaccine recipients

who lost detectable antibody, suggesting that VZV-specific

cell-mediated immunity affords protection to vaccine recipients in

the absence of a detectable antibody response

(94,95). Studies of the cellular immune response to vaccination among

children demonstrated that immunization with 1

dose of varicella vaccine induced VZV-specific T-cell proliferation that

was maintained in 26 (90%) of 29 children 1 year postvaccination and in 52 (87%) of 60

children 5 years postvaccination

(96). In this study, the mean stimulation index (SI), a marker of cell-mediated immunity, was 12.1 after

1 year and 22.1 after 5 years. Data obtained at 1 year postvaccination from a subset of children in a prelicensure study comparing the immune

response among children who received 1 and 2 doses administered 3 months apart demonstrated that the

varicella-specific lymphocyte proliferation responses were significantly higher for recipients of 2 doses than for recipients of 1 dose (mean SI: 34.7 and

23.1, respectively; p = 0.03) (97). In the study of the 2 doses administered 4--6 years apart, results also indicated that

the lymphocyte proliferation response was significantly higher at 6 weeks and 3 months after the second dose than at the

same time points after the first dose (p<0.01)

(89; Table 2).

Among adults, vaccine-induced VZV-specific T-cell proliferation was maintained in 16 (94%) of 17 subjects 1 and 5

years postvaccination (96,98). The mean SI was 9.9 after 1 year and 22.4 after 5 years.

Correlates of Protection

For children, the varicella antibody response measured by gpELISA 6 weeks postvaccination correlates with

neutralizing antibody level, VZV-specific T-cell proliferative responses, vaccine efficacy, and long-term protection against varicella

after exposure to VZV (83,84,99,100). A titer of

>5 gpELISA units/mL is associated with protection against disease although

it should not be considered an absolute guarantee of protection. Breakthrough cases have occurred among children with

>5 gpELISA units/mL. A FAMA titer
>1:4 at 16 weeks post-vaccination also correlates with protection against disease
(82). However, neither of these antibody tests is available commercially. The
relationship between the antibody level measured
at other intervals postvaccination, especially immediately prior to
exposure and breakthrough disease has not been studied.
No correlates of protection have been evaluated for adults.

Vaccine Efficacy and Vaccine Effectiveness

One-Dose Regimen

Prelicensure Efficacy

In prelicensure studies carried out among children aged
12 months--14 years, the protective efficacy of
single-antigen varicella vaccine varied, depending on the amount of live
virus administered per dose, the exposure setting (community
or household), and the quality and length of the clinical follow-up. The majority of the
prelicensure studies reported efficacy of
1 dose of varicella vaccine within the range of 70%--90% against any clinical disease
and 95% against severe disease for
7--10 years after vaccination (81,101,102). A randomized placebo-controlled efficacy
trial was conducted among children aged
12 months--14 years, but the formulation differed from that of the current vaccine
(17,000 PFUs per dose

(103,104), with follow-up of children through 7 years postvaccination

(105). Reported efficacy was 100% at 1 year and 98% at 2 years

after vaccination, and 100% and 92%, respectively, after exposures to VZV that

occurred in the household. Although a

randomized control study was not conducted for adults, the efficacy of single-antigen

varicella vaccine was

determined by evaluation of protection when adult vaccine recipients were exposed to

varicella in the household. On the basis of the reported

historical

attack rate of 87% for natural varicella after household exposure among unvaccinated

children, estimated efficacy

among adults was approximately 80% (79). The attack rate of unvaccinated adults

exposed in households was not studied.

Postlicensure Efficacy and Effectiveness

Prevention of All Varicella Disease

Postlicensure studies have assessed the

effectiveness¶ of the single-antigen varicella vaccine under field conditions in

child care, school, household, and community settings using multiple methods.

Effectiveness frequently has been estimated

against all varicella and also against moderate and severe varicella (defined in different

ways). Outbreak investigations

have assessed effectiveness against clinically defined varicella. The majority of these

investigations have demonstrated

vaccine effectiveness for prevention of varicella in the same range

described in prelicensure trials (70%--90%)

(3--6,106--113), with some lower (44%, 56%)

(114,115) and some higher (100% in one of two schools investigated) estimates

(107). A retrospective cohort study in 11 childcare centers demonstrated vaccine effectiveness of 83% for prevention of

clinically diagnosed varicella (116). In a case-control study that measured vaccine effectiveness against laboratory-confirmed varicella

in a pediatric office setting during 1997--2003, vaccine effectiveness was 85% (CI = 78%--90%) during the first four years

and 87% (CI = 81%--91%) for the entire study period

(117,118). Finally, in a study of household secondary attack

rates, considered the most robust test of vaccine performance because of the intensity

of exposure, varicella vaccine was 79% (CI

= 70%--85%) effective in preventing clinically defined varicella in exposed household

contacts aged 12 months--14

years without a history of varicella disease or vaccination

(119). Postlicensure data on vaccine effectiveness against all disease

have been summarized (Table 5).

In a randomized clinical trial conducted postlicensure that compared the efficacy of 1

dose of varicella vaccine with that of

2 doses, the estimated vaccine efficacy for 1 dose for a

10-year observation period was 94.4% (CI = 92.9%--95.7%)

(85; Table 3). In the same study, the efficacy of 1 dose of vaccine in preventing

varicella after household exposure for 10 years was

90.2% (CI = 83.7%--96.7%) (Table 4). This study did not use placebo controls and used

historic data for attack rates

in unvaccinated children to calculate vaccine

efficacy.

Prevention of Moderate and Severe Varicella

Postlicensure studies assessing vaccine performance in preventing moderate and severe varicella have consistently demonstrated high effectiveness. Definitions for disease severity have varied among studies. Certain studies have used a defined scale of illness that included the number of skin lesions, fever, complications, and investigator assessment of illness severity, and others have used only the number of skin lesions, reported complications, or hospitalizations. Moderate varicella typically has been defined as either 50--500 or 250--500 lesions, and severe varicella has been defined as >500 lesions or any hospitalization or complication. In the randomized postlicensure clinical trial, severe varicella was defined as >300 lesions and fever of >102°F (38.9°C), oral equivalent. Regardless of different definitions, multiple studies have demonstrated that single-antigen varicella vaccine was >>95% effective in preventing combined moderate and severe disease (3--6,85,106,107,109--113,115--119); one study demonstrated effectiveness of 86% (114). Effectiveness was 100% against severe disease when measured separately (6,85,109,111,117,119). Postlicensure data on vaccine effectiveness against moderate and severe varicella have been summarized (Table 5).

Two-Dose Regimen

In a randomized clinical trial of single-antigen varicella vaccine that compared the

efficacy of 1 dose with that of 2

doses administered 3 months apart, the estimated vaccine efficacy of 2 doses for a

10-year observation period was 98.3% (CI

= 97.3%--99.0%), which was significantly higher than efficacy after 1 dose (p<0.001)

(85; Table 5). The 2-dose regimen also was 100% efficacious against severe varicella. In

the same study, the efficacy of 2 doses of single-antigen varicella vaccine

in preventing disease after household exposure over 10 years was 96.4% (CI =

92.4%--100%), not significantly different from

1 dose (90.2%) (p = 0.112) (Table 4). However, the number of cases involving

household exposure was limited.

Formal studies to evaluate the clinical efficacy of the combination MMRV vaccine have

not been performed. Efficacy of

the individual components was established previously in clinical studies with the

single-antigen vaccines.

Breakthrough Disease

Breakthrough disease is defined as a case of infection with wild-type VZV occurring >42

days after vaccination. In

clinical trials, varicella disease was substantially less severe among vaccinated persons

than among unvaccinated persons, who

usually have fever and several hundred vesicular lesions

(120). In cases of breakthrough disease, the median number of skin lesions

is commonly <50 (99,121--123). In addition,

compared with unvaccinated persons, vaccine recipients have had fewer

vesicular lesions (lesions more commonly are atypical, with papules that do not

progress to vesicles), shorter

duration of illness, and lower incidence of fever.

Multiple postlicensure investigations also have demonstrated that the majority of breakthrough varicella cases

are significantly milder than cases among unvaccinated children (p<0.05)

(3,5,107--114,116--118,124). However,

approximately 25%--30% of breakthrough cases are not mild, with clinical features more similar to those in unvaccinated children

(124). Since 1999, when varicella deaths became nationally notifiable, two deaths from breakthrough varicella disease have

been reported to CDC; one of a girl aged 9 years with a history of asthma who was receiving steroids when she had

the breakthrough infection, and the other of a girl aged 7 years with a history of malignant ependymoma who also was

under steroid therapy at the time of her death (CDC, unpublished data, 2006).

One-Dose Regimen

In clinical trials, 1,114 children aged 1--12 years received

1 dose of single-antigen varicella vaccine containing

2,900--9,000 PFUs of attenuated virus per dose and were actively followed for up to 10 years postvaccination

(79). Among a subset of 95 vaccine recipients with household exposure to varicella, eight (8%) reported a mild form of varicella (10--34 lesions).

In a randomized clinical trial that compared the efficacy of 1 dose of vaccine to that of 2 doses during a 10-year

observation period, the cumulative rate of breakthrough varicella among children who received 1 dose was 7.3%

(85). Breakthrough cases occurred annually in 0.2%--2.3% of recipients of 1 dose of

vaccine. Cases occurred throughout the observation period,

but the majority were reported 2--5 years after vaccination (Figure 4). Of 57 children

with breakthrough cases, 13 (23%) had

>50 lesions.

In cross-sectional studies, the attack rate for breakthrough disease has ranged between

11% and 17% (and as high as 40%

in certain classrooms) in outbreak investigations

(3) and 15% in household settings

(119).

Two-Dose Regimen

Data Among Children

In a randomized clinical trial that compared the efficacy of 1 dose of vaccine with that

of 2 doses, the cumulative rate

of breakthrough varicella during a 10-year observation period was 3.3-fold lower among

children who received 2 doses than

that among children who received 1 dose (2.2% and 7.3,

respectively; p<0.001) (85). Breakthrough cases occurred

occasionally in 0.8% of 2-dose vaccine recipients. The

majority of cases of breakthrough disease occurred 2--5 years after vaccination; no

cases were reported 7--10 years after vaccination (Figure 4). Of 16 children with

breakthrough cases, three (19%) had >50

lesions. The proportion of children with >50 lesions did not differ between the 1-dose

and 2-dose

regimens (p = 0.5).

Breakthrough Infections Among Adolescents and Adults

In postlicensure studies of adolescents and adults who received 2 doses, 40 (9%) cases of breakthrough varicella occurred among 461 vaccine recipients who were followed for 8 weeks--11.8 years (mean: 3.3 years) after vaccination (95), and 12 (10%) cases occurred among 120 vaccine recipients who were followed for 1 month--20.6 years (mean: 4.6 years) (94). One prelicensure study of persons who had received 2 doses of vaccine reported that 12 (8%) breakthrough cases had occurred among 152 vaccine recipients who were followed for 5--66 months (mean: 30 months) postvaccination (93).

Contagiousness

Prelicensure clinical trials reported the rate of disease transmission from vaccinated persons with varicella cases to their vaccinated siblings. In 10 trials that were conducted during 1981--1989, breakthrough infections occurred in 114 (5.3%) of 2,163 vaccinated children during the 1--8 year follow-up period of active surveillance, and secondary transmission occurred to 11 (12.2%) of their 90 vaccinated siblings (121). Illness was mild in both index and secondary case-patients. Household transmission from a vaccinated child with breakthrough disease to a susceptible adult

(one of whom died) have been

reported (CDC, unpublished data, 2006). One study examined secondary attack rates from vaccinated and unvaccinated persons

with varicella to both vaccinated and unvaccinated households contacts aged 12 months--14 years

(119). This study demonstrated that vaccinated persons with varicella with <50 lesions were only one third as contagious as unvaccinated persons

with varicella. However, vaccinated persons with varicella who had

>50 lesions were as contagious as unvaccinated persons

with varicella (119). Vaccinated persons with varicella tend to have milder disease, and, although they are less contagious

than unvaccinated persons with varicella, they might not receive a diagnosis and be isolated. As a result, they might have

more opportunities to infect others in community settings, thereby further contributing to VZV transmission. Vaccinated

persons with varicella also have been index case-patients in varicella outbreaks

(3,4,115).

Risk Factors for Vaccine Failure

Potential risk factors for vaccine failure have been identified in studies of vaccine effectiveness during outbreak

investigations and other specially designed studies

(5,108--110,113--115,118,125). In outbreak investigations, the low number of

cases limits the ability of researchers to conduct multivariate analyses and examine the

independent effect of each risk factor

for vaccine failure. An increased risk for breakthrough disease has been noted with

decreasing age at vaccination, with a

threefold increase in breakthrough disease risk for children vaccinated at age <14 months

(110), an increase of twofold in one study

and nearly fourfold in another for children vaccinated at age <16 months

(108,115), and a ninefold increase for

children vaccinated at age <19 months

(113). Other outbreak investigations have demonstrated that time since vaccination

(variably defined as >3, >5, or

>5 years) was associated with an increased risk for breakthrough disease (relative risk

[RR] = 2.6, 6.7,

and 2.6, respectively) (5,114,115). However, age at vaccination and time since

vaccination are highly correlated, and

their independent association with the risk for breakthrough disease has been assessed

in only one outbreak investigation

(113). A retrospective cohort study that adjusted for other potential risk factors

demonstrated an increased risk for breakthrough

disease for children vaccinated at age <15 months (adjusted relative risk [aRR] = 1.4;

CI = 1.1%--1.9%)

(125). A case-control study demonstrated that the effectiveness of vaccine in the first

year after vaccination was significantly lower (73%) among

children vaccinated at age <15 months than it was among children vaccinated at age

>15 months (99%) (p = 0.01) (118). However,

the difference in the overall effectiveness between children vaccinated at these ages

was not statistically significant for

subsequent years (8 years of follow-up) (81% and 88%, respectively; p = 0.17). Active

surveillance data collected during 1995--2004

from a sentinel population of 350,000 persons were analyzed to determine whether the severity and annual incidence

of breakthrough varicella cases increased with time since vaccination (126). Children vaccinated >5 years previously were

2.6 times more likely to have moderate and severe breakthrough varicella than those vaccinated <5 years previously (p =

0.016). The annual rates of breakthrough varicella among children aged 12 months--12 years increased significantly with time

since vaccination after adjusting for the effects of age at infection, age at vaccination, and year of infection (p<0.01).

Multiple other studies that examined possible reasons for lower vaccine effectiveness did not find age at vaccination

(3--5,111,114) or time since vaccination

(3,110,111) to be associated with vaccine failure. An ongoing study is examining these factors and risk for vaccine failure

(127). After 8 years of active follow-up of 7,449 children vaccinated at age 12--23 months, results do not indicate an increased risk for breakthrough disease among children vaccinated at age 12--14 months

compared with those vaccinated at age 15--23 months. Moreover, a test for trend revealed no change in the rate of

reported breakthrough disease for each additional month of age at vaccination

(127).

Two outbreak investigations noted an increased risk for breakthrough disease in children with asthma and

eczema (109,113). In these investigations, the use of steroids to treat asthma or eczema was not studied. Steroids have been

associated previously with severe varicella in unvaccinated persons

(128--130). Only one retrospective cohort study

controlled simultaneously for the effect of multiple risk factors, including the use of

steroids, and this study demonstrated no

association of risk for breakthrough disease with asthma or eczema

(125). However, this study documented an increased risk

for breakthrough disease if the child had received a prescription of oral steroids

(considered a proxy for taking oral steroids

when exposed to varicella) within 3 months of breakthrough disease (adjusted RR [aRR]

= 2.4; CI = 1.3%--4.4%) and

when varicella vaccination was administered within 28 days of MMR vaccine (aRR = 3.1;

CI = 1.5%--6.4%).

Evidence of Immunity

ACIP has approved criteria for evidence of immunity to varicella (Box). Only doses of

varicella vaccines for which

written documentation of the date of administration is presented should be considered

valid. Neither a self-reported dose nor a

history of vaccination provided by a parent is, by itself, considered adequate evidence

of immunity. Persons who lack

documentation of adequate vaccination or other evidence of

immunity should be vaccinated.

Historically, self-reporting of varicella disease by adults or by parents for their children

has been considered valid evidence

of immunity. The predictive value of a self-reported positive disease history was

extremely high in adults in the prevaccine

era although data on positive predictive value are lacking in parental reports regarding

their children

(131--133). As disease incidence decreases and the proportion of vaccinated persons with varicella having mild cases increases, varicella will be

less readily recognized clinically. A recent study demonstrated that only 75% of unvaccinated children aged 12

months--4 years who reported a positive history of

varicella were in fact immune (confirmed by serological testing), compared with 89% of children aged 5--9 years and 10--14 years

(134). To limit the number of false-positive

reports and ensure immunity, ACIP recommends that evidence of immunity should be either a diagnosis of varicella by a health-care provider or a

health-care provider verification of a history of disease rather than parental or

self-reporting. The above-cited study demonstrated

that 99% of persons aged 15--19 years and 100% of those aged 20--29 years who reported a history of varicella were immune

(134). Because serologic evidence of VZV infection

has been documented in 96%--97% of U.S.-born adults aged 20--29

years and in 97%--99% of adults aged >30 years tested during 1998--1999

(12), U.S. birth before 1980 is considered evidence

of immunity except for health-care personnel (HCP), pregnant women, and immunocomprised persons. For these three

groups, certainty regarding immunity is desirable because of the possibility of nosocomial transmission to

high-risk patients; transmission of the virus to the fetus, which might result in congenital

varicella syndrome; and the possibility of severe disease. Postvaccination serologic testing to verify an immune response to varicella vaccine is not

routinely recommended because available commercial assays lack sensitivity in detecting vaccine-induced immunity and might give

false negative results.

Simultaneous Administration of Vaccines

Single-antigen varicella vaccine is well-tolerated and effective in healthy children aged >12 months when administered simultaneously with MMR vaccine either at separate sites and with separate syringes or separately

>4 weeks apart. The number and types of adverse events occurring in children who have received VARIVAX and MMRII concurrently have not

differed from those in children who have been administered the vaccines at different visits

(79,135). Data concerning the effect of simultaneous administration of VARIVAX with vaccines containing various combinations of MMR, diphtheria and

tetanus toxoids and pertussis (DTP), and Haemophilus

influenzae type b (Hib) have not been published

(79). A randomized study of 694 subjects determined that the immune response to MMR, varicella, and Hib vaccines administered concurrently with

a fourth dose of pneumococal conjugate vaccine (PCV7) was not inferior to that of those vaccines when administered

without PCV7; the percentage of subjects who seroconverted was >90% for all antigens for both groups

(136).

Concomitant administration of the combination MMRV vaccine with other vaccines also has been assessed. In a

clinical trial involving 1,913 healthy children aged 12--15 months, three groups were

compared

(137). One group received concomitantly administered (at separate sites) MMRV vaccine, Diphtheria and Tetanus Toxoids and Acellular

Pertussis Vaccine Absorbed (DTaP), Hib conjugate (meningococcal

protein conjugate) vaccine, and hepatitis B (recombinant) (Hep

B) vaccine. The second group received MMRV vaccine at the initial visit, followed by DTaP, Hib, and Hep B

vaccines administered concomitantly 6 weeks later. The third group received MMR and varicella vaccines concomitantly followed

6 weeks later by DTaP, Hib, and Hep B vaccines. Seroconversion rates and antibody titers were comparable for the

measles, mumps, rubella, and varicella components for the first two groups. No immunologic data were reported for

the third group. The Hib and Hep B seroconversion rates for the two groups that received those vaccines also were comparable.

Data are absent or limited for the concomitant use of MMRV vaccine with inactivated polio, pneumococal

conjugate, influenza, and hepatitis A vaccines. Simultaneous administration of the majority of widely used live and inactivated

vaccines has produced seroconversion rates and rates of adverse reactions similar to those observed when the vaccines

are administered separately. Therefore, single-antigen and combination MMRV vaccines may be administered simultaneously

with other vaccines recommended for children aged 12--15 months and those aged 4--6 years. Simultaneous administration

is

particularly important when health-care providers anticipate

that, because of certain factors (e.g., previously

missed vaccination opportunities), a child might not return for subsequent vaccination.

Economic Analysis of Vaccination

A cost-effectiveness analysis was performed before initiation of the varicella

vaccination program in the United States

(138). The results of the study indicated a savings of $5.40 for each dollar spent on

routine vaccination of preschool-aged

children when direct and indirect costs were considered. When only direct medical costs

were considered, the benefit-cost ratio

was 0.9:1.0. Benefit-cost ratios were only slightly lower when lower estimates of the

short- and long-term effectiveness of

the vaccine were used.

A recent analysis was performed that used current estimates of morbidity and mortality

(20,28,33) and current direct and indirect costs (ACIP, unpublished presentation, 2006).

The model considered that the second dose will reduce varicella

disease residual after the first dose by 79%. From a societal perspective, both 1-dose

and 2-dose vaccination programs are cost

saving compared with no program. The vaccine program cost was estimated at $320

million for 1 dose and $538 million for 2

doses. The savings from varicella disease prevented were estimated at approximately

$1.3 billion for the 1-dose program

and approximately $1.4 billion for the 2-dose program. Compared with the 1-dose

program, the incremental cost for the

second dose was estimated to be $96,000 per quality-adjusted life year (QALY) saved. If benefits from preventing group

A streptococcus infections and HZ among vaccinated persons are added, incremental costs per QALY saved are $91,000

and $17,000, respectively. Because of the uncertainty of the modeled predictions of an increase in HZ among persons with

a history of varicella and the fact that no consistent trends

demonstrate an increase in HZ attributable to the

varicella vaccination program in the United States, HZ among persons with a history of varicella was not included in the model.

Storage, Handling, and Transportation of Varicella Vaccines

Single-antigen varicella and combination MMRV vaccines have similar but not identical distribution, handling, and

storage requirements (79,80). For potency to be maintained, the lyophilized varicella vaccines must be stored frozen at an

average temperature of 5°F (-15°C) or colder. Household freezers manufactured since the mid-1980s are designed to

maintain temperatures from -4°F (-20°C) to 5°F (-15°C). When tested, VARIVAX has remained stable in frost-free freezers.

Freezers that reliably maintain an average temperature of <5°F (<-15°C) and that have a separate sealed freezer door are acceptable

for storing VARIVAX and ProQuad. Health-care providers may use stand-alone freezers or the freezer compartment

of refrigerator-freezer combinations, provided that the freezer compartment has its own separate, sealed, and insulated

exterior door. Units with an internal freezer door are not acceptable. Temperatures should be documented at the beginning and end

of each day. Providers should document the required temperature in a newly purchased unit for a minimum of 1 week

before using it to store vaccine and routinely thereafter. When varicella vaccines are stored in the freezer compartment of a

combined refrigerator-freezer, temperatures in both compartments should be monitored carefully. Setting the thermostat low enough

for storage of varicella-containing vaccines might inadvertently expose refrigerated vaccines to freezing temperatures.

Refrigerators with ice compartments that either are not tightly enclosed or are enclosed with unsealed, uninsulated doors (e.g.,

small, dormitory-style refrigerators) are not acceptable

for the storage of varicella vaccines.

Diluent should be stored separately either at room temperature or in the refrigerator. Vaccines should be

reconstituted according to the directions in the package insert and only with the diluent supplied with the vaccine, which does not

contain preservative or other antiviral substances that could inactivate the vaccine virus. Once reconstituted, vaccine should be

used immediately to minimize loss of potency. Vaccine should be discarded if not used within 30 minutes after reconstitution.

Handling and Transportation of Varicella Vaccines Within Off-Site Clinics

When an immunization session is being held at a site distant from the freezer in which the vaccine is stored, the number

of vaccine vials needed for the immunization session should be packed in either a vaccine shipping container (as received

from the manufacturer) or in an insulated cooler, with an

adequate quantity of dry ice (i.e., a minimum of 6 lbs per box) to

preserve potency. When placed in a suitable container, dry ice will maintain a temperature of

<5°F (<-15°C). Dry ice should remain

in

the container upon arrival at the clinic site. If no dry ice remains when the container is opened at the receiving site,

the manufacturer (Merck and Company, Inc.) should be contacted for guidance (telephone: 1-800-982-7482). If dry ice

is available at the receiving site, it may be used to store vaccine. Thermometers or temperature indicators cannot be used in

a container with dry ice. Diluent should not be transported on dry ice.

If dry ice is not available, only single-antigen varicella vaccine may be transported, with frozen packs to keep

the temperatures between 36°F--46°F (2°C--8°C). Transport temperatures should be monitored, and a temperature indicator

or thermometer should be placed in the container and checked on arrival. The container should be kept closed as much

as possible during the immunization session; temperatures should be checked and recorded hourly. If the temperature

remains between 36°F--46°F (2°C--8°C), the single-antigen varicella vaccine may be used for up to 72 hours after its removal from

the freezer. The date and time should be marked on the vaccine vial. Single-antigen

varicella vaccine stored at

refrigerated temperatures for any period of time may not be refrozen for future use.

Transportation and storage of combination MMRV vaccine at temperatures between

36°F--46°F (2°C--8°C) is not

permissible for any length of time. In contrast to single-antigen varicella vaccine,

combination MMRV vaccine must be maintained

at temperatures of <5°F

(<-15°C) until the time of reconstitution and administration. This difference in vaccine

storage temperatures must be considered when planning off-site clinics. For this

reason, transportation of MMRV vaccine to

off-site clinics is not advised. If any concerns arise regarding the storage of

single-antigen varicella or combination MMRV vaccines,

the manufacturer should be contacted for guidance.

Minimizing Wastage of Vaccine

Vaccine wastage can be minimized by accurately determining the number of doses

needed for a given patient population.

To ensure maximal vaccine potency, smaller shipments of vaccine should be ordered

more frequently (preferably at least

once every 3 months). Single-antigen varicella vaccine should not be distributed to

providers who do not have the capacity to

store it properly in a freezer until it is used. Transportation of varicella vaccine should

be kept to a minimum to prevent loss

of potency. Off-site clinic sites should receive only such amounts of vaccine as they can

use within a short time (72 hours

if storing single-antigen varicella vaccine at refrigerated temperatures).

Adverse Events After Vaccination

Because adverse events after vaccination might continue to be caused by wild-type VZV even as varicella disease

declines, health-care providers should obtain event-appropriate clinical specimens (e.g., cerebrospinal fluid for encephalitis,

bronchial lavage or lung biopsy for pneumonia) for laboratory evaluation, including strain identification. Information regarding

strain identification is available from Merck's VZV Identification Program (telephone: 1-800-652-6372) or from CDC's

National Varicella Reference Laboratory (telephone: 404--639--0066; e-mail: vzvlab@cdc.gov) or at

http://www.cdc.gov/nip/diseases/varicella/surv/default.htm. Commercial

laboratories do not have the capability for strain identification.

The National Vaccine Injury Act of 1986 requires physicians and other health-care providers who administer vaccines

to maintain permanent immunization records and to report occurrences of adverse events for selected vaccines,

including varicella vaccines. Serious adverse events (i.e., all events

requiring medical attention) suspected to have been caused by

varicella vaccines should be reported to the Vaccine

Adverse Event Reporting System (VAERS). Forms and instructions are available

at https://secure.vaers.org/vaersDataEntryintro.htm, in the FDA Drug Bulletin at

http://www.fda.gov/medwatch, or from the 24-hour VAERS information recording at

1-800 822-7967.

Prelicensure

Single-Antigen Varicella Vaccine

Single-antigen varicella vaccine was well-tolerated when administered to >11,000 healthy children, adolescents, and adults during prelicensure clinical trials. In a double-blind, placebo-controlled study among 914 susceptible healthy children aged 12 months--14 years, the only statistically significant (p<0.05) adverse events reported that were more common among vaccine recipients than among placebo recipients were pain and redness at the injection site (103). This study also described the presence of unspecific rash among 2% of placebo and 4% of vaccine recipients occurring within 43 days of vaccination. Of

the 28 reported rashes, 10 (36%) were examined by a physician; among those that were examined, four of the seven noninjection site rashes in vaccine recipients were judged to be varicella-like, compared with none of the rashes in the placebo recipients.

In a study comparing the safety of 1 dose of single-antigen varicella vaccine with that of 2 doses administered 3 months apart, no serious adverse events related to vaccination were reported among approximately 2,000 healthy subjects aged 12 months--12 years who were followed for 42 days after each injection. The 2-dose

vaccine regimen was generally well-tolerated, and its safety profile was comparable to that of the 1-dose regimen. Incidence of injection site complaints observed <3 days after vaccination was slightly higher after dose 2 (25.4%) than after dose 1 (21.7%). Incidence of systemic clinical complaints was lower after dose 2; fever incidence from days 7--21 was 7% after dose 1 and 4% after dose 2 (p = 0.009), and varicelliform rash incidence after dose 1 was 3%, compared with 1% after dose 2 (p = 0.008), with peak occurrence 8--21 days after vaccination (139).

In uncontrolled trials of persons aged >13 years , approximately 1,600 vaccine recipients who received 1 dose of single-antigen varicella vaccine and 955 who received 2 doses of vaccine were monitored for 42 days for adverse events (79). After the first and second doses, 24.4% and 32.5% of vaccine recipients, respectively, had complaints regarding the injection site. Varicella-like rash at the injection site occurred in 3% of vaccine recipients after the first injection and in 1% after the second. A nonlocalized rash occurred in 5.5% of vaccine recipients after the first injection and in 0.9% of vaccine recipients after the second, at a peak of 7--21 and 0--23 days postvaccination, respectively.

Combination MMRV Vaccine

In clinical trials, combination MMRV vaccine was administered to 4,497 children aged 12--23 months without concomitant administration with other vaccines (80). The safety profile of the first dose was compared with the safety

of MMRII vaccine and VARIVAX administered concomitantly at separate injection sites. The follow-up period was 42

days postvaccination. Systemic vaccine-related adverse events were reported at a statistically significantly greater rate in persons

who received MMRV vaccine than in persons who received the two vaccines administered concomitantly at separate

injection sites: fever (>102°F

[>38.9°C] oral equivalent), (21.5% and 14.9%, respectively), and measles-like rash (3.0% and

2.1%, respectively). Both fever and measles-like rash usually occurred within 5--12 days after the vaccination, were of short

duration, and resolved with no long-term sequelae. Pain, tenderness, and soreness at the injection site were reported at a

statistically significantly lower rate in persons who received the combination MMRV vaccine (22.0%) than in those who received

MMRII and VARIVAX vaccines (26.7%). Rash at the injection site was more frequent among recipients of

1-dose MMRV vaccine (2.3%) than among recipients of the two vaccines administered separately as first doses (1.5%). A study that also

compared use of MMRV with MMRII and VARIVAX administered as a first dose demonstrated similar results

(90). During days 5--12, children in the group that received MMRV had higher rates of elevated temperatures than those in the group that

received MMRII and VARIVAX (27.7% and 18.7%, respectively; p = 0.034).

To demonstrate that MMRV vaccine could be administered as a second dose, a study was conducted involving 799

children aged 4--6 years who had received primary doses of MMRII and VARIVAX

vaccines, either concomitantly or not, at age

>12 months and >1 month before study enrollment

(91). These children were vaccinated randomly (with MMRV and

placebo, MMR and placebo, or MMRII and VARIVAX) and then monitored for safety. No serious vaccine-related adverse

experiences were reported. Overall, the proportions of subjects with one or more adverse event were comparable among groups

receiving MMRV, MMRII, and MMRII and VARIVAX. The group receiving MMRV vaccine had a statistically significantly

greater proportion of subjects with erythema (p = 0.01) and swelling (p = 0.008) at the injection site 1--5 days after

vaccination. Another study examined the safety of 2 doses of MMRV administered 3 months apart to 480 children aged 12--23

months (90). The rate of adverse events typically was lower after the second dose of MMRV than after the first dose. The incidence

of varicella-like rashes was lower after a second dose of MMRV than after concomitant administration of MMRII and

VARIVAX vaccines (0.0% and 1.9%, respectively; p = 0.01).

Postlicensure

During March 1, 1995--December 31, 2005, a total of 47.7 million doses of varicella vaccine were distributed in the

United States, and 25,306 adverse events that occurred after varicella vaccine administration were reported to VAERS, 1,276 (5%)

of which were classified as serious. The overall adverse event reporting rate was 52.7 cases per 100,000 doses distributed. The

rate

of reporting of serious adverse events was 2.6 per 100,000 doses distributed. Half of all adverse events reported

occurred among children aged 12--23 months (VAERS,

unpublished data, 2006).

Not all adverse events that occur after vaccination are

reported, and many reports describe events that might have

been caused by confounding or unrelated factors (e.g., medications and other diseases). Because varicella disease continues to

occur, wild-type virus might account for certain reported events. For serious adverse events for which background incidence data

are known, VAERS reporting rates are lower than expected after natural varicella or than background rates of disease in

the community. Inherent limitations of passive safety surveillance impede comparing adverse event rates after vaccination

reported to VAERS with those from complications after natural disease. Nevertheless, the magnitude of these differences suggests

that serious adverse events occur at a substantially

lower rate after vaccination than after natural disease. This assumption

is corroborated by the substantial decline in the number of severe complications, hospitalizations, and deaths related to

varicella that have been reported since implementation of the varicella vaccination program

(22,23,28).

Similar to the prelicensure experience, postlicensure safety surveillance data after administration of single-antigen

varicella vaccine indicated that rash, fever, and injection-site reactions were the most frequently reported adverse events

(140,141). Using these reports from passive surveillance of adverse events during the first 4 years of the vaccination program, when

wild-type VZV was still circulating widely, polymerase chain reaction (PCR) analysis confirmed that the majority of rash

events occurring within 42 days of vaccination were caused primarily by wild-type varicella-zoster virus. Rashes from the

wild-type virus occurred a median of 8 days after vaccination (range: 1--24 days), whereas rashes from the vaccine strain occurred

a median of 21 days after vaccination (range: 5--42 days)

(140).

As part of postmarketing evaluation of the short-term safety of VARIVAX, 89,753 vaccinated adults and children

were identified from automated clinical databases of hospitals, emergency room visits, and clinic visits during April

1995--December 1996 (56). Out of all potential adverse events identified, no consistent time association or clustering of any

events was noted during the exposure follow-up period. No cases of ataxia or encephalitis were identified after receipt of

varicella vaccine in this group of vaccine recipients. In the prevaccine era, among children aged <15 years, acute cerebellar ataxia

was estimated to occur at a rate of one in 4,000 varicella cases, and varicella encephalitis without ataxia was estimated to

occur at one in 33,000 varicella cases (142).

Severe complications that are laboratory-confirmed to be caused by vaccine virus strain are rare and include

pneumonia (140), hepatitis (143), severe disseminated varicella infection

(140,141,144,145), and secondary transmission from

five vaccine recipients (140,146--148). Except for the secondary transmission cases, these cases all occurred

in immunocompromised patients or in persons who had other serious medical conditions that were undiagnosed at the time

of vaccination.

Although other serious adverse events have been reported, vaccine strain involvement was not

laboratory-confirmed. Thrombocytopenia

(140,141,149) and acute cerebellar ataxia

(140,141,150) have been described as potentially

associated with single-antigen varicella vaccine. Two children had acute hemiparesis diagnosed after varicella vaccination (one at 5

days and the other at 3 weeks) (151). In both cases, unilateral

infarction of the basal ganglia and internal capsule was noted;

this distribution is consistent with varicella angiopathy. Urticaria after varicella vaccine has been associated with gelatin

allergy (152). Recurrent papular urticaria has been reported to be potentially associated with varicella vaccination

(153). However, available data regarding the potential adverse events after

varicella vaccination are insufficient to determine a

causal association. The quality of reported information varies widely, and simultaneous administration with other

vaccines (especially MMR) might confound attribution.

Herpes Zoster. Similar to wild-type VZV, vaccine virus can establish latent infection and subsequently reactivate, causing

HZ disease in vaccine recipients. Before vaccine licensure, studies in children with leukemia had demonstrated a much lower rate

of HZ in vaccinated children compared with those (age and protocol matched) with previous varicella

(54). Cases of HZ in healthy vaccine recipients have been confirmed to be caused by both vaccine virus and wild-type virus, suggesting that certain HZ cases

in vaccine recipients might result from antecedent natural

varicella infection that might not have been detected by the

patient or from infection after vaccination

(140). A single case has been reported of a child who received a diagnosis of

neuroblastoma and had severe chronic zoster attributed to vaccine virus strain that with time became drug resistant

(145). A large postlicensure safety study performed through surveys conducted every 6 months and validated by medical chart review in the first 9 years of a

15-year follow-up study of >7,000 enrolled children vaccinated with

single-antigen varicella vaccine at age 12--24 months estimated

HZ disease incidence to be 22 per 100,000 person-years (CI = 13--37) as reported by parents (Steven Black, MD,

Northern

California Kaiser Permanente Medical Care Program, unpublished presentation, 2005). The incidence of HZ was 30 per

100,000 person-years among healthy children aged 5--9 years

(154) and 46 per 100,000 person-years for those aged

<14 years (64). However, these rates are drawn from different populations and based on different methodologies. In addition, a proportion

of children in these age groups would not have experienced varicella disease; those

rates are likely to underestimate rates in a

cohort of children all infected with wild-type VZV, making direct comparison

difficult with a vaccinated cohort.

Transmission of Vaccine Virus

Results from prelicensure vaccine trials of the

single-antigen varicella vaccine suggest that transmission of varicella

vaccine virus from healthy persons to susceptible contacts is rare. This risk was

assessed in siblings of healthy vaccinated children

who themselves received placebo (103). Six (1%) of 439 placebo recipients

seroconverted without rash; the vaccinated siblings

of these six children also did not develop rash. Serologic data suggested that three of

these six seroconverters received

vaccine mistakenly in lieu of their siblings. In a smaller study, immunocompromised

siblings of healthy children

receiving varicella vaccine were evaluated clinically and by testing for humoral or

cell-mediated immune responses

(155). No evidence was demonstrated of vaccine virus transmission to any of 30

immunocompromised

siblings from 37 healthy children receiving varicella vaccine.

Accumulated data from postlicensure surveillance activities suggest that the risk for

transmission of varicella vaccine

virus from healthy persons to susceptible contacts is low. With >55 million doses of

VARIVAX distributed since

licensure, transmission from immunocompetent persons after vaccination has been

documented by PCR analysis from only five

persons, resulting in six secondary infections, all of them mild (140,146--148). Three episodes involved transmission from healthy children aged 1 year to healthy household contacts, including a sibling aged 4 months, a father, and a pregnant mother. In the latter episode, the mother chose to terminate the pregnancy, but fetal tissue tested subsequently by PCR was negative for varicella vaccine virus (147). The children in these episodes had 2, 12, and 30 lesions, respectively. A fourth episode involved transmission from an immunocompetent adolescent who was a resident in an institution for chronically disabled children. The adolescent had >500 lesions after vaccination, and vaccine virus was transmitted to another immunocompetent resident of the institution and to a health-care worker, both of whom had histories of varicella (146). The fifth episode represented a tertiary spread from a healthy sibling contact of a vaccinee with leukemia (148). Rashes for both healthy siblings were mild (i.e., 40 and 11 lesions, respectively), and vaccine virus was isolated from all three case-patients. The third sibling had rash 18 days after the onset of the secondary case-patient and 33 days after rash onset in the vaccinated leukemic child. In addition to these five episodes, one child has been reported to have transmitted vaccine virus from HZ that occurred 5 months after varicella vaccination; 2 weeks later, a mild varicella-like rash from which vaccine varicella virus was isolated occurred in the child's vaccinated brother (156).

Although varicella vaccine is not recommended for children with cellular immune deficiencies, the experience

from prelicensure vaccine trials involving children with leukemia is instructive. Data from a study of varicella vaccination

in children with leukemia indicated that varicella virus vaccine transmission occurred in 15 (17%) of 88 healthy,

susceptible siblings of leukemic vaccine recipients; the rash was mild in 11 (73%) of the 15 infected siblings

(148). The risk for transmission was correlated with the number of skin lesions in the immunocompromised vaccine recipients.

These data suggest that healthy, vaccinated persons have a minimal risk for transmitting vaccine virus to their

contacts, particularly in the absence of vaccine rash in the vaccine

recipient. Vaccine recipients who have a vaccine-related

rash, particularly HCP and household contacts of immunocompromised persons, should avoid contact with persons

without evidence of immunity who are at high risk for severe complications (see Health-Care Personnel)

Summary of Rationale for Varicella Vaccination

Varicella vaccine is an effective prevention tool for decreasing the burden attributable to varicella disease and

its complications in the United States. In the prevaccine era, varicella was a childhood disease with >90% of the 4 million

cases, two thirds of approximately 11,000 hospitalizations, and

approximately half of 100--150 annual deaths occurring

among persons aged <20 years. Single-antigen varicella vaccine is

licensed for use among healthy persons aged

>12 months, and the combination MMRV vaccine is licensed for use in healthy children aged 12 months--12 years. Prelicensure and

postlicensure

studies have demonstrated that 1 dose of single-antigen varicella vaccine is approximately 85% effective in preventing

varicella. Breakthrough varicella disease that occurs

after vaccination frequently is mild and modified.

Varicella vaccine is >95% effective in preventing severe varicella disease. Since implementation of the varicella vaccination program in 1995, varicella

incidence, hospitalizations, and deaths have declined substantially. MMRV was licensed on the basis of immunological noninferiority

to its vaccine antigenic components. Initial varicella vaccine policy recommendations were for 1 dose of varicella vaccine

for children aged 12 months--12 years and 2 doses, 4--8 weeks apart, for persons aged >13 years. In June 2006, ACIP approved a routine 2-dose recommendation for children.

The first dose should be administered at age 12--15 months and the second

dose at age 4--6 years.

The rationale for the second dose of varicella vaccine for children is to further decrease varicella disease and its

complications in the United States. Despite the successes of the

1-dose vaccination program in children, vaccine effectiveness of 85% has

not been sufficient to prevent varicella outbreaks, which, although less than in the prevaccine era, have continued to occur

in highly vaccinated school populations. Breakthrough varicella is contagious. Studies of the immune response after 1 and

2 doses of varicella vaccine demonstrate a greater-than-tenfold boost in GMTs when

measured 6 weeks after the second

varicella vaccine dose. A higher proportion (>99%) of children achieve an antibody response of

>5 gpELISA units after the second dose compared with 76%--85% of children after a single dose of varicella vaccine. The second dose of varicella vaccine is

expected to provide improved protection to the 15%--20% of children who do not respond adequately to the first dose. Data from

a randomized clinical trial conducted postlicensure indicated that vaccine efficacy after

2 doses of single-antigen varicella vaccine in children (98.3%; CI = 97.3%--99.0%) was

significantly higher than that after a single dose (94.4%; CI

=92.9%--95.7%). The risk for breakthrough disease was 3.3-fold lower among children who

received 2 doses than it was among children who received

1 dose. How this increase in vaccine efficacy (typically higher than observed under field conditions) will translate

into vaccine effectiveness under conditions of community use will be an important area of study.

The recommended ages for routine first (at age 12--15 months) and second (at age 4--6 years) doses of varicella vaccine

are harmonized with the recommendations for MMR vaccine use and intended to limit the period when children have

no varicella antibody. The recommended age for the

second dose is supported by the current epidemiology of

varicella, with low incidence and few outbreaks among preschool-aged children and

higher incidence and more outbreaks among

elementary-school--aged children. However, the second dose may be administered at

an earlier age, provided that the interval between

the first and second doses is 3 months. The recommendation for the minimum interval between doses is made on the basis of

the design of the studies evaluating 2 doses among children aged 12 months--12 years. MMRV vaccine may be used to

vaccinate children against measles, mumps, rubella, and varicella simultaneously. Because the risk for transmission can be high

among students in schools, colleges, and other postsecondary educational institutions, students without evidence of immunity

should receive 2 doses of varicella vaccine. All children and adolescents who received

1 dose of varicella vaccine previously should receive a second dose.

Varicella disease is more severe and its complications more frequent among adolescents and adults. The recommendation

for vaccination of all adolescents and adults without

evidence of immunity will provide protection in these age groups.

Because varicella might be more severe in immunocompromised persons who might not be eligible for vaccination, and because of

the risk of VZV transmission in health-care settings, HCP must be vaccinated. Varicella disease during the first two trimesters of pregnancy might

infect the fetus and result in congenital varicella syndrome. Therefore, routine antenatal screening

for evidence of immunity and postpartum vaccination for those without evidence of immunity now is recommended.

Recommendations for the Use of Varicella Vaccines

Two 0.5-mL doses of varicella vaccine administered subcutaneously are recommended for children aged

>12 months, adolescents, and adults without evidence of immunity. For children aged 12 months--12 years, the recommended

minimum interval between the two doses is 3 months. However, if the second dose was administered

>28 days after the first dose, the second dose is considered valid and need not be repeated. For persons aged >13 years, the recommended minimum

interval is 4 weeks. Single-antigen varicella vaccine is approved for use among healthy persons aged

>12 months. Combination MMRV vaccine is approved for use among healthy children aged 12 months--12 years. MMRV vaccine is indicated for

simultaneous vaccination against measles, mumps, rubella, and varicella. Whenever any components of the combination vaccine

are

indicated and the other components are not

contraindicated, use of licensed combination vaccines, such as MMRV vaccine,

is preferred over separate injection of equivalent component vaccines

(157).

Routine Vaccination

Persons Aged 12 Months--12 Years

Preschool-Aged Children

All healthy children should receive their first dose of varicella-containing vaccine routinely at age 12--15 months.

School-Aged Children

A second dose of varicella vaccine is recommended routinely for all children aged 4--6 years (i.e., before

entering prekindergarten, kindergarten, or first grade). However, it may be administered at an earlier age provided that the

interval between the first and second dose is >3 months.

Because of the risk for transmission of VZV in schools, all children entering school should have received 2 doses of

varicella-containing vaccine or have other evidence of immunity to varicella (see Evidence of Immunity).

Persons Aged >13 Years

Persons aged >13 years without evidence of varicella immunity should receive two 0.5-mL doses of single-antigen

varicella vaccine administered subcutaneously, 4--8 weeks apart. If >8 weeks elapse after the first dose, the second dose may

be administered without restarting the schedule. Only single-antigen varicella vaccine may be used for vaccination of persons

in this age group. MMRV is not licensed for use among persons aged

>13 years.

School-Aged Children, College Students, and Students in Other Postsecondary Educational Institutions

All students should be assessed for varicella immunity, and those without evidence of immunity should routinely receive

2 doses of single-antigen varicella vaccine 4--8 weeks apart. The risk for transmission of varicella among school-aged

children, college students, and students in other postsecondary educational institutions can be high because of high contact rates.

Other Adults

All healthy adults should be assessed for varicella immunity, and those who do not have evidence of immunity

should receive 2 doses of single-antigen varicella vaccine 4--8 weeks apart. Adults who might be at increased risk for exposure

or transmission and who do not have evidence of immunity should receive special consideration for vaccination,

including 1) HCP, 2) household contacts of immunocompromised persons, 3) persons who live or work in environments in

which transmission of VZV is likely (e.g., teachers, day-care employees, residents and staff in institutional settings), 4) persons

who live or work in environments in which transmission has been reported (e.g., college students, inmates and staff members

of correctional institutions, and military personnel), 5) nonpregnant women of childbearing age, 6) adolescents and adults

living in households with children, and 7) international travelers.

Second Dose Catch-Up Vaccination

To improve individual protection against varicella and to have a more rapid impact on school outbreaks, second dose

catch-up varicella vaccination is recommended for children, adolescents, and adults who previously

received 1 dose. The recommended minimum interval between the first dose and the catch-up second dose is 3 months for children aged

<12 years and 4 weeks for persons aged

>13 years. However, the catch-up second dose may be administered at any interval

longer

than the minimum recommended interval. Catch-up vaccination may be implemented during routine health-care provider

visits and through school- and college-entry requirements.

As part of comprehensive health services for all adolescents, ACIP, AAP, and AAFP recommend a health maintenance visit

at age 11--12 years. This visit also should serve as an immunization visit to evaluate vaccination status and administer

necessary vaccinations (158). Physicians should use this and other routine visits to ensure that all children without evidence of

varicella immunity have received 2 doses of varicella vaccine.

Requirements for Entry to Child Care, School, College, and Other

Postsecondary Educational Institutions

Child care and school entry requirements for varicella

immunity have been recommended previously

(2). In 2005, ACIP recommended expanding the requirements to cover students in all grade levels. Official health agencies should take

necessary steps, including developing and enforcing school immunization requirements, to ensure that students at all grade

levels (including college) and children in child care centers are protected against varicella and other vaccine-preventable

diseases (157).

Prenatal Assessment and Postpartum Vaccination

Prenatal assessment of women for evidence of varicella immunity is recommended. Birth before 1980 is not considered evidence of immunity for pregnant women because of potential severe consequences of varicella infection during pregnancy, including infection of the fetus. Upon completion or termination of their pregnancies, women who do not have evidence of varicella immunity should receive the first dose of vaccine before discharge from the health-care facility. The second dose should be administered 4--8 weeks later, which coincides with the postpartum visit (6--8 weeks after delivery). For women who gave birth, the second dose should be administered at the postpartum visit. Women should be counseled to avoid conception for 1 month after each dose of varicella vaccine. Health-care settings in which completion or termination of pregnancy occurs should use standing orders to ensure the administration of varicella vaccine to women without evidence of immunity.

Special Considerations for Vaccination

Vaccination of HIV-Infected Persons

HIV-infected children with CD4+ T-lymphocyte percentage >15% should be considered for vaccination with the single-antigen varicella vaccine. Varicella vaccine was recommended previously for HIV-infected children in CDC clinical

and immunologic categories N1 and A1 with age-specific CD4+ T-lymphocyte percentage

>25% (2). Limited data from a

clinical trial in which 2 doses of single-antigen varicella vaccine were administered 3 months apart to 37 HIV-infected children

(CDC clinical categories N, A, or B and immunologic category 2 [CD4+ T-lymphocyte percentage

>15%--24%]) aged 1--8 years indicated that the vaccine was well-tolerated and that >80% of subjects had detectable VZV specific

immune response (either antibody or cell immune response or both) at 1 year after immunization

(159). These children were no less likely to have

an antibody response to the varicella vaccine than were subjects who were less affected immunologically by HIV

infection. Because children infected with HIV are at increased risk for morbidity from varicella and HZ (i.e., shingles) compared

with healthy children, ACIP recommends that, after weighing potential risks and benefits, single-antigen varicella vaccine should

be considered for HIV-infected children with CD4+ T-lymphocyte percentages

>15%. Eligible children should receive 2 doses

of single-antigen varicella vaccine 3 months apart. Because persons with impaired cellular immunity are potentially at greater

risk for complications after vaccination with a live vaccine, these vaccine

recipients should be encouraged to return for evaluation

if they experience a postvaccination varicella-like rash. Data are not available regarding safety, immunogenicity, or efficacy

of MMRV vaccine in HIV-infected children, MMRV vaccine should not be administered as

a substitute for the

single-antigen varicella vaccine when vaccinating these children. The titer of Oka/Merck VZV is higher in combination

MMRV vaccine than in single-antigen varicella vaccine. Recommendations for vaccination of HIV-infected children with

measles, mumps, or rubella vaccines have been published previously

(160).

Data on use of varicella vaccine in HIV-infected adolescents and adults are lacking. However, on the basis of expert

opinion, the safety of varicella vaccine in HIV-infected persons aged >8 years with comparable levels of immune function

(CD4+T-lymphocyte count >200

cells/µL) is likely to be similar to that of children aged <8 years. Immunogenicity might be lower

in older HIV-infected children, adolescents, and adults compared to children aged 1--8 years. However, weighing the risk

for severe disease from wild VZV and potential benefit of vaccination, vaccination may be considered (2 doses, administered

3

months apart) for HIV-infected persons with CD4+T-lymphocytes count

>200 cells/µL in these age groups. If vaccination

of HIV-infected persons results in clinical disease, the use of acyclovir might modify the severity of disease.

Situations in Which Some Degree of Immunodeficiency Might be Present

Persons with impaired humoral immunity may be vaccinated. No data have been published concerning whether

persons without evidence of immunity receiving only inhaled, nasal, or topical doses of steroids can be vaccinated safely.

However, clinical experience suggests that vaccination is well-tolerated among these persons. Persons without evidence of immunity

who are receiving systemic steroids for certain conditions (e.g., asthma) and who are not otherwise immunocompromised may

be vaccinated if they are receiving <2 mg/kg of body weight or a total of <20 mg/day of prednisone or its equivalent.

Certain experts suggest withholding steroids for 2--3 weeks after vaccination if it can be done safely

(1). Data from a Japanese study using the Oka/Biken varicella vaccine (which is not available in the United States but whose immunogenicity and efficacy

are similar to those of the varicella vaccine used in the United States) indicated that children taking steroids for nephrosis

were vaccinated safely when the steroids were suspended for 1--2 weeks before vaccination, although no

serious reactions occurred among children vaccinated when steroid therapy was not suspended

(161). Persons who are receiving high doses of

systemic steroids (i.e., >2 mg/kg prednisone) for

>2 weeks may be vaccinated once steroid therapy has been discontinued for

>1 month, in accordance with the general recommendations for the use of live-virus vaccines

(157).

Vaccination of leukemic children who are in remission and who do not have evidence of

immunity to varicella should

be undertaken only with expert guidance and with the availability of antiviral therapy should complications ensue. Patients

with leukemia, lymphoma, or other malignancies whose disease is in remission and whose chemotherapy has been terminated for

at least 3 months can receive live-virus vaccines

(157). When immunizing persons in whom some degree of

immunodeficiency might be present, only single-antigen varicella vaccine should be used.

Vaccination of Household Contacts of Immunocompromised Persons

Immunocompromised persons are at high risk for serious varicella infections. Severe disease occurs in approximately 30%

of such persons with primary infection. Because varicella vaccine now is recommended for all healthy children and

adults without evidence of immunity, household contacts of immunocompromised persons should be vaccinated routinely.

Although the risk for exposure to wild VZV for immunocompromised persons now is lower than it was previously, vaccine should

be offered to child and adult household contacts without evidence of immunity of immunocompromised persons. Vaccination

of household contacts provides protection for immunocompromised persons by decreasing the likelihood that wild-type

VZV will be introduced into the household. Vaccination of household contacts of immunocompromised persons

theoretically might pose a minimal risk for transmission of vaccine virus to

immunocompromised persons, although in one study,

no evidence of transmission of vaccine virus was demonstrated after vaccination of 37 healthy siblings of 30 children

with malignancy (155). No cases have been documented of transmission of vaccine virus to immunocompromised persons in

the postlicensure period in the United States, with >55 million doses of vaccine distributed. Other data indicate that

disease caused by vaccine virus in immunocompromised persons is milder than wild-type disease and can be treated with

acyclovir (148,159). The benefits of vaccinating susceptible household contacts of immunocompromised persons outweigh

the extremely low potential risk for transmission of vaccine virus to immunocompromised contacts. Vaccine recipients in

whom vaccine-related rash occurs, particularly HCP and household contacts of immunocompromised persons, should avoid

contact with susceptible persons who are at high risk for severe complications. If a susceptible, immunocompromised person

is inadvertently exposed to a person who has a vaccine-related rash, postexposure prophylaxis with VZIG is not

needed because disease associated with this type of virus is expected to be mild.

Nursing Mothers

Postpartum vaccination of women without evidence of immunity need not be delayed because of breastfeeding.

Women who have received varicella vaccination postpartum may continue to breastfeed. The majority of live vaccines are

not associated with virus secretion in breast milk
(157). A study involving 12 women who received single-antigen varicella
vaccine while breastfeeding indicated no evidence of VZV DNA either in 217 breast milk
samples collected or in infants tested
after both vaccine doses (162). No infants seroconverted. Another study did not detect
varicella gene sequences in
the

postvaccination breast milk samples (163). Therefore, single-antigen varicella vaccine
should be administered to
nursing mothers without evidence of immunity. Combination MMRV vaccine is not
licensed for use among persons aged
>13 years.

Health-Care Personnel

Nosocomial transmission of VZV is well-recognized
(131,164--173), and guidelines for the prevention of nosocomial
VZV infection and for infection control in HCP have been published
(174,175). Sources of nosocomial exposure have
included patients, hospital staff, and visitors (e.g., the children of hospital employees)
who are infected with varicella or HZ.
In hospitals, airborne transmission of VZV has been demonstrated when varicella has
occurred in susceptible persons who had
no direct contact with the index case-patient
(176--180).
To prevent disease and nosocomial spread of VZV, health-care institutions should

ensure that all HCP have evidence

of immunity to varicella. Birth before 1980 is not considered evidence of immunity for HCP because of the possibility

of nosocomial transmission to high-risk patients. In health-care institutions, serologic screening before vaccination of

personnel who have a negative or uncertain history of varicella and who are unvaccinated is likely to be cost effective. Institutions

may elect to test all HCP regardless of disease history because a small proportion of persons with a positive history of

disease might be susceptible.

Routine testing for varicella immunity after 2 doses of vaccine is not recommended for the management of vaccinated

HCP. Available commercial assays are not sensitive enough to detect antibody after vaccination in all instances. Sensitive tests

have indicated that 99% of adults develop antibodies after the second dose. However, seroconversion does not always result in

full protection against disease, and no data regarding correlates of protection are available for adults.

HCP who have received 2 doses of vaccine and who are exposed to VZV should be monitored daily during days 10--21

after exposure through the employee health program or by an infection control nurse to determine clinical status (i.e., daily

screen for fever, skin lesions, and systemic symptoms). Persons with varicella might be infectious up to 2 days before rash onset.

In addition, HCP should be instructed to report fever, headache, or other constitutional symptoms and any atypical skin

lesions immediately. HCP should be placed on sick leave immediately if symptoms

occur. Health-care institutions should

establish protocols and recommendations for screening and vaccinating HCP and for

management of HCP after exposures in the

work place.

HCP who have received 1 dose of vaccine and who are

exposed to VZV should receive the second dose with

single-antigen varicella vaccine within 3--5 days after exposure to rash (provided 4

weeks have elapsed after the first dose). After

vaccination, management is similar to that of 2-dose vaccine recipients.

Unvaccinated HCP who have no other evidence of immunity who are exposed to VZV

are potentially infective from

days 10--21 after exposure and should be furloughed during this period. They should

receive postexposure vaccination as soon

as possible. Vaccination within 3--5 days of exposure to rash might modify the disease

if infection occurred. Vaccination >5

days postexposure still is indicated because it induces protection against subsequent

exposures (if the current

exposure did not cause infection).

The risk for transmission of vaccine virus from vaccine

recipients in whom varicella-like rash occurs after vaccination is

low and has been documented after exposures in households and long-term care

facilities

(140,146--148). No cases have been documented after vaccination of HCP. The benefits

of vaccinating HCP without evidence of immunity outweigh

this extremely low potential risk. As a safeguard, institutions should consider

precautions for personnel in whom rash occurs

after vaccination. HCP in whom a vaccine-related rash occurs should avoid contact with

persons without

evidence of immunity who are at risk for severe disease and complications until all

lesions resolve (i.e., are crusted over or fade away) or no

new lesions appear within a 24-hour period.

Varicella IgG Antibody Testing

The tests most widely used to detect varicella IgG antibody after natural varicella

infection among HCP are

latex agglutination (LA) and ELISA. A commercially available LA test using latex

particles coated with VZV glycoprotein

antigens can be completed in 15 minutes and does not require special equipment

(181). The sensitivity and specificity of the LA

test are comparable to those of FAMA in detecting antibody response after natural

varicella infection. The LA test generally

is more sensitive than commercial ELISAs. The LA test has detected antibody for up to

11 years after varicella vaccination

(182).

However, for the purpose of screening HCP for varicella susceptibility, a less sensitive

and more specific commercial

ELISA should be considered. A recent report indicated that the LA test can

produce false-positive results, particularly when only

a single concentration of serum is evaluated

(183); this led to documented cases of false-positive results in HCP

who consequently remained unvaccinated and subsequently contracted varicella.

Vaccination for Outbreak Control

Varicella vaccination is recommended for outbreak control. Persons who do not have adequate evidence of immunity

should receive their first or second dose as appropriate. Additionally, in outbreaks among preschool-aged children, 2-dose vaccination

is recommended for optimal protection, and children vaccinated with 1 dose should receive their second dose provided

3 months have elapsed since the first dose. State and local health departments may advise exposed persons who do not have evidence

of immunity to contact their health-care providers for vaccination, or they may offer vaccination through the health department

or school (or other institutions) vaccination clinics. Although outbreak control efforts optimally should be implemented as soon

as an outbreak is identified, vaccination should be offered even if the outbreak is identified late. Varicella outbreaks in

certain settings (e.g., child care facilities, schools, or institutions) can last as long as 4--5 months. Thus, offering vaccine during

an outbreak might provide protection to persons not yet exposed and shorten the duration of the outbreak

(184). Persons receiving either their first or second dose as part of the outbreak control program may be readmitted to school

immediately. Those vaccinated with the first dose as part of outbreak control measures should be scheduled for the second dose as

age appropriate. Persons who are unvaccinated and without other evidence of immunity who do not receive vaccine should

be excluded from institutions in which the outbreak is occurring until 21 days after the

onset of rash in the last case of varicella.

In addition, for school-aged persons covered by the 2-dose school vaccination requirements, exclusion during an outbreak

is recommended for those vaccine recipients who had

received the first dose before the outbreak but not the second as part of

the oubtreak control program. Persons at increased risk for severe varicella who have contraindications to vaccination

should receive VZIG within 96 hours of exposure.

Contraindications

General

Adequate treatment provisions for anaphylactic reactions, including epinephrine injection (1:1000), should be available

for immediate use should an anaphylactic reaction occur.

Before administering a vaccine, health-care providers should obtain

the vaccine recipient's vaccination history and determine whether the individual had any previous reactions to any

vaccine including Varivax, ProQuad or any measles, mumps, or rubella containing vaccines.

Allergy to Vaccine Components

The administration of live varicella-containing vaccines rarely results in hypersensitivity. The information in the

package insert should be reviewed carefully before vaccine is

administered. Vaccination is contraindicated for persons who have

a history of anaphylactic reaction to any component of the vaccine, including gelatin.

Single-antigen varicella vaccine does

not contain preservatives or egg protein; these substances have caused hypersensitive

reactions to other vaccines. For

the combination MMRV vaccine, live measles and live mumps vaccines are produced in

chick embryo culture. However,

among persons who are allergic to eggs, the risk for serious allergic reactions after

administration of measles- or

mumps-containing vaccines is low. Because skin testing with vaccine is not predictive

of allergic reaction to vaccination, skin testing is

not required before administering combination MMRV vaccine to persons who are

allergic to eggs

(160). The majority of anaphylactic reactions to measles- and

mumps-containing vaccines are associated not with hypersensitivity to egg antigens

but with other vaccine components. Neither single-antigen varicella nor combination

MMRV vaccines should be administered

to persons who have a history of anaphylactic reaction to neomycin. However,

neomycin allergy usually is manifested as a

contact dermatitis, which is a delayed-type immune response rather than anaphylaxis.

For persons who experience such a response,

the adverse reaction, if any, would appear as an erythematous, pruritic nodule or

papule present 48--96 hours after vaccination.

A history of contact dermatitis to neomycin is not a contraindication to receiving

varicella vaccines.

Altered Immunity

Single-antigen varicella and combination MMRV vaccines are not licensed for use in persons who have any malignant condition, including blood dyscrasias, leukemia, lymphomas of any type, or other malignant neoplasms affecting the bone marrow or lymphatic systems. Combination MMRV vaccine should not be administered to persons with primary or acquired immunodeficiency, including immunosuppression associated with AIDS or other clinical manifestations of HIV infections, cellular immunodeficiencies, hypogammaglobulinemia, and dysgammaglobulinemia. Combination MMRV vaccine should not be administered as a substitute for the component vaccines when vaccinating HIV-infected children.

Varicella vaccines should not be administered to persons who have a family history of congenital or hereditary immunodeficiency in first-degree relatives (e.g., parents and siblings) unless the immune competence of the potential vaccine recipient has been clinically substantiated or verified by a laboratory.

Varicella vaccines should not be administered to persons receiving high-dose systemic immunosuppressive therapy, including persons on oral steroids >2 mg/kg of body weight or a total of >20 mg/day of prednisone or equivalent for persons who weigh >10 kg, when administered for >2 weeks. Such persons are more susceptible to infections than healthy

persons. Administration of varicella vaccines can result in a more extensive vaccine-associated rash or disseminated disease in

persons receiving immunosuppressive doses of corticosteroids

(185). This contraindication does not apply

to persons who are receiving inhaled, nasal, or topical corticosteroids or low-dose corticosteroids as are used

commonly for asthma prophylaxis or for

corticosteroid-replacement therapy (see Situations in Which Some Degree of Immunodeficiency Might Be Present).

Pregnancy

Because the effects of the varicella virus vaccine on the fetus are unknown, pregnant women should not be

vaccinated. Nonpregnant women who are vaccinated should avoid

becoming pregnant for 1 month after each injection. For

persons without evidence of immunity, having a pregnant household member is not a contraindication to vaccination.

If a pregnant woman is vaccinated or becomes pregnant within 1 month of vaccination, she should be counseled

about potential effects on the fetus. Wild-type varicella poses a low risk to the fetus (see Prenatal and Perinatal

Exposure). Because the virulence of the attenuated virus used in the vaccine is less than that of the wild-type virus, the risk to the fetus,

if any, should be even lower. In 1995, Merck and Co., Inc., in collaboration with CDC, established the VARIVAX

Pregnancy Registry to monitor the maternal-fetal outcomes of pregnant women who

were inadvertently administered

varicella vaccine 3 months before or at any time during pregnancy (to report, call: 1-800-986-8999)

(186). During the first 10 years of the pregnancy registry no cases of congenital varicella syndrome or birth defects compatible with congenital varicella

syndrome have been documented (187,188). Among 131 live-born infants of prospectively reported seronegative women (82 of

whom were born to mothers vaccinated during the highest risk period [i.e., the first or second trimester of pregnancy]), no

birth defects consistent with congenital varicella syndrome have been documented (prevalence

rate = 0; CI = 0--6.7%), and three major birth defects were reported (prevalence rate = 2.3%; CI = 0.5%--6.7%). The rate of occurrence of major birth

defects from prospective reports in the registry was similar to the rate reported in the general U.S. population (3.2%), and the

defects indicated no specific pattern or target organ. Although the study results do not exclude the possibility of risk for women

who received inadvertent varicella vaccination before or during pregnancy, the potential risk, if any, is low.

Precautions

Illness

Vaccination of persons who have acute severe illness,

including untreated, active tuberculosis, should be postponed

until recovery. The decision to delay vaccination depends on the severity of symptoms and on the etiology of the disease. No
data are available regarding whether either single-antigen varicella or combination MMRV vaccines exacerbate tuberculosis.

Live attenuated measles, mumps, and rubella virus vaccines administered individually might result in a temporary depression
of tuberculin skin sensitivity. Therefore, if a tuberculin test is to be performed, it should be administered either any time
before, simultaneously with, or at least 4--6 weeks after combination MMRV vaccine. However, tuberculin skin testing is not
a prerequisite for vaccination with single-antigen varicella or combination MMRV vaccines.

Varicella vaccines may be administered to children without evidence of immunity who have mild illnesses, with or
without low-grade fever (e.g., diarrhea or upper-respiratory infection)
(189). Physicians should be alert to the
vaccine-associated temperature elevations that might occur predominantly in the second week after vaccination, especially with
combination MMRV vaccine. Studies suggest that failure to vaccinate children with minor illnesses can impede
vaccination efforts (190).

Thrombocytopenia

Thrombocytopenia is not a contraindication for
single-antigen varicella vaccine. No clinical data are available regarding
the development or worsening of thrombocytopenia in persons vaccinated with

combination MMRV vaccine. Cases

of thrombocytopenia have been reported after MMR vaccine and after varicella vaccination. Postmarketing experience with

live MMR vaccine indicates that persons with thrombocytopenia might develop more severe thrombocytopenia after

vaccination. For vaccination of thrombocytopenic children with combination MMRV vaccine, health-care providers should refer to

the ACIP recommendations on MMR vaccination

(160).

Recent Administration of Blood, Plasma, or Immune Globulin

Although passively acquired antibody is known to interfere with response to measles and rubella vaccines

(191), the effect of the administration of immune globulin (IG) on the

response to varicella virus vaccine is unknown. The duration

of interference with the response to measles vaccination is dose-related and ranges from 3--11 months. Because of the

potential inhibition of the response to varicella vaccination by passively transferred antibodies, varicella vaccines should not

be administered for the same intervals as measles vaccine (3--11 months, depending on the dosage) after

administration of blood (except washed red blood cells), plasma, or IG. Suggested intervals between administration of antibody-containing

products for different indications and varicella vaccine have been published previously

(157). In addition, persons who received a varicella vaccine should not be administered an antibody-containing product for 2 weeks after vaccination unless the

benefits exceed those of vaccination. In such cases, the vaccine recipient should either be

revaccinated or tested for immunity at the appropriate intervals, depending on the dose

received, and then revaccinated if seronegative.

Use of Salicylates

No adverse events associated with the use of salicylates after varicella vaccination have been reported; however, the

vaccine manufacturer recommends that vaccine recipients avoid

using salicylates for 6 weeks after receiving varicella vaccines

because of the association between aspirin use and Reye syndrome after varicella. Vaccination with subsequent close monitoring

should be considered for children who have rheumatoid arthritis or other conditions

requiring therapeutic aspirin. The risk for

serious complications associated with aspirin is likely to be greater in children in whom

natural varicella develops than it is in

children who receive the vaccine containing attenuated

VZV. No association has been documented between Reye syndrome

and analgesics or antipyretics that do not contain salicylic acid.

Postexposure Prophylaxis

Healthy Persons

Prelicensure data from the United States and Japan on varicella exposures in children

from household, hospital,

and community settings indicate that single-antigen varicella vaccine is effective in preventing illness or modifying varicella

severity if administered to unvaccinated children within 3 days, and possibly up to 5 days, of exposure to rash

(78,101,192). Vaccination within 3 days of exposure to rash was

>90% effective in preventing varicella whereas vaccination within 5 days

of exposure to rash was approximately 70% effective in preventing varicella and 100% effective in modifying severe

disease (101,192). Limited postlicensure studies also have demonstrated that varicella vaccine is highly effective in either preventing

or modifying disease if administered within 3 days of exposure

(193,194). Varicella vaccine is recommended for

postexposure administration for unvaccinated persons without other evidence of immunity. If exposure to VZV does not cause

infection, postexposure vaccination should induce protection against subsequent exposures. If the exposure results in infection,

no

evidence indicates that administration of single-antigen varicella vaccine during the presymptomatic or prodromal stage

of illness increases the risk for vaccine-associated

adverse events. No data are available regarding the potential benefit

of administering a second dose to 1-dose vaccine recipients after exposure. However, administration of a second dose should

be considered for persons who have previously received 1 dose to bring them up-to-date. Studies on postexposure use of

varicella vaccine have been conducted exclusively in children. A higher proportion of adults do not respond to the first dose of

varicella vaccine. Nevertheless, postexposure vaccination should be offered to adults without evidence of immunity.

Although postexposure use of varicella vaccine has potential applications in hospital settings, vaccination is recommended routinely

for all HCP without evidence of immunity and is the preferred method for preventing varicella in health-care settings

(195). Preferably, HCP should be vaccinated when they begin employment. No data are available on the use of combination

MMRV raccine for postexposure prophylaxis.

Persons Without Evidence of Immunity Who Have Contraindications

for Vaccination and Who Are at Risk for Severe Disease and Complications

Studies conducted in 1969 indicated that clinical varicella was prevented in nonimmune, healthy children by

the administration of zoster immune globulin (ZIG) (prepared from patients recovering from HZ) within 72 hours of

exposure (196). ZIG also lowered attack rates among immunocompromised persons if administered no later than 96 hours

after exposure (196). VZIG (prepared from plasma obtained from healthy, volunteer blood donors identified by routine

screening to have high antibody titers to VZV) became

available in 1978. Both serologic and clinical evaluations have demonstrated

that the product is equivalent to ZIG in preventing or modifying clinical illness in non-immune, immunocompromised

persons who are exposed to varicella

(197,198). In a study of immunocompromised children who were administered VZIG within

96 hours of exposure, approximately one in five exposures resulted in clinical varicella, and one in 20 resulted in

subclinical disease (198). The severity of clinical varicella (evaluated by percentage of patients with >100 lesions or complications)

was lower than expected on the basis of historic controls.

The VZIG product currently used in the United States,

VariZIG™(Cangene Corporation, Winnipeg, Canada), is

available under an Investigational New Drug Application

Expanded Access protocol (available at

http://www.fda.gov/cber/infosheets/mphvzig020806.htm). A request for licensure in the United States might be submitted to FDA in the

future. VariZIG is a lyophilized presentation which, when properly reconstituted, is approximately a 5% solution of IgG that can be

administered intramuscularly (199). VariZIG can be

obtained 24 hours a day from the sole authorized U.S.

distributor (FFF Enterprises, Temecula, California) at 1-800-843-7477 or online at

http://www.fffenterprises.com.

Administration of VZIG

VZIG provides maximum benefit when administered as soon as possible after exposure, but it might be effective

if administered as late as 96 hours after exposure. The effectiveness of VZIG when administered >96 hours after

initial exposure has not been evaluated. The duration of protection provided after administration of VZIG is unknown,

but protection should last at least one half-life of the IG (i.e.,

approximately 3 weeks). Susceptible persons at high risk for

whom varicella vaccination is contraindicated and who are again exposed

>3 weeks after receiving a dose of VZIG should

receive another full dose of VZIG. Patients receiving monthly high-dose immune globulin intravenous (IGIV)

(>400 mg/kg) are likely to be protected and probably do not require VZIG if the last dose of IGIV was administered <3 weeks before

exposure (200). VZIG has not been proven to be useful in treating clinical varicella or HZ or in preventing disseminated zoster and

is not recommended for such use. VZIG might extend the incubation period of the virus from 10--21 days to

>28 days. This should be taken into account after exposures when VZIG is administered.

Dosage

VariZIG is supplied in 125-U vials. The recommended dose is 125 units/10 kg of body weight, up to a maximum of

625 units (five vials). The minimum dose is 125 U. The human IgG content is 60--200 mg per 125 units dose of VariZIG.

Indications for the Use of VZIG for Postexposure Prophylaxis

The decision to administer VZIG depends on three factors: 1) whether the patient lacks

evidence of immunity, 2)

whether the exposure is likely to result in infection, and 3) whether the patient is at greater risk for complications than the

general population.

Both healthy and immunocompromised children and adults who have verified positive histories of varicella (except

for bone-marrow transplant recipients) may be considered immune (see Evidence of Immunity). The association between

positive histories of varicella in bone-marrow donors and susceptibility to varicella in recipients after transplants has not been

studied adequately. Thus, persons who receive bone-marrow transplants should be considered nonimmune, regardless of

previous history of varicella disease or varicella vaccination in themselves or in their donors. Bone-marrow recipients in whom

varicella or HZ develops after transplantation should subsequently be considered immune.

VZIG is not indicated for persons who received 2 doses of varicella vaccine and became immunocompromised as a

result of disease or treatment later in life. These persons should be monitored closely; if disease occurs, treatment with acyclovir

should be instituted at the earliest signs or symptoms. For patients without evidence of immunity and on steroid therapy doses

>2 mg/kg of body weight or a total of 20 mg/day of prednisone or equivalent, VariZIG is indicated.

Types of Exposure

Certain types of exposure can place persons without evidence of immunity at risk for varicella. Direct contact exposure is defined as face-to-face contact with an infectious person while indoors. The duration of face-to-face contact that warrants administration of VZIG is not certain. However, the contact should not be transient. Certain experts suggest a contact of >5 minutes as constituting significant exposure for this purpose, whereas others define close contact as >1 hour (200). Substantial exposure for hospital contacts consists of sharing the same hospital room with an infectious patient or direct, face-to-face contact with an infectious person (e.g., HCP). Brief contacts with an infectious person (e.g., contact with x-ray technicians or housekeeping personnel) are less likely than more prolonged contacts to result in VZV transmission.

Persons with continuous exposure to household members who have varicella or disseminated HZ are at greatest risk for infection. Varicella occurs in approximately 85% (range: 65%--100%) of susceptible household contacts exposed to VZV. Localized HZ is much less infectious than varicella or disseminated HZ (52). Transmission from localized HZ is more likely after close contact, such as in household settings. Physicians may consider recommending postexposure prophylaxis with VZIG in such circumstances. After household exposure to varicella, attack rates among immunocompromised children who were administered VZIG were up to 60% (197). No comparative data are available for immunocompromised children without evidence of immunity who were not administered VZIG. However, the

incidence of severe disease

(defined as >100 skin lesions) was less than that predicted from the natural history of

disease in normal children (27% and 87%,

respectively), and the incidence of pneumonia was less than that described in children

with neoplasm (6% and 25%, respectively)

(201). The risk for varicella after close contact (e.g., contact with playmates) or hospital

exposure is estimated to be

approximately 20% of the risk occurring from household exposure.

The attack rate in healthy neonates who were exposed in utero within 7 days of

delivery and who received VZIG after

birth was 62%, which does not differ substantially from rates reported for neonates who

were similarly exposed but not treated

with VZIG (49). However, the occurrence of complications and fatal outcomes was

substantially lower for neonates who

were treated with VZIG than for those who were not.

In a study of pregnant women without immunity to VZV who were exposed to varicella

and administered VZIG,

the infection rate was 30%. This is substantially lower than the expected rate of >70%

in unimmunized women exposed

to varicella (199,202).

Recommendations for the Use of VZIG

The following patient groups are at risk for severe disease and complications from

varicella and should receive VZIG:

Immunocompromised patients. VZIG is used primarily for passive immunization of

immunocompromised

persons without evidence of immunity after direct exposure to varicella or disseminated HZ patients, including persons who 1)

have primary and acquired immune-deficiency disorders, 2) have neoplastic diseases, and 3) are receiving

immunosuppressive

treatment. Patients receiving monthly high-dose IGIV

(>400 mg/kg) are likely to be protected and probably do not

require VZIG if the last dose of IGIV was administered

<3 weeks before exposure (200).

Neonates whose mothers have signs and symptoms of varicella around the time of delivery. VZIG is indicated for neonates whose mothers have signs and symptoms of varicella from 5 days before to 2 days after delivery. VZIG is

not necessary for neonates whose mothers have signs and symptoms of varicella more than 5 days before delivery, because

those infants should be protected from severe varicella by transplacentally acquired maternal antibody. No evidence suggests

that infants born to mothers in whom varicella occurs >48 hours after delivery are at increased risk for serious complications

(e.g., pneumonia or death).

Premature neonates exposed postnatally. Transmission of varicella in the hospital nursery is rare because the majority

of neonates are protected by maternal antibody. Premature

infants who have substantial postnatal exposure should be

evaluated on an individual basis. The risk for complications of postnatally acquired varicella in premature infants is

unknown. However, because the immune system of premature infants is not fully

developed, administration of VZIG to premature infants born

at >28 weeks of gestation who are exposed during the neonatal period and whose

mothers do not have evidence of immunity

is indicated. Premature infants born at <28 weeks of gestation or who weigh

<1,000 g at birth and were exposed during

the neonatal period should receive VZIG regardless of maternal immunity because such

infants might not have acquired

maternal antibody. The majority of premature infants born at

>28 weeks of gestation to immune mothers have enough

acquired maternal antibody to protect them from severe disease and complications.

Although infants are at higher risk than older children for serious and fatal

complications, the risk for healthy, full-term infants who have varicella after postnatal

exposure

is substantially less than that for infants whose mothers were infected

5 days before to 2 days after delivery. VZIG is

not recommended for healthy, full-term infants who are exposed postnatally, even if

their mothers have no history of

varicella infection.

Pregnant women. Because pregnant women might be at higher risk for severe varicella

and complications

(37,42,203), VZIG should be strongly considered for pregnant women without evidence

of immunity who have been

exposed. Administration of VZIG to these women has not been found to prevent

viremia, fetal infection, congenital varicella

syndrome, or neonatal varicella. Thus, the primary indication for VZIG in pregnant

women is to prevent complications of

varicella in the mother rather than to protect the fetus.

Neonates born to mothers who have signs and symptoms of varicella from 5

days before to 2 days after delivery should receive VZIG, regardless of whether the

mother received VZIG.

Interval Between Administration of VZIG and Varicella Vaccine

Any patient who receives VZIG to prevent varicella should receive varicella vaccine

subsequently, provided the vaccine is

not contraindicated. Varicella vaccination should be delayed until 5 months after VZIG

administration. Varicella vaccine is

not needed if the patient has varicella after administration of VZIG.

Antiviral Therapy

Because VZIG might prolong the incubation period by

>1 week, any patient who receives VZIG should be observed

closely for signs or symptoms of varicella for 28 days after exposure. Antiviral therapy

should be instituted immediately if signs

or symptoms of varicella disease occur. The route and duration of antiviral therapy

should be determined by specific host

factors, extent of infection, and initial response to therapy. Information regarding how

to obtain VariZIG is available at

http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5508a5.htm

(204).

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CDC. A new product (VariZIG™) for postexposure prophylaxis of varicella available

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 Two live, attenuated varicella zoster virus--containing vaccines are available in the United States for prevention of

varicella: 1) a single-antigen varicella vaccine

(VARIVAX,® Merck & Co., Inc., Whitehouse Station, New Jersey), which was licensed

in the United States in 1995 for use among healthy children aged

>12 months, adolescents, and adults; and 2) a

combination measles, mumps, rubella, and varicella vaccine

(ProQuad,® Merck & Co., Inc., Whitehouse Station, New Jersey), which

was licensed in the United States in 2005 for use among healthy children aged 12

months--12 years. Initial Advisory

Committee on Immunization Practices (ACIP) recommendations for prevention of varicella issued in 1995 (CDC. Prevention

of varicella: recommendations of the Advisory Committee on Immunization Practices [ACIP]. MMWR 1996;45[No.

RR-11]) included routine vaccination of children aged 12--18 months, catch-up vaccination of susceptible children aged 19

months--12 years, and vaccination of susceptible persons who have close contact with persons at high risk for serious complications

(e.g., health-care personnel and family contacts of immunocompromised persons). One dose of vaccine was recommended

for children aged 12 months--12 years and 2 doses, 4--8 weeks apart, for persons aged >13 years. In 1999, ACIP updated the recommendations (CDC. Prevention of varicella: updated recommendations of the Advisory Committee on

Immunization Practices [ACIP]. MMWR 1999;48[No. RR-6]) to include establishing child care and school entry requirements, use of

the vaccine following exposure and for outbreak control, use of the vaccine for certain children infected with

human immunodeficiency virus, and vaccination of adolescents and adults at high risk for exposure or transmission.

 In June 2005 and June 2006, ACIP adopted new recommendations regarding the use of live, attenuated varicella

vaccines for prevention of varicella. This report revises, updates, and replaces the 1996 and 1999 ACIP statements for prevention

of varicella. The new recommendations include 1) implementation of a routine 2-dose varicella vaccination program

for children, with the first dose administered at age 12--15 months and the second dose at age 4--6 years; 2) a second dose

catch-up varicella vaccination for children, adolescents, and adults who previously had received 1 dose; 3) routine vaccination of

all healthy persons aged >13 years without evidence of immunity; 4) prenatal assessment and postpartum vaccination;

5) expanding the use of the varicella vaccine for HIV-infected children with age-specific CD4+T lymphocyte percentages of

15%--24% and adolescents and adults with CD4+T lymphocyte counts

>200 cells/µL; and 6) establishing middle school,

high school, and college entry vaccination requirements. ACIP also approved criteria for evidence of immunity to varicella.

Introduction

Varicella is a highly infectious disease caused by the varicella-zoster virus (VZV). Secondary attack rates for this virus

might reach 90% for susceptible household contacts. VZV causes a systemic infection that results typically in lifetime immunity.

In otherwise healthy persons, clinical illness after reexposure is rare.

In 1995, a vaccine to prevent varicella

(VARIVAX,® Merck & Co., Inc., Whitehouse Station, New Jersey) was licensed

in the United States for use among healthy children aged

>12 months, adolescents, and adults; recommendations of the

Advisory Committee on Immunization Practices (ACIP)

regarding use of the varicella vaccine have been published previously

(1,2) This report revises, updates, and replaces earlier ACIP statements

(Table 1).

Methods

 In response to increasing reports of varicella outbreaks among highly vaccinated populations
(3--6), ACIP's measles-mumps-rubella and varicella (MMRV) workgroup first met in February 2004 to review data related to varicella vaccine use in
the United States since implementation of the vaccination program in 1995 and to consider recommendation options
for improving control of varicella disease. The workgroup held monthly conference calls and met in person three times a year.
The workgroup reviewed data on the impact of the 1-dose varicella vaccination program, including data on vaccination
coverage, changes in varicella epidemiology, transmission from vaccinated persons with varicella, vaccine effectiveness,
immune response to vaccination, evidence of immunity, and potential risk factors for vaccine failure. Published and
unpublished data related to correlates of protection, safety, immunogenicity, and
efficacy† of the new quadrivalent MMRV vaccine and
the immunogenicity and efficacy of a second dose of varicella vaccine also were reviewed.
Cost-benefit and cost-effectiveness analyses were considered, including revised cost-benefit analysis of both the 1- and 2-dose programs for children
compared with no vaccination program and the incremental benefit of a second dose. Presentations were made to the full ACIP
meetings in October 2004, February 2005, June 2005, and June 2006. Recommendation options were developed and discussed by
the MMRV workgroup. When definitive research evidence was lacking, the

recommendations incorporated expert opinion of
the workgroup members. The workgroup sought input from partner organizations (i.e., the American Academy of
Pediatrics [AAP], the American Academy of Family Physicians [AAFP], the American College of Obstetricians and Gynecologists,
the Council of State and Territorial Epidemiologists, and the
Association of Immunization Managers) and from state public
health professionals and immunization program directors. Proposed recommendations and a draft statement were presented to
the full ACIP in June 2005 and June 2006. After deliberations, final ACIP recommendations were approved in 2005 and
2006. Modifications to the draft statement were made following CDC and external review process to update and clarify wording
in the document.

Epidemiology of Varicella

General

 VZV is transmitted from person to person by direct contact, inhalation of aerosols from vesicular fluid of skin lesions
of acute varicella or zoster, or infected respiratory tract secretions that also might be aerosolized. The virus enters the
host through the upper-respiratory tract or the conjunctiva.
 The average incubation period for varicella is 14--16
days§ after exposure to rash; however, this period can vary (range:

10--21 days). The period of contagiousness of infected persons is estimated to begin 1--2 days before the onset of rash and to

end when all lesions are crusted, typically 4--7 days after onset of rash

(7). Persons who have progressive varicella

(i.e., development of new lesions for >7 days) might be contagious longer, presumably because their immune response is

depressed, which allows viral replication to persist. VZV

remains dormant in sensory-nerve ganglia and might be

reactivated at a later time, causing herpes zoster (HZ) (i.e., shingles), a painful vesicular rash typically appearing in a dermatomal distribution

of one or two sensory-nerve roots.

 Since implementation of a universal childhood varicella vaccination program in 1995, the epidemiology and

clinical characteristics of varicella in the United States have changed, with substantial declines in morbidity and mortality

attributable to varicella. No consistent changes in HZ epidemiology have been documented.

  Vaccinated persons might develop modified varicella disease with atypical presentation. Varicella disease that develops

>42 days after vaccination (i.e., breakthrough varicella) typically is mild, with <50 skin lesions, low or no fever, and shorter

(4--6 days) duration of illness. The rash is more likely to be predominantly maculopapular rather than vesicular.

Nevertheless, breakthrough varicella is contagious.

Prevaccine Era

Before the introduction of varicella vaccine in 1995, varicella was a universal childhood disease in the United States,
with peak incidence in the spring and an average annual incidence of 15--16 cases per 1,000 population. On the basis of data
from the National Health Interview Survey (NHIS) for 1980--1990, an average of 4 million cases were estimated to have
occurred

annually (annual incidence rate: 15 cases per 1,000 population)
(8). Varicella was not a nationally notifiable disease
when vaccine was introduced in 1995, and surveillance data were limited. In 1994, only 28 states, the District of Columbia,
and New York City reported cases to CDC's National Notifiable Disease Surveillance System (NNDSS); reporting was
passive, with estimated completeness ranging from <0.1% to 20%
(9).
 In multiple studies, age-specific incidence data were derived from NHIS and from state and local surveys
(8,10,11). During 1980--1990, an estimated 33% of cases occurred among preschool-aged children (i.e., children aged 12 months--4 years),
and 44% occurred among school-aged children (i.e., children aged 5--9 years) (annual incidence rates: 82.8 and 91.1 cases
per 1,000 children, respectively). Approximately 90%--92% of cases occurred among persons aged <15 years, and cases
occurred rarely among persons aged >50 years. However, studies using data from state and local surveys conducted during
1990--1992 and during 1994--1995 indicated that the highest incidence of varicella

occurred among preschool-aged rather than

school-aged children, indicating that the disease was being acquired at earlier ages

(10,11). National seroprevalence data for

1988--1994 indicated that 95.5% of adults aged 20--29 years, 98.9% of adults aged

30--39 years, and >99.6% of adults aged

>40 years were immune to VZV (12). However, for reasons that are not well

understood, the epidemiology of varicella differs between countries with temperate and

tropical climates

(13--18). In the majority of countries with temperate climates,

>90% of persons are infected by adolescence whereas in countries with tropical

climates, a higher

proportion of infections are acquired at older ages, which results in higher susceptibility

among adults

(19).

   Estimates of the burden of varicella hospitalization varied according to the year(s)

studied, the source of data, and

the definitions used for a varicella-related hospitalization (20--23). Estimates were

higher if varicella was listed as either a

principal or a secondary cause of hospitalization, in which case some incidental

varicella hospitalization might have been

included. During 1988--1995, an estimated 10,632 hospitalizations were attributable

annually to varicella in the United States

(range: 8,198--16,586) (20). Another study demonstrated an annual average of 15,073

hospitalizations during 1993--1995, but

this period might have included an epidemic year

(22). Overall rates of hospitalization for varicella during 1988--1995

ranged from 2.3 to 6.0 cases per 100,000 population. If any

varicella-related hospital discharge diagnostic code was included, rates varied between 5.0 and 7.0 cases per 100,000 population (20--23).

 During 1988--1995, persons without severe immuno-compromising conditions or treatments comprised the largest proportion (89%) of annual varicella-related hospitalizations (20). Before vaccination, children aged <4 years accounted for 43%--44% of hospitalizations, and persons aged >20 years accounted for 32%--33% (20,22). The rate of complications from varicella was substantially higher for persons aged >20 years and for infants (i.e., children aged <1 year). Adults aged >20 years were 13 times more likely to be hospitalized when they had varicella than children aged 5--9 years, and infants aged <1 year were six times more likely to be hospitalized than children aged 5--9 years (20). The most common complications of varicella that resulted in hospitalizations were skin and soft tissue infections (especially invasive group A streptococcal infections), pneumonia, dehydration, and encephalitis. In 1980, an association was identified between Reye syndrome and the use of aspirin during varicella or influenza-like illness; since then, Reye syndrome, which was once considered a common complication resulting from varicella infection, has become rare (24--26).

 During 1970--1994, the average annual number of deaths for which varicella was recorded as the underlying cause was 105; the overall average annual varicella mortality rate was 0.4 deaths per 1 million

population. The age distribution of varicella deaths has shifted during this period. During 1970--1974, persons aged <20 years accounted for 80% of varicella deaths, compared with 46% during 1990--1994. During 1970--1994, the average case-fatality rate (CFR) for varicella for all ages combined ranged from 2.0 to 3.6 per 100,000 cases, with higher rates among infants and adults aged >20 years (27). Although CFRs declined substantially during this period, the risk for varicella-related death during 1990--1994 was still 25 times higher for adults than for children aged 12 months--4 years (CFR: 21.3 and 0.8 per 100,000 cases, respectively). During the same period, 89% of varicella deaths among children and 75% of varicella deaths among adults occurred in persons without severe underlying immunocompromising medical conditions. The most common complications among persons who died of varicella were pneumonia, central nervous system complications (including encephalitis), secondary infection, and hemorrhagic conditions. A recent reanalysis of varicella deaths also considered varicella when listed as a contributing cause of death in addition to the underlying cause studied in the previous report (28). During 1990--1994, a varicella diagnosis was listed on an average of 145 death certificates per year (105 as an underlying cause and 40 as a contributing cause), with an overall annual varicella mortality rate of 0.6 deaths per 1 million population.

Varicella during pregnancy can have adverse consequences for the fetus and infant, including congenital varicella

syndrome (see Prenatal and Perinatal Exposure). Reliable data on the number of cases of congenital varicella syndrome are not

available. However, on the basis of age-specific varicella incidence (from NHIS), the annual number of births, and the risk

for congenital varicella syndrome (1.1% overall risk in the first 20 weeks of pregnancy), 44 cases of congenital

varicella syndrome are estimated to have occurred each year in the United States during the prevaccine era

(29).

Postvaccine Era

 In 1995, a varicella vaccine

(VARIVAX,® Merck & Co., Inc., Whitehouse Station, New Jersey) was licensed in the United States for use among healthy children aged

>12 months, adolescents, and adults. At that time, ACIP recommended

routine varicella vaccination of children aged 12--18 months, catch-up vaccination of susceptible children aged 19 months--12

years, and vaccination of susceptible persons who have close contact with persons at high risk for serious complications (e.g.,

health-care workers and family contacts of

immunocompromised persons) (1; Table 1). In 1999, ACIP updated the recommendations

to include child care and school entry requirements, use of the vaccine after exposure and for outbreak control, use of the vaccine

for certain children infected with human immunodeficiency virus (HIV), and vaccination of adolescents and adults at high risk

for exposure or transmission (2; Table 1).

During 1997--2005, national varicella vaccination coverage among children aged 19--35 months increased from 27%

to 88%, with no statistically significant difference in coverage by race or ethnicity

(30). In 2005, state-specific varicella vaccination coverage ranged from 69% to 96%

(31). National surveillance data continue to be limited, but passive

surveillance data in certain states have documented a decline in

varicella incidence.

In four states (Illinois, Michigan, Texas, and West Virginia) with adequate

(>5% of expected cases during

1990--1994) reporting to NNDSS, varicella incidence for 2004 declined 53%--88%

compared with the average incidence for

1990--1994, with vaccination coverage among children aged 19--35 months ranging

from 82% to 88%

(32; CDC, unpublished data, 2006). During 2003--2005, the number of cases increased

in Illinois and Texas; the biggest increase (56%) occurred in

Texas (Figure 1). The number of cases remained stable in Michigan (Figure 1) and

declined minimally in West Virginia.

In 1995, along with implementation of the national vaccination program, CDC instituted

active surveillance for varicella

in three communities (Antelope Valley, California; Travis County, Texas; and West

Philadelphia, Pennsylvania) in

collaboration with state and local health departments to establish baseline data and to

monitor trends in varicella disease after

introduction of varicella vaccine. By 2000, vaccination coverage among children 19--35

months in these three communities had

reached 74%--84%, and reported total varicella cases had declined 71%--84%

(33). Although incidence declined to the greatest

extent (83%--90%) among children aged 12 months--4 years, incidence declined in all

age groups, including infants and

adults, indicating the herd immunity effects of the vaccination program. Since 2001,

only two sites were funded to

continue surveillance (Antelope Valley and West Philadelphia). By 2005, vaccination

coverage in these two sites had increased to

90%, and the reduction in incidence had reached 90% and 91%, respectively

(34). During 1996--2005, as vaccination

coverage continued to increase, the proportion of persons with varicella who had been

vaccinated increased from 2% to 56%.

During 1995--2004, peak incidence for varicella cases in active surveillance sites shifted

from age 3--6 years to age 9--11 years.

 After introduction of vaccine in 1995, the number and rate of annual varicella-related

hospitalizations declined. In

one study of a nationally representative sample that was conducted during 1993--2001,

varicella hospitalizations declined

75% (22). In another study, the annual varicella-related hospitalization rate declined

88% during 1994--2002

(23) (Figure 2). Hospitalization rates declined 100% among

infants, and substantial declines also were recorded in all other age groups (up

to age 50 years); hospitalization rates declined 91% among children aged <10 years,

92% among children and adolescents

aged 10--19 years, and 78% among adults aged 20--49 years. The greater decline in

hospitalizations among children led to

an increase in the proportion of varicella-related

hospitalizations among adults (40% of hospitalizations in 2002 occurred

among persons aged >20 years) (23). In the

combined active surveillance area, varicella-related hospitalizations declined from

2.4--4.2 hospitalizations per 100,000 population during 1995--1998 to 1.5 per 100,000

population in 2000

(33) and to 0.8 per 100,000 population in 2005

(34).

   During 1995--2001, the number of deaths for which varicella was listed as the

underlying cause decreased from 115 to

26 (28) (Figure 3). Since then, the number of deaths declined further; 16 deaths were

reported in 2003. Age-adjusted

mortality rates decreased 66%, from an average of 0.41 deaths per 1 million population

during 1990--1994 to 0.14 during

1999--2001. The decline was observed in all age groups <50 years, with the greatest

reduction (92%) occurring among children aged

12

months--4 years (0.09 deaths per 1 million population), followed by an 88% reduction

among children aged 5--9 years

(0.10 deaths per 1 million population). Deaths among persons aged

>50 years did not decline to the same extent; however,

the validity of reported varicella deaths in this age group is low

(35), and the majority of these deaths are not considered to

be caused by varicella. During 1999--2001, the average rate of mortality attributed to

varicella among all racial and

ethnic populations was <0.15 deaths per 1 million persons. Persons without high-risk

conditions (e.g.,

malignancies, HIV/acquired immunodeficiency syndrome [AIDS], and other

immune deficiencies) accounted for 92% of deaths attributable

to varicella. The average rates of deaths for which varicella was listed as a contributing

cause of death also

declined during 1999--2001, compared with 1990--1994.

Despite high 1-dose vaccination coverage and the success of the vaccination program

in reducing varicella morbidity

and mortality, reports to CDC from active surveillance sites and from states with

well-implemented vaccination programs and surveillance indicate that in certain states

and in one

active surveillance site, the number of reported varicella cases

has remained constant or declined minimally, and outbreaks have continued to occur.

During 2001--2005, outbreaks

were reported in schools with high varicella vaccination coverage (range 96%--100%)

(3,4). The outbreaks were similar in

certain respects: 1) all occurred in elementary schools, 2) vaccine effectiveness was

similar (range: 72%--85%), 3) the highest

attack rates occurred among the younger students, 4) each outbreak lasted

approximately

2 months, and 5) index cases occurred among vaccinated students (although their

disease was mild). Overall attack rates among vaccinated children varied

(range: 11%--17%), with attack rates in certain classrooms as high as 40%. These data

indicate that even in settings in

which vaccination coverage was nearly universal and vaccine performed as expected,

the 1-dose vaccination program could

not prevent varicella outbreaks completely.

Prenatal and Perinatal Exposure

In the prevaccine era, prenatal infection was uncommon because the majority of women of childbearing age were immune to VZV (12,36). Varicella in pregnant women is associated with a risk for VZV transmission to the fetus or newborn. Intrauterine VZV infection might result in congenital varicella syndrome, neonatal varicella, or HZ during infancy or early childhood (37--46). Infants who are exposed prenatally to VZV, even if asymptomatic, might have measurable varicella-specific IgM antibody during the newborn period, have persistent varicella-specific IgG immunity after age 1 year without a history of postnatal varicella, or demonstrate positive lymphocyte transformation in response to VZV antigen (37).

Congenital varicella syndrome was first recognized in 1947 (40). Congenital varicella syndrome can occur among infants born to mothers infected during the first half of pregnancy and might be manifested by low birthweight, cutaneous scarring, limb hypoplasia, microcephaly, cortical atrophy, chorioretinitis, cataracts, and other anomalies. In one study, incidence of congenital varicella syndrome was calculated using aggregate data from nine cohort studies carried out during 1986--2002 (47). Rates were 0.6% (4 of 725) for 2--12 weeks' gestation, 1.4% (9 of 642) for 13--28 weeks, and 0 (0 of 385) after 28 weeks.

In a prospective study of 1,373 mothers with varicella during pregnancy conducted in the United Kingdom and

West Germany during 1980--1993, the highest risk (2%) for congenital varicella syndrome was observed when maternal

infection occurred during 13--20 weeks' gestation

(43). The risk was 0.4% after maternal infection during 0--12 weeks' gestation.

No cases of congenital varicella syndrome occurred among the infants of 366 mothers with HZ during pregnancy. Nine

isolated cases involving birth defects consistent with congenital varicella syndrome have been reported after maternal varicella

beyond 20 weeks' gestation (with the latest occurring at 28 weeks)

(47,48). In a prospective study, HZ occurred

during infancy or early childhood in four (0.8%) of 477 infants who were exposed to VZV during 13--24 weeks' gestation and in six (1.7%)

of 345 infants who were exposed during 25--36 weeks' gestation

(43).

 The onset of varicella in pregnant women from 5 days

before to 2 days after delivery results in severe varicella infection in

an estimated 17%--30% of their newborn infants. These infants are exposed to VZV without sufficient maternal

antibody to lessen the severity of disease. The risk for neonatal death has been estimated to be 31% among infants whose mothers

had onset of rash <4 days before giving birth

(45). This estimate was made on the basis of a limited number of infant deaths

and might be higher than the actual risk because the study was performed before neonatal intensive care was available. In

addition, certain cases were not part of prospective studies but were reported retrospectively, making the results subject to selection

bias. When these cases were reevaluated subsequently by another investigator, certain

infants were demonstrated to have been at

higher risk for death because of low birthweight; in at least one case, another cause of

death was probable

(46). Varicella-zoster immune globulin (VZIG) has been reported to reduce incidence of

severe neonatal varicella disease

(49) and therefore is indicated in such situations. Nevertheless, the risk for death

among neonates who do not receive postexposure

prophylaxis with VZIG is likely to be substantially lower than was estimated previously.

Herpes Zoster Surveillance

After primary infection, VZV persists as a latent infection in sensory-nerve ganglia. The

virus can reactivate, causing

HZ. Mechanisms controlling VZV latency are not well understood. Risk factors for HZ

include aging, immunosuppression,

and initial infection with varicella in utero or during early childhood (i.e., age <18

months). An estimated 15%--30% of

the general population experience HZ during their lifetimes

(50,51); this proportion is likely to increase

as life expectancy increases. The most common complication of HZ, particularly in older

persons, is postherpetic neuralgia (PHN),

the persistence of sometimes debilitating pain weeks to months after resolution of HZ.

Life-threatening complications of HZ also can occur; these include herpes ophthalmicus,

which can lead to blindness. Another severe manifestation is

dissemination, which might involve generalized skin eruptions, and central nervous

system, pulmonary, hepatic, and

pancreatic complications. Dissemination, pneumonia, and

visceral involvement typically are restricted to immunocompromised

persons. VZV can be transmitted from the lesions of patients who have HZ to

susceptible contacts. Although few data are available

to assess this risk, one household contact study reported

that the risk for VZV transmission from HZ was approximately

20% of the risk for transmission from varicella

(52).

Varicella vaccination might alter the risk for HZ at the level of both the individual and

the population (i.e., herd

immunity). Just as wild-type VZV can cause wild-type HZ, attenuated vaccine virus has

the potential to become latent and later reactivate

to cause vaccine virus strain (also called Oka-strain) HZ

(53). Multiple studies have evaluated the risk for Oka-strain HZ

after vaccination of immunocompromised or healthy children

(54--58). In a study of leukemic children, the rate of HZ after a

mean 4.1 years of follow-up (range: 6 months--10 years) was 2% in vaccine recipients

and 15% in controls with a history of

varicella (54). A subset of 96 of these vaccine recipients was matched prospectively

according to chemotherapeutic protocol with

96 leukemic children who had experienced natural varicella. Analysis indicated that the

incidence of HZ was

approximately three times lower in vaccine recipients (0.80 per 100 person-years) than

in the matched leukemic children who had experienced

natural varicella (2.46 per 100 person-years) (p = 0.01). Data for healthy children are

more limited, and findings might be influenced

by multiple factors (e.g., incomplete ascertainment, limited duration of follow up or no follow up of subjects of older ages,

no comprehensive screening for wild-type varicella infection before or after vaccination, or lack of testing all cases to distinguish

Oka- from wild-type HZ). Nonetheless, these studies suggest that the risk for Oka-strain HZ after a single dose of varicella vaccine

is lower than that after wild-type varicella infection

(56--58). Over time, the risk for and manifestation of Oka-strain HZ should

be examined in older persons who are at greater risk for HZ complications. Persons who experience varicella infection

before vaccination (i.e., as a result of in utero or unapparent infection) or after vaccination (i.e., as a result of breakthrough

infection) presumably are latently infected with two strains of VZV. The risk for HZ in these persons is unknown. No long-term

studies have been conducted that compare the risk for Oka-strain HZ in persons who receive 1 dose of varicella vaccine with the risk

for those who receive 2 doses.

 Varicella vaccination also might change the risk for HZ at the population level. With the development of herd

immunity and reduction in the likelihood of exposure, the varicella vaccination program prevents wild-type VZV infection

among vaccine recipients and nonvaccine recipients, eliminating the risk for wild-type HZ in these persons. Reduction in

the likelihood of wild-type varicella infection also increases the

median age for acquiring varicella (although age-specific

incidence rates themselves are lower). This reduces the risk for varicella infection during early childhood (i.e., age <18 months),

thereby reducing a risk factor for childhood HZ.

Exposure of persons with latent wild-type VZV infection to persons with varicella is thought to boost specific

immunity, which might contribute to controlling reactivation of VZV and the development of HZ

(50). Concern has been expressed that by providing fewer opportunities for varicella exposure among persons with previous wild-type varicella

infection, reduction in the likelihood of exposure might

increase the risk for HZ, possibly within as few as 5 years after introduction of

varicella vaccination (59) and reaching a vaccination

coverage of >90%.

Herpes zoster is not a nationally notifiable disease in the United States, and HZ surveillance has been conducted

using multiple methods, study sites, or data sources. For certain studies, baseline data were available before the start of the

varicella vaccination program. One study that included baseline data was a retrospective analysis of electronic medical records from

a health maintenance organization (HMO) during 1992--2002

(60). This HMO study indicated that age-adjusted incidence

of HZ remained stable during 1992--2002 as incidence of

varicella decreased (60). Age-adjusted and -specific

annual incidence rates of HZ fluctuated slightly over time; the age-adjusted rate was highest in 1992, at 4.1 cases per 1,000

person-years, and was 3.7 cases per 1,000 person-years in 2002. For other studies initiated in the postvaccine era, baseline data are

not available (61--63). An analysis of national incidence data from the Medstat database (available at

http://www.medstat.com/Products/view/?id=71) demonstrated

an overall incidence of HZ in 2000 and 2001 of 3.2 (95% confidence interval [CI]

= 3.1--3.2) per 1,000 person-years (61), representing no increase in age-adjusted HZ in

the past 20 years in the United

States compared with earlier published data

(64). Data from two HMOs in Oregon and Washington for 1997--2003 indicated

no statistically significant increase in HZ incidence rates except among

children aged 10--17 years (relative risk [RR] = 1.12, CI

= 1.05--1.18); these increases were attributed to increased use of oral steroids

(62). Another study of data gathered from a statewide telephone survey during

1999--2003 in Massachusetts demonstrated an increase in HZ

(63). Age groups particularly affected included persons aged 25--44 years and those

aged >65 years. Finally, in the two active varicella surveillance

sites (Antelope Valley, California, and West Philadelphia, Pennsylvania), active

surveillance for HZ in children aged <20 years

has been ongoing since 2000. During 2000--2004, incidence of HZ in children aged <10

years declined significantly

(p<0.05) from 0.75 to 0.23 cases per 1,000 children

(65; CDC unpublished data, 2006). In summary, multiple studies and

surveillance data demonstrate no consistent trends in HZ incidence in the United States

since implementation of the varicella

vaccination program in 1995.

Use of Acyclovir to Treat and Prevent Varicella

 Acyclovir is a synthetic nucleoside analog that inhibits replication of human herpes

viruses, including VZV. Since the

early 1980s, intravenous acyclovir has been available to treat immunocompromised persons who have varicella.

When administered within 24 hours of onset of rash, acyclovir has been demonstrated to be effective in reducing

varicella-associated morbidity and mortality in this population

(66--68).

In 1992, the Food and Drug Administration (FDA)

approved the use of oral acyclovir for the treatment of varicella

in otherwise healthy children. This approval was made on the basis of

placebo-controlled, double-blind studies

(69,70) that demonstrated the beneficial clinical effects (i.e., a decrease in the number

of days in which new lesions appeared, the

duration of fever, and the severity of cutaneous and systemic signs and symptoms) that

occurred when acyclovir was

administered within 24 hours of rash onset. No serious adverse events occurred during

the period of drug

administration. Administration of acyclovir did not decrease transmission of varicella or

reduce the duration of absence from school. Because few

complications occurred (1%--2%), these studies could not determine whether acyclovir

had a statistically significant effect on disease

severity among healthy children. In these studies, antibody titers after infection in

children receiving acyclovir did not

differ substantially from titers of children in the control group

(69,70). Clinical trials among adolescents and adults have

indicated that acyclovir is well-tolerated and effective in

reducing the duration and severity of clinical illness if the drug is

administered within 24 hours of rash onset

(71--73).

In 1993, AAP's Committee on Infectious Diseases published a statement

regarding the use of acyclovir (74). AAP did

not consider administration of acyclovir to healthy children to have clinical benefit

sufficient to justify its routine

administration; however, AAP stated that certain circumstances might justify its use.

AAP recommended that oral acyclovir should

be considered for otherwise healthy persons at increased risk for moderate to severe

varicella (e.g., persons aged >12 years,

persons with chronic cutaneous or pulmonary disorders, persons

receiving long-term salicylate therapy, and persons receiving

short, intermittent, or aerosolized courses of corticosteroids). Certain experts also

recommend use of oral acyclovir

for secondary case-patients who live in the same households as infected children

(74).

Acyclovir is classified as a Category B drug in the FDA

use-in-pregnancy rating. Although studies involving animals

have not indicated teratogenic effects, adequate, well-controlled studies in pregnant

women have not been conducted.

However, a prospective registry of acyclovir use during pregnancy that collected data

on outcomes of 596 infants whose mothers

were exposed to systemic acyclovir during the first trimester of pregnancy indicated

that the rate and types of birth

defects

approximated those in the general population

(75). AAP has not recommended routine use of oral acyclovir for

pregnant women because the risks and benefits to the fetus and mother were unknown. However, in instances of serious,

viral-mediated complications (e.g., pneumonia), AAP has recommended that intravenous acyclovir should be considered

(74).

Two nucleoside analogs, acyclovir and famciclovir, have been approved by FDA for treating HZ. If administered within

72 hours of rash onset, acyclovir has accelerated the rate of cutaneous healing and reduced the severity of acute pain in adults

who have HZ (76). Oral famciclovir, when administered

during the same period, has similar efficacy

(77).

Acyclovir is not indicated for prophylactic use among

otherwise healthy children, adolescents, or adults without evidence

of immunity after exposure to varicella. Vaccination is the method of choice in these

situations. No studies have been

conducted regarding prophylactic use of acyclovir among immunocompromised persons; therefore, VZIG is recommended in

these situations.

Vaccines for Prevention of Varicella

Two live attenuated varicella virus vaccines are licensed in the United States for prevention of varicella:

single-antigen varicella vaccine

(VARIVAX,® Merck & Co., Inc., Whitehouse Station, New Jersey) and combination MMRV

vaccine (ProQuad,® Merck & Co., Inc., Whitehouse, New Jersey). Both vaccines are derived from the Oka strain of live,

attenuated VZV. The Oka strain was isolated in Japan

(78) in the early 1970s from vesicular fluid in a healthy child who had

natural varicella and was attenuated through sequential propagation in cultures of human embryonic lung cells,

embryonic guinea-pig cells, and human diploid cells (WI-38). The virus in the Oka/Merck vaccine has undergone further passage through

human diploid-cell cultures (MRC-5) for a total of 31 passages.

 In 1995, the single-antigen varicella vaccine was licensed in the United States for use among healthy persons aged

>12 months. This vaccine is lyophilized; when reconstituted as directed in the package insert and stored at room temperature for

a maximum of 30 minutes, it contains a minimum of 1,350 plaque forming units (PFUs) of Oka/Merck VZV in each 0.5

mL dose (79). Each dose also contains 12.5 mg of hydrolyzed gelatin, trace amounts of neomycin and fetal bovine serum, 25

mg of sucrose, and trace residual components of MRC-5 cells (including DNA and protein). The vaccine does

not contain preservatives. Since 1995, >55 million doses have been distributed in the United States. Reporting of serious

adverse events has been rare (see Vaccine-Associated Adverse Events).

 In 2005, the combination MMRV vaccine was licensed in the United States for use among healthy children aged

12 months--12 years. The attenuated measles, mumps, and rubella vaccine viruses in ProQuad® are identical and of equal titer

to those in the measles, mumps, and rubella (MMR) vaccine,

MMRII® (80). The titer of Oka/Merck VZV is higher in

MMRV than in single-antigen varicella vaccine, a minimum of 3.99

log10 PFUs compared with 1,350 PFUs (approximately

3.13 log10) in each 0.5 mL dose. The other constituents are similar to those in the

single-antigen varicella vaccine.

Immune Response to Vaccination

 In clinical trials of the single-antigen varicella vaccine conducted before licensure,

seroconversion was assessed using lots

of vaccine with different amounts of PFUs and laboratory

assays with different levels of sensitivity and specificity. Using

a specially developed, sensitive gp-enzyme-linked immunosorbent assay (ELISA) test

that is not available

commercially, seroconversion (defined by the acquisition of any detectable varicella

antibodies >0.3 gpELISA units) was

observed at approximately 4--6 weeks after vaccination with

1 dose of varicella vaccine in approximately 97% of 6,889

susceptible children aged 1--12 years (79). The seroconversion rate was 98% for

children aged 12--15 months and 95% among those

aged 5--12 years (81). Adolescents aged 13--17 years had a lower seroconversion rate

(79%) after a single dose of vaccine. A

study performed postlicensure used fluorescent antibody

to membrane antigen (FAMA) titers 16 weeks after vaccination to

assess serologic response and demonstrated that 61 (76%) of 80 healthy child vaccine

recipients seroconverted (FAMA titers

>1:4) after 1 dose of single-antigen varicella

vaccine (82).

Primary antibody response to the vaccine at 6 weeks postvaccination is correlated with protection against disease

(83,84). In clinical trials, rates of breakthrough disease were lower among children with varicella antibody titers of

>5 gpELISA units than among those with titers of <5 units

(84); children with a 6-week postvaccination antibody titer of <5 gpELISA units were

3.5 times more likely to have breakthrough varicella than those with a titer of

>5 gpELISA units. Later studies of

immunogenicity

(85) have reported the proportion of vaccinated children who achieved this antibody level

instead of seroconversion. After 1 dose of the

single-antigen varicella vaccine, 86% of children had gpELISA levels of

>5 units/mL (85). Studies performed

using FAMA indicated that a titer >1:4 at 16 weeks postvaccination is correlated with protection against disease

(82). Of healthy persons with a titer of >1:4 at 16 weeks post vaccination, <1% have had varicella after a household exposure (n = 130).

In contrast, the attack rate among those with a titer of <1:4 was 55% (n = 60).

Persistence of antibody in children after 1 dose of single-antigen varicella vaccine was demonstrated in both short- and

long-term follow-up studies. In a clinical study, the rate of antibody persistence detected by gpELISA was nearly 100% after 9

years of follow-up for 277 children (85). Another study demonstrated that although antibody titers (detected by FAMA)

might decline 12--24 months after vaccination, the median titer did not change after

1--4 years and even rose after 10 years

(86). In Japan, VZV antibodies were present in 37 (97%) of 38 children who received

varicella vaccine 7--10 years earlier (with

titers comparable to those of 29 children who had had natural varicella infection within

the previous 10 years)

(87) and in 100% of 25 children when followed for as long as 20 years (i.e., antibody

levels were higher than those observed 10 years earlier)

(88). Interpretation of long-term studies is complicated by at least two factors. First,

asymptomatic boosting of

vaccine-induced immunity by exposure to wild-type VZV is likely. Because varicella

vaccine is not routinely recommended in Japan,

coverage of children was estimated to be low (approximately 20%) during 1991--1993.

Second, sample sizes were limited as a result

of the decrease in the number of children followed-up with increasing time since

vaccination.

 The second dose of varicella vaccine in children produced an improved immunologic

response that is correlated

with improved protection. A comparative study of healthy children who received 1 or 2

doses of single-antigen varicella

vaccine administered 3 months apart indicated that a second dose provided higher

antibody levels as measured by the proportion

of subjects with titers of >5 gpELISA units and by

geometric mean titers (GMTs) and higher efficacy

(85; Tables 2--4). The proportion of subjects with antibody titers of

>5 gpELISA units in the 2-dose recipients was higher 6 weeks after the

second dose than after the first dose (99.6% and 85.7%, respectively) and remained

high at the end of the 9-year follow-up

period, although the difference between the two regimens narrowed (97% and 95%, respectively). GMT 6 weeks after the

second dose was substantially higher than that after a single dose (142 and 12, respectively). The difference in GMTs between the

two regimens did not persist over 9 years of follow-up among subjects who seroconverted after vaccination, although GMTs

in both regimens remained high by the end of the study period. However, receipt of a second dose decreased the rate

of breakthrough varicella significantly (3.3-fold) and increased vaccine efficacy ($p<0.001$). Another study that assessed

the immunogenicity of a second dose received 4--6 years after the first dose demonstrated a substantial increase in antibody

levels in the first 7--10 days in the majority of those tested, indicating an anamnestic response. On the day of the second dose,

GMT was 25.7, compared with 143.6 GMT 7--10 days after the second dose; 60% of recipients had at least a fourfold increase

in antibody titers, and an additional 17% had at least a twofold increase

(89). Three months after the second dose,

GMT remained higher than on the day of second dose (119.0 and 25.7, respectively). Among children, VZV antibody levels

and GMTs after 2 doses administered 4--6 years apart were comparable to those

obtained when the 2 doses were administered 3 months apart.

The combination MMRV vaccine was licensed on the basis of noninferiority of immunogenicity of the

antigenic components compared with MMR and varicella vaccines administered concomitantly at separate inspection sites rather

than on clinical efficacy (80). Clinical studies of healthy children aged 12--23 months indicated that those who received 1 dose

of MMRV vaccine had levels of antibody to measles, mumps, rubella, and varicella similar to levels of children who received

1 dose of MMR and 1 dose of varicella vaccines concomitantly at separate injection sites. For the varicella component

in MMRV, 91.2% (CI = 87.0%--94.4%) of children achieved antibody titers of

>5 gpELISA units/mL 6 weeks after

vaccination (90). A subgroup of children received a second dose of MMRV vaccine approximately 3 months after the first dose.

The serologic response (>5 gpELISA units/mL) after 2 doses was 99.2% (CI = 97.0%--99.9%) (Table 2). Also, GMT for

varicella after the second dose of MMRV vaccine increased approximately

forty-onefold (90). Administration of combination

MMRV vaccine to healthy children aged 4--6 years who had been vaccinated previously with MMR and single-antigen

varicella vaccines resulted in similar antibody levels and a

twenty-fivefold increase in GMT levels (91).

Among persons aged >13 years, multiple studies have

described seroconversion rates after receipt of the

single-antigen varicella vaccine (range: 72%--94% after 1 dose and 94%--99% after a second dose administered 4--8 weeks

later) (79,92,93). In clinical studies, detectable antibody levels have persisted for at least 5 years in 97% of adolescents and

adults who were administered 2 doses of vaccine 4--8 weeks apart

(79). However, other studies demonstrated that 25%--31%

of

adult vaccine recipients who seroconverted lost detectable antibodies (by FAMA) at multiple intervals (range: 1--11

years) after vaccination (93,94). For persons who had breakthrough disease after exposure to varicella, the severity of illness or

the attack rates did not increase over time

(95).

 Innate (i.e., nonspecific) and adaptive (i.e., humoral and cellular) immunity are important in the control of primary

varicella infection. The capacity to elicit cell-mediated immunity is important for viral clearance, providing

long-term protection against disease and preventing symptomatic VZV reactivation. Studies among children and adults have

indicated that breakthrough varicella typically is mild, even among vaccine recipients without seroconversion or vaccine recipients

who lost detectable antibody, suggesting that VZV-specific

cell-mediated immunity affords protection to vaccine recipients in

the absence of a detectable antibody response

(94,95). Studies of the cellular immune response to vaccination among

children demonstrated that immunization with 1

dose of varicella vaccine induced VZV-specific T-cell proliferation that

was maintained in 26 (90%) of 29 children 1 year postvaccination and in 52 (87%) of 60 children 5 years postvaccination

(96). In this study, the mean stimulation index (SI), a marker of cell-mediated immunity, was 12.1 after

1 year and 22.1 after 5 years. Data obtained at 1 year postvaccination from a subset of children in a prelicensure study comparing the immune

response among children who received 1 and 2 doses administered 3 months apart demonstrated that the

varicella-specific lymphocyte proliferation responses were significantly higher for recipients of 2 doses than for recipients of 1 dose (mean SI: 34.7 and

23.1, respectively; p = 0.03) (97). In the study of the 2 doses administered 4--6 years apart, results also indicated that

the lymphocyte proliferation response was significantly higher at 6 weeks and 3 months after the second dose than at the

same time points after the first dose (p<0.01)

(89; Table 2).

Among adults, vaccine-induced VZV-specific T-cell proliferation was maintained in 16 (94%) of 17 subjects 1 and 5

years postvaccination (96,98). The mean SI was 9.9 after 1 year and 22.4 after 5 years.

Correlates of Protection

For children, the varicella antibody response measured by gpELISA 6 weeks postvaccination correlates with

neutralizing antibody level, VZV-specific T-cell proliferative responses, vaccine efficacy, and long-term protection against varicella

after exposure to VZV (83,84,99,100). A titer of

>5 gpELISA units/mL is associated with protection against disease although

it should not be considered an absolute guarantee of protection. Breakthrough cases have occurred among children with

>5 gpELISA units/mL. A FAMA titer

>1:4 at 16 weeks post-vaccination also correlates with protection against disease

(82). However, neither of these antibody tests is available commercially. The relationship between the antibody level measured

at other intervals postvaccination, especially immediately prior to
exposure and breakthrough disease has not been studied.
No correlates of protection have been evaluated for adults.

Vaccine Efficacy and Vaccine Effectiveness

One-Dose Regimen

Prelicensure Efficacy

In prelicensure studies carried out among children aged
12 months--14 years, the protective efficacy of
single-antigen varicella vaccine varied, depending on the amount of live
virus administered per dose, the exposure setting (community
or household), and the quality and length of the clinical follow-up. The majority of the
prelicensure studies reported efficacy of
1 dose of varicella vaccine within the range of 70%--90% against any clinical disease
and 95% against severe disease for
7--10 years after vaccination (81,101,102). A randomized placebo-controlled efficacy
trial was conducted among children aged
12 months--14 years, but the formulation differed from that of the current vaccine
(17,000 PFUs per dose
(103,104), with follow-up of children through 7 years postvaccination
(105). Reported efficacy was 100% at 1 year and 98% at 2 years
after vaccination, and 100% and 92%, respectively, after exposures to VZV that
occurred in the household. Although a

randomized control study was not conducted for adults, the efficacy of single-antigen varicella vaccine was

determined by evaluation of protection when adult vaccine recipients were exposed to varicella in the household. On the basis of the reported

historical

attack rate of 87% for natural varicella after household exposure among unvaccinated children, estimated efficacy

among adults was approximately 80% (79). The attack rate of unvaccinated adults exposed in households was not studied.

Postlicensure Efficacy and Effectiveness
Prevention of All Varicella Disease
Postlicensure studies have assessed the

effectiveness¶ of the single-antigen varicella vaccine under field conditions in

child care, school, household, and community settings using multiple methods. Effectiveness frequently has been estimated

against all varicella and also against moderate and severe varicella (defined in different ways). Outbreak investigations

have assessed effectiveness against clinically defined varicella. The majority of these investigations have demonstrated

vaccine effectiveness for prevention of varicella in the same range

described in prelicensure trials (70%--90%)

(3--6,106--113), with some lower (44%, 56%)

(114,115) and some higher (100% in one of two schools investigated) estimates

(107). A retrospective cohort study in 11 childcare centers demonstrated vaccine effectiveness of 83% for prevention of

clinically diagnosed varicella (116). In a case-control study that measured vaccine effectiveness against laboratory-confirmed varicella

in a pediatric office setting during 1997--2003, vaccine effectiveness was 85% (CI = 78%--90%) during the first four years

and 87% (CI = 81%--91%) for the entire study period

(117,118). Finally, in a study of household secondary attack

rates, considered the most robust test of vaccine performance because of the intensity of exposure, varicella vaccine was 79% (CI

= 70%--85%) effective in preventing clinically defined varicella in exposed household

contacts aged 12 months--14

years without a history of varicella disease or vaccination

(119). Postlicensure data on vaccine effectiveness against all disease

have been summarized (Table 5).

In a randomized clinical trial conducted postlicensure that compared the efficacy of 1 dose of varicella vaccine with that of

2 doses, the estimated vaccine efficacy for 1 dose for a

10-year observation period was 94.4% (CI = 92.9%--95.7%)

(85; Table 3). In the same study, the efficacy of 1 dose of vaccine in preventing varicella after household exposure for 10 years was

90.2% (CI = 83.7%--96.7%) (Table 4). This study did not use placebo controls and used historic data for attack rates

in unvaccinated children to calculate vaccine

efficacy.

Prevention of Moderate and Severe Varicella

Postlicensure studies assessing vaccine performance in

preventing moderate and severe varicella have

consistently demonstrated high effectiveness. Definitions for disease

severity have varied among studies. Certain studies have used

a defined scale of illness that included the number of skin

lesions, fever, complications, and investigator assessment of

illness severity, and others have used only the number of skin

lesions, reported complications, or hospitalizations.

Moderate varicella typically has been defined as either 50--500 or 250--500 lesions, and

severe varicella has been defined as >500 lesions or

any hospitalization or complication. In the randomized postlicensure clinical trial, severe

varicella was defined as >300 lesions

and fever of >102°F (38.9°C), oral equivalent.

Regardless of different definitions, multiple studies have

demonstrated that single-antigen varicella vaccine was>>95% effective in preventing

combined moderate and severe disease

(3--6,85,106,107,109--113,115--119); one study demonstrated effectiveness of 86%

(114). Effectiveness was 100% against severe disease

when measured separately

(6,85,109,111,117,119). Postlicensure data on vaccine effectiveness against moderate

and severe

varicella have been summarized (Table 5).

Two-Dose Regimen

 In a randomized clinical trial of single-antigen varicella vaccine that compared the

efficacy of 1 dose with that of 2

doses administered 3 months apart, the estimated vaccine efficacy of 2 doses for a

10-year observation period was 98.3% (CI

= 97.3%--99.0%), which was significantly higher than efficacy after 1 dose (p<0.001)

(85; Table 5). The 2-dose regimen also was 100% efficacious against severe varicella. In the same study, the efficacy of 2 doses of single-antigen varicella vaccine in preventing disease after household exposure over 10 years was 96.4% (CI = 92.4%--100%), not significantly different from 1 dose (90.2%) (p = 0.112) (Table 4). However, the number of cases involving household exposure was limited.

Formal studies to evaluate the clinical efficacy of the combination MMRV vaccine have not been performed. Efficacy of the individual components was established previously in clinical studies with the single-antigen vaccines.

Breakthrough Disease

Breakthrough disease is defined as a case of infection with wild-type VZV occurring >42 days after vaccination. In clinical trials, varicella disease was substantially less severe among vaccinated persons than among unvaccinated persons, who usually have fever and several hundred vesicular lesions (120). In cases of breakthrough disease, the median number of skin lesions is commonly <50 (99,121--123). In addition, compared with unvaccinated persons, vaccine recipients have had fewer vesicular lesions (lesions more commonly are atypical, with papules that do not progress to vesicles), shorter duration of illness, and lower incidence of fever.

Multiple postlicensure investigations also have demonstrated that the majority of breakthrough varicella cases are significantly milder than cases among unvaccinated children (p<0.05)

(3,5,107--114,116--118,124). However,

approximately 25%--30% of breakthrough cases are not mild, with clinical features more similar to those in unvaccinated children

(124). Since 1999, when varicella deaths became nationally notifiable, two deaths from breakthrough varicella disease have

been reported to CDC; one of a girl aged 9 years with a history of asthma who was receiving steroids when she had

the breakthrough infection, and the other of a girl aged 7 years with a history of malignant ependymoma who also was

under steroid therapy at the time of her death (CDC, unpublished data, 2006).

One-Dose Regimen

In clinical trials, 1,114 children aged 1--12 years received

1 dose of single-antigen varicella vaccine containing

2,900--9,000 PFUs of attenuated virus per dose and were actively followed for up to 10 years postvaccination

(79). Among a subset of 95 vaccine recipients with household exposure to varicella, eight (8%) reported a mild form of varicella (10--34 lesions).

In a randomized clinical trial that compared the efficacy of 1 dose of vaccine to that of 2 doses during a 10-year

observation period, the cumulative rate of breakthrough varicella among children who received 1 dose was 7.3%

(85). Breakthrough cases occurred annually in 0.2%--2.3% of recipients of 1 dose of vaccine. Cases occurred throughout the observation period,

but the majority were reported 2--5 years after vaccination (Figure 4). Of 57 children with breakthrough cases, 13 (23%) had

>50 lesions.

In cross-sectional studies, the attack rate for breakthrough disease has ranged

between 11% and 17% (and as high as 40%

in certain classrooms) in outbreak investigations

(3) and 15% in household settings

(119).

Two-Dose Regimen

Data Among Children

In a randomized clinical trial that compared the efficacy of 1 dose of vaccine with that

of 2 doses, the cumulative rate

of breakthrough varicella during a 10-year observation period was 3.3-fold lower among

children who received 2 doses than

that among children who received 1 dose (2.2% and 7.3,

respectively; p<0.001) (85). Breakthrough cases occurred

occasionally in 0.8% of 2-dose vaccine recipients. The

majority of cases of breakthrough disease occurred 2--5 years after vaccination; no

cases were reported 7--10 years after vaccination (Figure 4). Of 16 children with

breakthrough cases, three (19%) had >50

lesions. The proportion of children with >50 lesions did not differ between the 1-dose

and 2-dose

regimens (p = 0.5).

Breakthrough Infections Among Adolescents and Adults

In postlicensure studies of adolescents and adults who

received 2 doses, 40 (9%) cases of breakthrough

varicella occurred among 461 vaccine recipients who were followed for 8 weeks--11.8 years (mean: 3.3 years) after vaccination

(95), and 12 (10%) cases occurred among 120 vaccine recipients who were followed for 1 month--20.6 years (mean: 4.6

years) (94). One prelicensure study of persons who had

received 2 doses of vaccine reported that 12 (8%) breakthrough cases

had occurred among 152 vaccine recipients who were followed for 5--66 months (mean: 30 months) postvaccination

(93).

Contagiousness

 Prelicensure clinical trials reported the rate of disease transmission from vaccinated persons with varicella cases to

their vaccinated siblings. In 10 trials that were conducted during 1981--1989, breakthrough infections occurred in 114 (5.3%)

of 2,163 vaccinated children during the 1--8 year follow-up period of active surveillance, and secondary transmission occurred

to 11 (12.2%) of their 90 vaccinated siblings

(121). Illness was mild in both index and secondary case-patients.

Household

transmission from a vaccinated child with breakthrough disease to a susceptible adult (one of whom died) have been

reported (CDC, unpublished data, 2006). One study examined secondary attack rates from vaccinated and unvaccinated persons

with varicella to both vaccinated and unvaccinated households contacts aged 12

months--14 years

(119). This study demonstrated that vaccinated persons with varicella with <50 lesions

were only one third as contagious as unvaccinated persons

with varicella. However, vaccinated persons with varicella who had

>50 lesions were as contagious as unvaccinated persons

with varicella (119). Vaccinated persons with varicella tend to have milder disease, and,

although they are less contagious

than unvaccinated persons with varicella, they might not receive a diagnosis and be

isolated. As a result, they might have

more opportunities to infect others in community settings, thereby further contributing

to VZV transmission. Vaccinated

persons with varicella also have been index case-patients in varicella outbreaks

(3,4,115).

Risk Factors for Vaccine Failure

 Potential risk factors for vaccine failure have been identified in studies of vaccine

effectiveness during outbreak

investigations and other specially designed studies

(5,108--110,113--115,118,125). In outbreak investigations, the low number of

cases limits the ability of researchers to conduct multivariate analyses and examine the

independent effect of each risk factor

for vaccine failure. An increased risk for breakthrough disease has been noted with

decreasing age at vaccination, with a

threefold increase in breakthrough disease risk for children vaccinated at age <14

months

(110), an increase of twofold in one study

and nearly fourfold in another for children vaccinated at age <16 months

(108,115), and a ninefold increase for

children vaccinated at age <19 months

(113). Other outbreak investigations have demonstrated that time since vaccination

(variably defined as >3, >5, or

>5 years) was associated with an increased risk for breakthrough disease (relative risk

[RR] = 2.6, 6.7,

and 2.6, respectively) (5,114,115). However, age at vaccination and time since

vaccination are highly correlated, and

their independent association with the risk for breakthrough disease has been assessed

in only one outbreak investigation

(113). A retrospective cohort study that adjusted for other potential risk factors

demonstrated an increased risk for breakthrough

disease for children vaccinated at age <15 months (adjusted relative risk [aRR] = 1.4;

CI = 1.1%--1.9%)

(125). A case-control study demonstrated that the effectiveness of vaccine in the first

year after vaccination was significantly lower (73%) among

children vaccinated at age <15 months than it was among children vaccinated at age

>15 months (99%) (p = 0.01) (118). However,

the difference in the overall effectiveness between children vaccinated at these ages

was not statistically significant for

subsequent years (8 years of follow-up) (81% and 88%, respectively; p = 0.17). Active

surveillance data collected during 1995--2004

from a sentinel population of 350,000 persons were analyzed to

determine whether the severity and annual incidence

of breakthrough varicella cases increased with time since vaccination

(126). Children vaccinated >5 years previously were

2.6 times more likely to have moderate and severe breakthrough

varicella than those vaccinated <5 years previously (p =

0.016). The annual rates of breakthrough varicella among children aged 12 months--12

years increased significantly with time

since vaccination after adjusting for the effects of age at infection, age at vaccination,

and year of infection (p<0.01).

 Multiple other studies that examined possible reasons for lower vaccine effectiveness

did not find age at vaccination

(3--5,111,114) or time since vaccination

(3,110,111) to be associated with vaccine failure. An ongoing study is examining

these factors and risk for vaccine failure

(127). After 8 years of active follow-up of 7,449 children vaccinated at age 12--23

months, results do not indicate an increased risk for breakthrough disease among

children vaccinated at age 12--14 months

compared with those vaccinated at age 15--23 months. Moreover, a test for trend

revealed no change in the rate of

reported breakthrough disease for each additional month of age at vaccination

(127).

 Two outbreak investigations noted an increased risk for breakthrough disease in

children with asthma and

eczema (109,113). In these investigations, the use of steroids to treat asthma or

eczema was not studied. Steroids have been

associated previously with severe varicella in unvaccinated persons

(128--130). Only one retrospective cohort study

controlled simultaneously for the effect of multiple risk factors, including the use of

steroids, and this study demonstrated no

association of risk for breakthrough disease with asthma or eczema

(125). However, this study documented an increased risk

for breakthrough disease if the child had received a prescription of oral steroids (considered a proxy for taking oral steroids

when exposed to varicella) within 3 months of breakthrough disease (adjusted RR [aRR] = 2.4; CI = 1.3%--4.4%) and

when varicella vaccination was administered within 28 days of MMR vaccine (aRR = 3.1; CI = 1.5%--6.4%).

Evidence of Immunity

 ACIP has approved criteria for evidence of immunity to varicella (Box). Only doses of varicella vaccines for which

written documentation of the date of administration is presented should be considered valid. Neither a self-reported dose nor a

history of vaccination provided by a parent is, by itself, considered adequate evidence of immunity. Persons who lack

documentation of adequate vaccination or other evidence of

immunity should be vaccinated.

 Historically, self-reporting of varicella disease by adults or by parents for their children has been considered valid evidence

of immunity. The predictive value of a self-reported positive disease history was extremely high in adults in the prevaccine

era although data on positive predictive value are lacking in parental reports regarding their children

(131--133). As disease incidence decreases and the proportion of vaccinated persons with varicella having mild cases increases, varicella will be

less readily recognized clinically. A recent study demonstrated that only 75% of

unvaccinated children aged 12

months--4 years who reported a positive history of

varicella were in fact immune (confirmed by serological testing), compared with 89%

of children aged 5--9 years and 10--14 years

(134). To limit the number of false-positive

reports and ensure immunity, ACIP recommends that evidence of immunity should be

either a diagnosis of varicella by a health-care provider or a

health-care provider verification of a history of disease rather than parental or

self-reporting. The above-cited study demonstrated

that 99% of persons aged 15--19 years and 100% of those aged 20--29 years who

reported a history of varicella were immune

(134). Because serologic evidence of VZV infection

has been documented in 96%--97% of U.S.-born adults aged 20--29

years and in 97%--99% of adults aged >30 years tested during 1998--1999

(12), U.S. birth before 1980 is considered evidence

of immunity except for health-care personnel (HCP), pregnant women, and

immunocomprised persons. For these three

groups, certainty regarding immunity is desirable because of the possibility of

nosocomial transmission to

high-risk patients; transmission of the virus to the fetus, which might result in

congenital

varicella syndrome; and the possibility of severe disease. Postvaccination serologic

testing to verify an immune response to varicella vaccine is not

routinely recommended because available commercial assays lack sensitivity in

detecting vaccine-induced immunity and might give

false negative results.

Simultaneous Administration of Vaccines

Single-antigen varicella vaccine is well-tolerated and effective in healthy children aged >12 months when administered simultaneously with MMR vaccine either at separate sites and with separate syringes or separately >4 weeks apart. The number and types of adverse events occurring in children who have received VARIVAX and MMRII concurrently have not differed from those in children who have been administered the vaccines at different visits (79,135). Data concerning the effect of simultaneous administration of VARIVAX with vaccines containing various combinations of MMR, diphtheria and tetanus toxoids and pertussis (DTP), and Haemophilus influenzae type b (Hib) have not been published (79). A randomized study of 694 subjects determined that the immune response to MMR, varicella, and Hib vaccines administered concurrently with a fourth dose of pneumococcal conjugate vaccine (PCV7) was not inferior to that of those vaccines when administered without PCV7; the percentage of subjects who seroconverted was >90% for all antigens for both groups (136).

Concomitant administration of the combination MMRV vaccine with other vaccines also has been assessed. In a clinical trial involving 1,913 healthy children aged 12--15 months, three groups were compared (137). One group received concomitantly administered (at separate sites) MMRV vaccine, Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Absorbed (DTaP), Hib conjugate (meningococcal

protein conjugate) vaccine, and hepatitis B (recombinant) (Hep

B) vaccine. The second group received MMRV vaccine at the initial visit, followed by DTaP, Hib, and Hep B

vaccines administered concomitantly 6 weeks later. The third group received MMR and varicella vaccines concomitantly followed

6 weeks later by DTaP, Hib, and Hep B vaccines. Seroconversion rates and antibody titers were comparable for the

measles, mumps, rubella, and varicella components for the first two groups. No immunologic data were reported for

the third group. The Hib and Hep B seroconversion rates for the two groups that received those vaccines also were comparable.

Data are absent or limited for the concomitant use of MMRV vaccine with inactivated polio, pneumococal

conjugate, influenza, and hepatitis A vaccines. Simultaneous administration of the majority of widely used live and inactivated

vaccines has produced seroconversion rates and rates of adverse reactions similar to those observed when the vaccines

are administered separately. Therefore, single-antigen and combination MMRV vaccines may be administered simultaneously

with other vaccines recommended for children aged 12--15 months and those aged 4--6 years. Simultaneous administration

is

particularly important when health-care providers anticipate

that, because of certain factors (e.g., previously

missed vaccination opportunities), a child might not return for subsequent vaccination.

Economic Analysis of Vaccination

A cost-effectiveness analysis was performed before initiation of the varicella vaccination program in the United States
(138). The results of the study indicated a savings of $5.40 for each dollar spent on routine vaccination of preschool-aged
children when direct and indirect costs were considered. When only direct medical costs were considered, the benefit-cost ratio
was 0.9:1.0. Benefit-cost ratios were only slightly lower when lower estimates of the short- and long-term effectiveness of
the vaccine were used.

A recent analysis was performed that used current estimates of morbidity and mortality
(20,28,33) and current direct and indirect costs (ACIP, unpublished presentation, 2006). The model considered that the second dose will reduce varicella
disease residual after the first dose by 79%. From a societal perspective, both 1-dose and 2-dose vaccination programs are cost
saving compared with no program. The vaccine program cost was estimated at $320 million for 1 dose and $538 million for 2
doses. The savings from varicella disease prevented were estimated at approximately $1.3 billion for the 1-dose program
and approximately $1.4 billion for the 2-dose program. Compared with the 1-dose program, the incremental cost for the
second dose was estimated to be $96,000 per quality-adjusted life year (QALY) saved. If benefits from preventing group
A streptococcus infections and HZ among vaccinated persons are added, incremental costs per QALY saved are $91,000

and $17,000, respectively. Because of the uncertainty of the modeled predictions of an increase in HZ among persons with

a history of varicella and the fact that no consistent trends

demonstrate an increase in HZ attributable to the

varicella vaccination program in the United States, HZ among persons with a history of varicella was not included in the model.

Storage, Handling, and Transportation of Varicella Vaccines

Single-antigen varicella and combination MMRV vaccines have similar but not identical distribution, handling, and

storage requirements (79,80). For potency to be maintained, the lyophilized varicella vaccines must be stored frozen at an

average temperature of 5°F (-15°C) or colder. Household freezers manufactured since the mid-1980s are designed to

maintain temperatures from -4°F (-20°C) to 5°F (-15°C). When tested, VARIVAX has remained stable in frost-free freezers.

Freezers that reliably maintain an average temperature of <5°F (<-15°C) and that have a separate sealed freezer door are acceptable

for storing VARIVAX and ProQuad. Health-care providers may use stand-alone freezers or the freezer compartment

of refrigerator-freezer combinations, provided that the freezer compartment has its own separate, sealed, and insulated

exterior door. Units with an internal freezer door are not acceptable. Temperatures should be documented at the beginning and end

of each day. Providers should document the required temperature in a newly purchased unit for a minimum of 1 week

before using it to store vaccine and routinely thereafter. When varicella vaccines are stored in the freezer compartment of a

combined refrigerator-freezer, temperatures in both compartments should be monitored carefully. Setting the thermostat low enough

for storage of varicella-containing vaccines might inadvertently expose refrigerated vaccines to freezing temperatures.

Refrigerators with ice compartments that either are not tightly enclosed or are enclosed with unsealed, uninsulated doors (e.g.,

small, dormitory-style refrigerators) are not acceptable

for the storage of varicella vaccines.

Diluent should be stored separately either at room temperature or in the refrigerator. Vaccines should be

reconstituted according to the directions in the package insert and only with the diluent supplied with the vaccine, which does not

contain preservative or other antiviral substances that could inactivate the vaccine virus. Once reconstituted, vaccine should be

used immediately to minimize loss of potency. Vaccine should be discarded if not used within 30 minutes after reconstitution.

Handling and Transportation of Varicella Vaccines Within Off-Site Clinics

When an immunization session is being held at a site distant from the freezer in which the vaccine is stored, the number

of vaccine vials needed for the immunization session should be packed in either a vaccine shipping container (as received

from the manufacturer) or in an insulated cooler, with an

adequate quantity of dry ice (i.e., a minimum of 6 lbs per box) to

preserve potency. When placed in a suitable container, dry ice will maintain a temperature of

<5°F (<-15°C). Dry ice should remain

in

the container upon arrival at the clinic site. If no dry ice remains when the container is opened at the receiving site,

the manufacturer (Merck and Company, Inc.) should be contacted for guidance (telephone: 1-800-982-7482). If dry ice

is available at the receiving site, it may be used to store vaccine. Thermometers or temperature indicators cannot be used in

a container with dry ice. Diluent should not be transported on dry ice.

If dry ice is not available, only single-antigen varicella vaccine may be transported, with frozen packs to keep

the temperatures between 36°F--46°F (2°C--8°C). Transport temperatures should be monitored, and a temperature indicator

or thermometer should be placed in the container and checked on arrival. The container should be kept closed as much

as possible during the immunization session; temperatures should be checked and recorded hourly. If the temperature

remains between 36°F--46°F (2°C--8°C), the single-antigen varicella vaccine may be used for up to 72 hours after its removal from

the freezer. The date and time should be marked on the vaccine vial. Single-antigen varicella vaccine stored at

refrigerated temperatures for any period of time may not be refrozen for future use.

Transportation and storage of combination MMRV vaccine at temperatures between 36°F--46°F (2°C--8°C) is not

permissible for any length of time. In contrast to single-antigen varicella vaccine, combination MMRV vaccine must be maintained

at temperatures of <5°F

(<-15°C) until the time of reconstitution and administration. This difference in vaccine storage temperatures must be considered when planning off-site clinics. For this reason, transportation of MMRV vaccine to

off-site clinics is not advised. If any concerns arise regarding the storage of single-antigen varicella or combination MMRV vaccines,

the manufacturer should be contacted for guidance.

Minimizing Wastage of Vaccine

Vaccine wastage can be minimized by accurately determining the number of doses needed for a given patient population.

To ensure maximal vaccine potency, smaller shipments of vaccine should be ordered more frequently (preferably at least

once every 3 months). Single-antigen varicella vaccine should not be distributed to providers who do not have the capacity to

store it properly in a freezer until it is used. Transportation of varicella vaccine should be kept to a minimum to prevent loss

of potency. Off-site clinic sites should receive only such amounts of vaccine as they can use within a short time (72 hours

if storing single-antigen varicella vaccine at refrigerated temperatures).

Adverse Events After Vaccination

Because adverse events after vaccination might continue to be caused by wild-type

VZV even as varicella disease

declines, health-care providers should obtain event-appropriate clinical specimens (e.g.,

cerebrospinal fluid for encephalitis,

bronchial lavage or lung biopsy for pneumonia) for laboratory evaluation, including

strain identification. Information regarding

strain identification is available from Merck's VZV Identification Program (telephone:

1-800-652-6372) or from CDC's

National Varicella Reference Laboratory (telephone: 404--639--0066; e-mail:

vzvlab@cdc.gov) or at

http://www.cdc.gov/nip/diseases/varicella/surv/default.htm. Commercial

laboratories do not have the capability for strain identification.

 The National Vaccine Injury Act of 1986 requires physicians and other health-care

providers who administer vaccines

to maintain permanent immunization records and to report occurrences of adverse

events for selected vaccines,

including varicella vaccines. Serious adverse events (i.e., all events

requiring medical attention) suspected to have been caused by

varicella vaccines should be reported to the Vaccine

Adverse Event Reporting System (VAERS). Forms and instructions are available

at https://secure.vaers.org/vaersDataEntryintro.htm, in the FDA Drug Bulletin at

http://www.fda.gov/medwatch, or from the 24-hour VAERS information recording at

1-800 822-7967.

Prelicensure

Single-Antigen Varicella Vaccine

Single-antigen varicella vaccine was well-tolerated when administered to >11,000 healthy children, adolescents, and adults during prelicensure clinical trials. In a double-blind, placebo-controlled study among 914 susceptible healthy children aged 12 months--14 years, the only statistically significant (p<0.05) adverse events reported that were more common among vaccine recipients than among placebo recipients were pain and redness at the injection site (103). This study also described the presence of unspecific rash among 2% of placebo and 4% of vaccine recipients occurring within 43 days of vaccination. Of

the 28 reported rashes, 10 (36%) were examined by a physician; among those that were examined, four of the seven noninjection site rashes in vaccine recipients were judged to be varicella-like, compared with none of the rashes in the placebo recipients.

In a study comparing the safety of 1 dose of single-antigen varicella vaccine with that of 2 doses administered 3 months apart, no serious adverse events related to vaccination were reported among approximately 2,000 healthy subjects aged 12 months--12 years who were followed for 42 days after each injection. The 2-dose vaccine regimen was generally well-tolerated, and its safety profile was comparable to that of the 1-dose regimen. Incidence of injection site complaints observed <3 days after vaccination was slightly higher after dose 2 (25.4%) than after

dose 1 (21.7%). Incidence of systemic clinical

complaints was lower after dose 2; fever incidence from days 7--21 was 7% after dose 1

and 4% after dose 2 (p = 0.009), and

varicelliform rash incidence after dose 1 was 3%, compared with 1% after dose 2 (p = 0.008), with peak occurrence 8--21 days

after vaccination (139).

 In uncontrolled trials of persons aged

>13 years , approximately 1,600 vaccine recipients who received 1 dose of

single-antigen varicella vaccine and 955 who received 2 doses of vaccine were

monitored for 42 days for adverse events

(79). After the first and second doses, 24.4% and 32.5% of vaccine recipients,

respectively, had complaints regarding the injection

site. Varicella-like rash at the injection site occurred in 3% of vaccine recipients after

the first injection and in 1% after the

second. A nonlocalized rash occurred in 5.5% of vaccine recipients after the first

injection and in 0.9% of vaccine recipients after

the second, at a peak of 7--21 and 0--23 days postvaccination, respectively.

Combination MMRV Vaccine

 In clinical trials, combination MMRV vaccine was administered to 4,497 children aged

12--23 months

without concomitant administration with other vaccines

(80). The safety profile of the first dose was compared with the safety

of MMRII vaccine and VARIVAX administered concomitantly at separate injection sites.

The follow-up period was 42

days postvaccination. Systemic vaccine-related adverse events were reported at a

statistically significantly greater rate in persons

who received MMRV vaccine than in persons who received the two vaccines administered concomitantly at separate

injection sites: fever (>102°F

[>38.9°C] oral equivalent), (21.5% and 14.9%, respectively), and measles-like rash (3.0% and

2.1%, respectively). Both fever and measles-like rash usually occurred within 5--12 days after the vaccination, were of short

duration, and resolved with no long-term sequelae. Pain, tenderness, and soreness at the injection site were reported at a

statistically significantly lower rate in persons who received the combination MMRV vaccine (22.0%) than in those who received

MMRII and VARIVAX vaccines (26.7%). Rash at the injection site was more frequent among recipients of

1-dose MMRV vaccine (2.3%) than among recipients of the two vaccines administered separately as first doses (1.5%). A study that also

compared use of MMRV with MMRII and VARIVAX administered as a first dose demonstrated similar results

(90). During days 5--12, children in the group that received MMRV had higher rates of elevated temperatures than those in the group that

received MMRII and VARIVAX (27.7% and 18.7%, respectively; $p = 0.034$).

To demonstrate that MMRV vaccine could be administered as a second dose, a study was conducted involving 799

children aged 4--6 years who had received primary doses of MMRII and VARIVAX vaccines, either concomitantly or not, at age

>12 months and >1 month before study enrollment

(91). These children were vaccinated randomly (with MMRV and

placebo, MMR and placebo, or MMRII and VARIVAX) and then monitored for safety. No

serious vaccine-related adverse

experiences were reported. Overall, the proportions of subjects with one or more adverse event were comparable among groups

receiving MMRV, MMRII, and MMRII and VARIVAX. The group receiving MMRV vaccine had a statistically significantly

greater proportion of subjects with erythema (p = 0.01) and swelling (p = 0.008) at the injection site 1--5 days after

vaccination. Another study examined the safety of 2 doses of MMRV administered 3 months apart to 480 children aged 12--23

months (90). The rate of adverse events typically was lower after the second dose of MMRV than after the first dose. The incidence

of varicella-like rashes was lower after a second dose of MMRV than after concomitant administration of MMRII and

VARIVAX vaccines (0.0% and 1.9%, respectively; p = 0.01).

Postlicensure

 During March 1, 1995--December 31, 2005, a total of 47.7 million doses of varicella vaccine were distributed in the

United States, and 25,306 adverse events that occurred after varicella vaccine administration were reported to VAERS, 1,276 (5%)

of which were classified as serious. The overall adverse event reporting rate was 52.7 cases per 100,000 doses distributed. The

rate

of reporting of serious adverse events was 2.6 per 100,000 doses distributed. Half of all adverse events reported

occurred among children aged 12--23 months (VAERS,

unpublished data, 2006).

 Not all adverse events that occur after vaccination are

reported, and many reports describe events that might have

been caused by confounding or unrelated factors (e.g., medications and other

diseases). Because varicella disease continues to

occur, wild-type virus might account for certain reported events. For serious adverse

events for which background incidence data

are known, VAERS reporting rates are lower than expected after natural varicella or

than background rates of disease in

the community. Inherent limitations of passive safety surveillance impede comparing

adverse event rates after vaccination

reported to VAERS with those from complications after natural disease. Nevertheless,

the magnitude of these differences suggests

that serious adverse events occur at a substantially

lower rate after vaccination than after natural disease. This assumption

is corroborated by the substantial decline in the number of severe complications,

hospitalizations, and deaths related to

varicella that have been reported since implementation of the varicella vaccination

program

(22,23,28).

 Similar to the prelicensure experience, postlicensure safety surveillance data after

administration of single-antigen

varicella vaccine indicated that rash, fever, and injection-site reactions were the most

frequently reported adverse events

(140,141). Using these reports from passive surveillance of adverse events during the

first 4 years of the vaccination program, when

wild-type VZV was still circulating widely, polymerase chain reaction (PCR) analysis confirmed that the majority of rash

events occurring within 42 days of vaccination were caused primarily by wild-type varicella-zoster virus. Rashes from the

wild-type virus occurred a median of 8 days after vaccination (range: 1--24 days), whereas rashes from the vaccine strain occurred

a median of 21 days after vaccination (range: 5--42 days)

(140).

As part of postmarketing evaluation of the short-term safety of VARIVAX, 89,753 vaccinated adults and children

were identified from automated clinical databases of hospitals, emergency room visits, and clinic visits during April

1995--December 1996 (56). Out of all potential adverse events identified, no consistent time association or clustering of any

events was noted during the exposure follow-up period. No cases of ataxia or encephalitis were identified after receipt of

varicella vaccine in this group of vaccine recipients. In the prevaccine era, among children aged <15 years, acute cerebellar ataxia

was estimated to occur at a rate of one in 4,000 varicella cases, and varicella encephalitis without ataxia was estimated to

occur at one in 33,000 varicella cases (142).

Severe complications that are laboratory-confirmed to be caused by vaccine virus strain are rare and include

pneumonia (140), hepatitis (143), severe disseminated varicella infection

(140,141,144,145), and secondary transmission from

five vaccine recipients (140,146--148). Except for the secondary transmission cases, these cases all occurred

in immunocompromised patients or in persons who had other serious medical conditions that were undiagnosed at the time

of vaccination.

Although other serious adverse events have been reported, vaccine strain involvement was not

laboratory-confirmed. Thrombocytopenia

(140,141,149) and acute cerebellar ataxia

(140,141,150) have been described as potentially

associated with single-antigen varicella vaccine. Two children had acute hemiparesis

diagnosed after varicella vaccination (one at 5

days and the other at 3 weeks) (151). In both cases, unilateral

infarction of the basal ganglia and internal capsule was noted;

this distribution is consistent with varicella angiopathy. Urticaria after varicella vaccine has been associated with gelatin

allergy (152). Recurrent papular urticaria has been reported to be potentially associated with varicella vaccination

(153). However, available data regarding the potential adverse events after

varicella vaccination are insufficient to determine a

causal association. The quality of reported information varies widely, and simultaneous administration with other

vaccines (especially MMR) might confound attribution.

Herpes Zoster. Similar to wild-type VZV, vaccine virus can establish latent infection and subsequently reactivate, causing

HZ disease in vaccine recipients. Before vaccine licensure, studies in children with leukemia had demonstrated a much lower rate

of HZ in vaccinated children compared with those (age and protocol matched) with previous varicella

(54). Cases of HZ in healthy vaccine recipients have been confirmed to be caused by both vaccine virus and wild-type virus, suggesting that certain HZ cases

in vaccine recipients might result from antecedent natural

varicella infection that might not have been detected by the

patient or from infection after vaccination

(140). A single case has been reported of a child who received a diagnosis of

neuroblastoma and had severe chronic zoster attributed to vaccine virus strain that

with time became drug resistant

(145). A large postlicensure safety study performed through surveys conducted every 6

months and validated by medical chart review in the first 9 years of a

15-year follow-up study of >7,000 enrolled children vaccinated with

single-antigen varicella vaccine at age 12--24 months estimated

HZ disease incidence to be 22 per 100,000 person-years (CI = 13--37) as reported by

parents (Steven Black, MD,

Northern

California Kaiser Permanente Medical Care Program, unpublished presentation, 2005).

The incidence of HZ was 30 per

100,000 person-years among healthy children aged 5--9 years

(154) and 46 per 100,000 person-years for those aged

<14 years (64). However, these rates are drawn from different populations and based

on different methodologies. In addition, a proportion

of children in these age groups would not have experienced varicella disease; those

rates are likely to underestimate rates in a

cohort of children all infected with wild-type VZV, making direct comparison

difficult with a vaccinated cohort.

Transmission of Vaccine Virus

Results from prelicensure vaccine trials of the single-antigen varicella vaccine suggest that transmission of varicella vaccine virus from healthy persons to susceptible contacts is rare. This risk was assessed in siblings of healthy vaccinated children who themselves received placebo (103). Six (1%) of 439 placebo recipients seroconverted without rash; the vaccinated siblings of these six children also did not develop rash. Serologic data suggested that three of these six seroconverters received vaccine mistakenly in lieu of their siblings. In a smaller study, immunocompromised siblings of healthy children receiving varicella vaccine were evaluated clinically and by testing for humoral or cell-mediated immune responses (155). No evidence was demonstrated of vaccine virus transmission to any of 30 immunocompromised siblings from 37 healthy children receiving varicella vaccine.

Accumulated data from postlicensure surveillance activities suggest that the risk for transmission of varicella vaccine virus from healthy persons to susceptible contacts is low. With >55 million doses of VARIVAX distributed since licensure, transmission from immunocompetent persons after vaccination has been documented by PCR analysis from only five persons, resulting in six secondary infections, all of them mild (140,146--148). Three episodes involved transmission from healthy children aged 1 year to healthy household contacts, including a sibling aged 4 months, a father, and a pregnant mother. In

the latter episode, the mother chose to terminate the pregnancy, but fetal tissue tested subsequently by PCR was negative

for varicella vaccine virus (147). The children in these episodes had 2, 12, and 30 lesions, respectively. A fourth episode

involved transmission from an immunocompetent adolescent who was a resident in an institution for chronically disabled children.

The adolescent had >500 lesions after vaccination, and vaccine virus was transmitted to another immunocompetent resident of

the institution and to a health-care worker, both of whom had histories of varicella

(146). The fifth episode represented a

tertiary spread from a healthy sibling contact of a vaccinee with leukemia

(148). Rashes for both healthy siblings were mild (i.e.,

40 and 11 lesions, respectively), and vaccine virus was isolated from all three

case-patients. The third sibling had rash 18

days after the onset of the secondary case-patient and 33 days after rash onset in the vaccinated leukemic child. In addition to

these five episodes, one child has been reported to have transmitted vaccine virus from HZ that occurred 5 months after

varicella vaccination; 2 weeks later, a mild varicella-like rash from which vaccine varicella virus was isolated occurred in the

child's vaccinated brother (156).

 Although varicella vaccine is not recommended for children with cellular immune deficiencies, the experience

from prelicensure vaccine trials involving children with leukemia is instructive. Data from a study of varicella vaccination

in children with leukemia indicated that varicella virus vaccine transmission occurred in 15 (17%) of 88 healthy,

susceptible siblings of leukemic vaccine recipients; the rash was mild in 11 (73%) of the 15 infected siblings

(148). The risk for transmission was correlated with the number of skin lesions in the immunocompromised vaccine recipients.

  These data suggest that healthy, vaccinated persons have a minimal risk for transmitting vaccine virus to their

contacts, particularly in the absence of vaccine rash in the vaccine

recipient. Vaccine recipients who have a vaccine-related

rash, particularly HCP and household contacts of immunocompromised persons, should avoid contact with persons

without evidence of immunity who are at high risk for severe complications (see Health-Care Personnel)

Summary of Rationale for Varicella Vaccination

 Varicella vaccine is an effective prevention tool for decreasing the burden attributable to varicella disease and

its complications in the United States. In the prevaccine era, varicella was a childhood disease with >90% of the 4 million

cases, two thirds of approximately 11,000 hospitalizations, and

approximately half of 100--150 annual deaths occurring

among persons aged <20 years. Single-antigen varicella vaccine is

licensed for use among healthy persons aged

>12 months, and the combination MMRV vaccine is licensed for use in healthy children aged 12 months--12 years. Prelicensure and

postlicensure

studies have demonstrated that 1 dose of single-antigen varicella vaccine is approximately 85% effective in preventing

varicella. Breakthrough varicella disease that occurs

after vaccination frequently is mild and modified.

Varicella vaccine is >95% effective in preventing severe varicella disease. Since implementation of the varicella vaccination program in 1995, varicella

incidence, hospitalizations, and deaths have declined substantially. MMRV was licensed on the basis of immunological noninferiority

to its vaccine antigenic components. Initial varicella vaccine policy recommendations were for 1 dose of varicella vaccine

for children aged 12 months--12 years and 2 doses, 4--8 weeks apart, for persons aged >13 years. In June 2006, ACIP approved a routine 2-dose recommendation for children.

The first dose should be administered at age 12--15 months and the second

dose at age 4--6 years.

 The rationale for the second dose of varicella vaccine for children is to further decrease varicella disease and its

complications in the United States. Despite the successes of the

1-dose vaccination program in children, vaccine effectiveness of 85% has

not been sufficient to prevent varicella outbreaks, which, although less than in the prevaccine era, have continued to occur

in highly vaccinated school populations. Breakthrough varicella is contagious. Studies of the immune response after 1 and

2 doses of varicella vaccine demonstrate a greater-than-tenfold boost in GMTs when measured 6 weeks after the second

varicella vaccine dose. A higher proportion (>99%) of children achieve an antibody response of

>5 gpELISA units after the second dose compared with 76%--85% of children after a

single dose of varicella vaccine. The second dose of varicella vaccine is

expected to provide improved protection to the 15%--20% of children who do not

respond adequately to the first dose. Data from

a randomized clinical trial conducted postlicensure indicated that vaccine efficacy after

2 doses of single-antigen varicella vaccine in children (98.3%; CI = 97.3%--99.0%) was

significantly higher than that after a single dose (94.4%; CI

=92.9%--95.7%). The risk for breakthrough disease was 3.3-fold lower among children

who

received 2 doses than it was among children who received

1 dose. How this increase in vaccine efficacy (typically higher than observed under field

conditions) will translate

into vaccine effectiveness under conditions of community use will be an important area

of study.

 The recommended ages for routine first (at age 12--15 months) and second (at age

4--6 years) doses of varicella vaccine

are harmonized with the recommendations for MMR vaccine use and intended to limit

the period when children have

no varicella antibody. The recommended age for the

second dose is supported by the current epidemiology of

varicella, with low incidence and few outbreaks among preschool-aged children and

higher incidence and more outbreaks among

elementary-school--aged children. However, the second dose may be administered at

an earlier age, provided that the interval between

the first and second doses is 3 months. The recommendation for the minimum interval

between doses is made on the basis of

the design of the studies evaluating 2 doses among children aged 12 months--12 years.

MMRV vaccine may be used to

vaccinate children against measles, mumps, rubella, and varicella simultaneously. Because the risk for transmission can be high

among students in schools, colleges, and other postsecondary educational institutions, students without evidence of immunity

should receive 2 doses of varicella vaccine. All children and adolescents who received

1 dose of varicella vaccine previously should receive a second dose.

Varicella disease is more severe and its complications more frequent among adolescents and adults. The recommendation

for vaccination of all adolescents and adults without

evidence of immunity will provide protection in these age groups.

Because varicella might be more severe in immunocompromised persons who might not be eligible for vaccination, and because of

the risk of VZV transmission in health-care settings, HCP must be vaccinated. Varicella disease during the first two trimesters of pregnancy might

infect the fetus and result in congenital varicella syndrome. Therefore, routine antenatal screening

for evidence of immunity and postpartum vaccination for those without evidence of immunity now is recommended.

Recommendations for the Use of Varicella Vaccines

Two 0.5-mL doses of varicella vaccine administered subcutaneously are recommended for children aged

>12 months, adolescents, and adults without evidence of immunity. For children aged

12 months--12 years, the recommended

minimum interval between the two doses is 3 months. However, if the second dose was administered

>28 days after the first dose, the second dose is considered valid and need not be repeated. For persons aged >13 years, the recommended minimum

interval is 4 weeks. Single-antigen varicella vaccine is approved for use among healthy persons aged

>12 months. Combination MMRV vaccine is approved for use among healthy children aged 12 months--12 years. MMRV vaccine is indicated for

simultaneous vaccination against measles, mumps, rubella, and varicella. Whenever any components of the combination vaccine

are

indicated and the other components are not

contraindicated, use of licensed combination vaccines, such as MMRV vaccine,

is preferred over separate injection of equivalent component vaccines

(157).

Routine Vaccination

Persons Aged 12 Months--12 Years

Preschool-Aged Children

All healthy children should receive their first dose of varicella-containing vaccine routinely at age 12--15 months.

School-Aged Children

A second dose of varicella vaccine is recommended routinely for all children aged 4--6 years (i.e., before

entering prekindergarten, kindergarten, or first grade). However, it may be administered at an earlier age provided that the

interval between the first and second dose is >3 months.

Because of the risk for transmission of VZV in schools, all children entering school should have received 2 doses of

varicella-containing vaccine or have other evidence of immunity to varicella (see Evidence of Immunity).

Persons Aged >13 Years

Persons aged >13 years without evidence of varicella immunity should receive two 0.5-mL doses of single-antigen

varicella vaccine administered subcutaneously, 4--8 weeks apart. If >8 weeks elapse after the first dose, the second dose may

be administered without restarting the schedule. Only single-antigen varicella vaccine may be used for vaccination of persons

in this age group. MMRV is not licensed for use among persons aged

>13 years.

School-Aged Children, College Students, and Students in Other Postsecondary Educational Institutions

All students should be assessed for varicella immunity, and those without evidence of immunity should routinely receive

2 doses of single-antigen varicella vaccine 4--8 weeks apart. The risk for transmission of varicella among school-aged

children, college students, and students in other postsecondary educational institutions can be high because of high contact rates.

Other Adults

All healthy adults should be assessed for varicella immunity, and those who do not have evidence of immunity

should receive 2 doses of single-antigen varicella vaccine 4--8 weeks apart. Adults who

might be at increased risk for exposure

or transmission and who do not have evidence of immunity should receive special consideration for vaccination,

including 1) HCP, 2) household contacts of immunocompromised persons, 3) persons who live or work in environments in

which transmission of VZV is likely (e.g., teachers, day-care employees, residents and staff in institutional settings), 4) persons

who live or work in environments in which transmission has been reported (e.g., college students, inmates and staff members

of correctional institutions, and military personnel), 5) nonpregnant women of childbearing age, 6) adolescents and adults

living in households with children, and 7) international travelers.

Second Dose Catch-Up Vaccination

 To improve individual protection against varicella and to have a more rapid impact on school outbreaks, second dose

catch-up varicella vaccination is recommended for children, adolescents, and adults who previously

received 1 dose. The recommended minimum interval between the first dose and the catch-up second dose is 3 months for children aged

<12 years and 4 weeks for persons aged

>13 years. However, the catch-up second dose may be administered at any interval longer

than the minimum recommended interval. Catch-up vaccination may be implemented during routine health-care provider

visits and through school- and college-entry requirements.

As part of comprehensive health services for all adolescents, ACIP, AAP, and AAFP recommend a health maintenance visit

at age 11--12 years. This visit also should serve as an immunization visit to evaluate vaccination status and administer

necessary vaccinations (158). Physicians should use this and other routine visits to ensure that all children without evidence of

varicella immunity have received 2 doses of varicella vaccine.

Requirements for Entry to Child Care, School, College, and Other

Postsecondary Educational Institutions

Child care and school entry requirements for varicella

immunity have been recommended previously

(2). In 2005, ACIP recommended expanding the requirements to cover students in all grade levels. Official health agencies should take

necessary steps, including developing and enforcing school immunization requirements, to ensure that students at all grade

levels (including college) and children in child care centers are protected against varicella and other vaccine-preventable

diseases (157).

Prenatal Assessment and Postpartum Vaccination

Prenatal assessment of women for evidence of varicella

immunity is recommended. Birth before 1980 is not

considered evidence of immunity for pregnant women because of potential severe

consequences of varicella infection during

pregnancy, including infection of the fetus. Upon completion or termination of their pregnancies, women who do not have evidence

of varicella immunity should receive the first dose of vaccine before discharge from the health-care

facility. The second dose should be administered 4--8 weeks later, which

coincides with the postpartum visit (6--8 weeks after delivery). For

women who gave birth, the second dose should be administered

at the postpartum visit. Women should be counseled to

avoid conception for 1 month after each dose of varicella vaccine. Health-care settings in which completion or termination

of pregnancy occurs should use standing orders to ensure the administration of varicella vaccine to women

without evidence of immunity.

Special Considerations for Vaccination

Vaccination of HIV-Infected Persons

HIV-infected children with CD4+ T-lymphocyte percentage >15% should be considered for vaccination with the

single-antigen varicella vaccine. Varicella vaccine was recommended previously for HIV-infected children in CDC clinical

and immunologic categories N1 and A1 with age-specific CD4+ T-lymphocyte percentage

>25% (2). Limited data from a

clinical trial in which 2 doses of single-antigen varicella vaccine were administered 3

months apart to 37 HIV-infected children

(CDC clinical categories N, A, or B and immunologic category 2 [CD4+ T-lymphocyte percentage

>15%--24%]) aged 1--8 years indicated that the vaccine was well-tolerated and that >80% of subjects had detectable VZV specific

immune response (either antibody or cell immune response or both) at 1 year after immunization

(159). These children were no less likely to have

an antibody response to the varicella vaccine than were subjects who were less affected immunologically by HIV

infection. Because children infected with HIV are at increased risk for morbidity from varicella and HZ (i.e., shingles) compared

with healthy children, ACIP recommends that, after weighing potential risks and benefits, single-antigen varicella vaccine should

be considered for HIV-infected children with CD4+ T-lymphocyte percentages

>15%. Eligible children should receive 2 doses

of single-antigen varicella vaccine 3 months apart. Because persons with impaired cellular immunity are potentially at greater

risk for complications after vaccination with a live vaccine, these vaccine

recipients should be encouraged to return for evaluation

if they experience a postvaccination varicella-like rash. Data are not available regarding safety, immunogenicity, or efficacy

of MMRV vaccine in HIV-infected children, MMRV vaccine should not be administered as a substitute for the

single-antigen varicella vaccine when vaccinating these children. The titer of Oka/Merck VZV is higher in combination

MMRV vaccine than in single-antigen varicella vaccine. Recommendations for

vaccination of HIV-infected children with

measles, mumps, or rubella vaccines have been published previously

(160).

 Data on use of varicella vaccine in HIV-infected adolescents and adults are lacking. However, on the basis of expert

opinion, the safety of varicella vaccine in HIV-infected persons aged >8 years with

comparable levels of immune function

(CD4+T-lymphocyte count >200

cells/µL) is likely to be similar to that of children aged <8 years. Immunogenicity might be lower

in older HIV-infected children, adolescents, and adults compared to children aged 1--8

years. However, weighing the risk

for severe disease from wild VZV and potential benefit of vaccination, vaccination may

be considered (2 doses, administered

3

months apart) for HIV-infected persons with CD4+T-lymphocytes count

>200 cells/µL in these age groups. If vaccination

of HIV-infected persons results in clinical disease, the use of acyclovir might modify the

severity of disease.

Situations in Which Some Degree of Immunodeficiency Might be Present

 Persons with impaired humoral immunity may be vaccinated. No data have been published concerning whether

persons without evidence of immunity receiving only inhaled, nasal, or topical doses of

steroids can be vaccinated safely.

However, clinical experience suggests that vaccination is well-tolerated among these persons. Persons without evidence of immunity

who are receiving systemic steroids for certain conditions (e.g., asthma) and who are not otherwise immunocompromised may

be vaccinated if they are receiving <2 mg/kg of body weight or a total of <20 mg/day of prednisone or its equivalent.

Certain experts suggest withholding steroids for 2--3 weeks after vaccination if it can be done safely

(1). Data from a Japanese study using the Oka/Biken varicella vaccine (which is not available in the United States but whose immunogenicity and efficacy

are similar to those of the varicella vaccine used in the United States) indicated that children taking steroids for nephrosis

were vaccinated safely when the steroids were suspended for 1--2 weeks before vaccination, although no

serious reactions occurred among children vaccinated when steroid therapy was not suspended

(161). Persons who are receiving high doses of

systemic steroids (i.e., >2 mg/kg prednisone) for

>2 weeks may be vaccinated once steroid therapy has been discontinued for

>1 month, in accordance with the general recommendations for the use of live-virus vaccines

(157).

 Vaccination of leukemic children who are in remission and who do not have evidence of immunity to varicella should

be undertaken only with expert guidance and with the availability of antiviral therapy should complications ensue. Patients

with leukemia, lymphoma, or other malignancies whose disease is in remission and

whose chemotherapy has been terminated for

at least 3 months can receive live-virus vaccines

(157). When immunizing persons in whom some degree of

immunodeficiency might be present, only single-antigen varicella vaccine should be

used.

Vaccination of Household Contacts of Immunocompromised Persons

 Immunocompromised persons are at high risk for serious varicella infections. Severe

disease occurs in approximately 30%

of such persons with primary infection. Because varicella vaccine now is recommended

for all healthy children and

adults without evidence of immunity, household contacts of immunocompromised

persons should be vaccinated routinely.

Although the risk for exposure to wild VZV for immunocompromised persons now is

lower than it was previously, vaccine should

be offered to child and adult household contacts without evidence of immunity of

immunocompromised persons. Vaccination

of household contacts provides protection for immunocompromised persons by

decreasing the likelihood that wild-type

VZV will be introduced into the household. Vaccination of household contacts of

immunocompromised persons

theoretically might pose a minimal risk for transmission of vaccine virus to

immunocompromised persons, although in one study,

no evidence of transmission of vaccine virus was demonstrated after vaccination of 37

healthy siblings of 30 children

with malignancy (155). No cases have been documented of transmission of vaccine

virus to immunocompromised persons in

the postlicensure period in the United States, with >55 million doses of vaccine distributed. Other data indicate that

disease caused by vaccine virus in immunocompromised persons is milder than wild-type disease and can be treated with

acyclovir (148,159). The benefits of vaccinating susceptible household contacts of immunocompromised persons outweigh

the extremely low potential risk for transmission of vaccine virus to immunocompromised contacts. Vaccine recipients in

whom vaccine-related rash occurs, particularly HCP and household contacts of immunocompromised persons, should avoid

contact with susceptible persons who are at high risk for severe complications. If a susceptible, immunocompromised person

is inadvertently exposed to a person who has a vaccine-related rash, postexposure prophylaxis with VZIG is not

needed because disease associated with this type of virus is expected to be mild.

Nursing Mothers

 Postpartum vaccination of women without evidence of immunity need not be delayed because of breastfeeding.

Women who have received varicella vaccination postpartum may continue to breastfeed. The majority of live vaccines are

not associated with virus secretion in breast milk

(157). A study involving 12 women who received single-antigen varicella

vaccine while breastfeeding indicated no evidence of VZV DNA either in 217 breast milk samples collected or in infants tested

after both vaccine doses (162). No infants seroconverted. Another study did not detect varicella gene sequences in

the

postvaccination breast milk samples (163). Therefore, single-antigen varicella vaccine should be administered to

nursing mothers without evidence of immunity. Combination MMRV vaccine is not licensed for use among persons aged

>13 years.

Health-Care Personnel

 Nosocomial transmission of VZV is well-recognized

(131,164--173), and guidelines for the prevention of nosocomial

VZV infection and for infection control in HCP have been published

(174,175). Sources of nosocomial exposure have

included patients, hospital staff, and visitors (e.g., the children of hospital employees) who are infected with varicella or HZ.

In hospitals, airborne transmission of VZV has been demonstrated when varicella has occurred in susceptible persons who had

no direct contact with the index case-patient

(176--180).

 To prevent disease and nosocomial spread of VZV, health-care institutions should ensure that all HCP have evidence

of immunity to varicella. Birth before 1980 is not considered evidence of immunity for HCP because of the possibility

of nosocomial transmission to high-risk patients. In health-care institutions, serologic

screening before vaccination of

personnel who have a negative or uncertain history of varicella and who are unvaccinated is likely to be cost effective. Institutions

may elect to test all HCP regardless of disease history because a small proportion of persons with a positive history of

disease might be susceptible.

 Routine testing for varicella immunity after 2 doses of vaccine is not recommended for the management of vaccinated

HCP. Available commercial assays are not sensitive enough to detect antibody after vaccination in all instances. Sensitive tests

have indicated that 99% of adults develop antibodies after the second dose. However, seroconversion does not always result in

full protection against disease, and no data regarding correlates of protection are available for adults.

 HCP who have received 2 doses of vaccine and who are exposed to VZV should be monitored daily during days 10--21

after exposure through the employee health program or by an infection control nurse to determine clinical status (i.e., daily

screen for fever, skin lesions, and systemic symptoms). Persons with varicella might be infectious up to 2 days before rash onset.

In addition, HCP should be instructed to report fever, headache, or other constitutional symptoms and any atypical skin

lesions immediately. HCP should be placed on sick leave immediately if symptoms occur. Health-care institutions should

establish protocols and recommendations for screening and vaccinating HCP and for management of HCP after exposures in the

work place.

HCP who have received 1 dose of vaccine and who are

exposed to VZV should receive the second dose with

single-antigen varicella vaccine within 3--5 days after exposure to rash (provided 4

weeks have elapsed after the first dose). After

vaccination, management is similar to that of 2-dose vaccine recipients.

Unvaccinated HCP who have no other evidence of immunity who are exposed to VZV

are potentially infective from

days 10--21 after exposure and should be furloughed during this period. They should

receive postexposure vaccination as soon

as possible. Vaccination within 3--5 days of exposure to rash might modify the disease

if infection occurred. Vaccination >5

days postexposure still is indicated because it induces protection against subsequent

exposures (if the current

exposure did not cause infection).

The risk for transmission of vaccine virus from vaccine

recipients in whom varicella-like rash occurs after vaccination is

low and has been documented after exposures in households and long-term care

facilities

(140,146--148). No cases have been documented after vaccination of HCP. The benefits

of vaccinating HCP without evidence of immunity outweigh

this extremely low potential risk. As a safeguard, institutions should consider

precautions for personnel in whom rash occurs

after vaccination. HCP in whom a vaccine-related rash occurs should avoid contact with

persons without

evidence of immunity who are at risk for severe disease and complications until all

lesions resolve (i.e., are crusted over or fade away) or no

new lesions appear within a 24-hour period.

Varicella IgG Antibody Testing

The tests most widely used to detect varicella IgG antibody after natural varicella infection among HCP are latex agglutination (LA) and ELISA. A commercially available LA test using latex particles coated with VZV glycoprotein antigens can be completed in 15 minutes and does not require special equipment (181). The sensitivity and specificity of the LA test are comparable to those of FAMA in detecting antibody response after natural varicella infection. The LA test generally is more sensitive than commercial ELISAs. The LA test has detected antibody for up to 11 years after varicella vaccination (182).

However, for the purpose of screening HCP for varicella susceptibility, a less sensitive and more specific commercial ELISA should be considered. A recent report indicated that the LA test can produce false-positive results, particularly when only a single concentration of serum is evaluated (183); this led to documented cases of false-positive results in HCP who consequently remained unvaccinated and subsequently contracted varicella.

Vaccination for Outbreak Control

Varicella vaccination is recommended for outbreak control. Persons who do not have adequate evidence of immunity

should receive their first or second dose as appropriate. Additionally, in outbreaks among preschool-aged children, 2-dose vaccination

is recommended for optimal protection, and children vaccinated with 1 dose should receive their second dose provided

3 months have elapsed since the first dose. State and local health departments may advise exposed persons who do not have evidence

of immunity to contact their health-care providers for vaccination, or they may offer vaccination through the health department

or school (or other institutions) vaccination clinics. Although outbreak control efforts optimally should be implemented as soon

as an outbreak is identified, vaccination should be offered even if the outbreak is identified late. Varicella outbreaks in

certain settings (e.g., child care facilities, schools, or institutions) can last as long as 4--5 months. Thus, offering vaccine during

an outbreak might provide protection to persons not yet exposed and shorten the duration of the outbreak

(184). Persons receiving either their first or second dose as part of the outbreak control program may be readmitted to school

immediately. Those vaccinated with the first dose as part of outbreak control measures should be scheduled for the second dose as

age appropriate. Persons who are unvaccinated and without other evidence of immunity who do not receive vaccine should

be excluded from institutions in which the outbreak is occurring until 21 days after the onset of rash in the last case of varicella.

In addition, for school-aged persons covered by the 2-dose school vaccination requirements, exclusion during an outbreak

is recommended for those vaccine recipients who had

received the first dose before the outbreak but not the second as part of

the oubtreak control program. Persons at increased risk for severe varicella who have contraindications to vaccination

should receive VZIG within 96 hours of exposure.

Contraindications

General

Adequate treatment provisions for anaphylactic reactions, including epinephrine injection (1:1000), should be available

for immediate use should an anaphylactic reaction occur.

Before administering a vaccine, health-care providers should obtain

the vaccine recipient's vaccination history and determine whether the individual had any previous reactions to any

vaccine including Varivax, ProQuad or any measles, mumps, or rubella containing vaccines.

Allergy to Vaccine Components

The administration of live varicella-containing vaccines rarely results in hypersensitivity. The information in the

package insert should be reviewed carefully before vaccine is

administered. Vaccination is contraindicated for persons who have

a history of anaphylactic reaction to any component of the vaccine, including gelatin.

Single-antigen varicella vaccine does

not contain preservatives or egg protein; these substances have caused hypersensitive reactions to other vaccines. For

the combination MMRV vaccine, live measles and live mumps vaccines are produced in chick embryo culture. However,

among persons who are allergic to eggs, the risk for serious allergic reactions after administration of measles- or

mumps-containing vaccines is low. Because skin testing with vaccine is not predictive of allergic reaction to vaccination, skin testing is

not required before administering combination MMRV vaccine to persons who are allergic to eggs

(160). The majority of anaphylactic reactions to measles- and

mumps-containing vaccines are associated not with hypersensitivity to egg antigens

but with other vaccine components. Neither single-antigen varicella nor combination MMRV vaccines should be administered

to persons who have a history of anaphylactic reaction to neomycin. However, neomycin allergy usually is manifested as a

contact dermatitis, which is a delayed-type immune response rather than anaphylaxis. For persons who experience such a response,

the adverse reaction, if any, would appear as an erythematous, pruritic nodule or papule present 48--96 hours after vaccination.

A history of contact dermatitis to neomycin is not a contraindication to receiving varicella vaccines.

Altered Immunity

 Single-antigen varicella and combination MMRV vaccines are not licensed for use in persons who have any

malignant condition, including blood dyscrasias, leukemia, lymphomas of any type, or other malignant neoplasms affecting the

bone marrow or lymphatic systems. Combination MMRV vaccine should not be administered to persons with primary or

acquired immunodeficiency, including immunosuppression associated with AIDS or other clinical manifestations of HIV

infections, cellular immunodeficiencies, hypogammaglobulinemia, and dysgammaglobulinemia. Combination MMRV vaccine should

not be administered as a substitute for the component vaccines when vaccinating HIV-infected children.

 Varicella vaccines should not be administered to persons who have a family history of congenital or

hereditary immunodeficiency in first-degree relatives (e.g., parents and siblings) unless the immune competence of the potential

vaccine recipient has been clinically substantiated or verified by a

laboratory.

 Varicella vaccines should not be administered to persons receiving high-dose systemic immunosuppressive

therapy, including persons on oral steroids

>2 mg/kg of body weight or a total of

>20 mg/day of prednisone or equivalent for

persons who weigh >10 kg, when administered for

>2 weeks. Such persons are more susceptible to infections than healthy

persons. Administration of varicella vaccines can result in a more extensive vaccine-associated rash or disseminated disease in

persons receiving immunosuppressive doses of corticosteroids

(185). This contraindication does not apply

to persons who are receiving inhaled, nasal, or topical corticosteroids or low-dose corticosteroids as are used
commonly for asthma prophylaxis or for
corticosteroid-replacement therapy (see Situations in Which Some Degree of Immunodeficiency Might Be Present).

Pregnancy

Because the effects of the varicella virus vaccine on the fetus are unknown, pregnant women should not be
vaccinated. Nonpregnant women who are vaccinated should avoid
becoming pregnant for 1 month after each injection. For
persons without evidence of immunity, having a pregnant household member is not a contraindication to vaccination.

If a pregnant woman is vaccinated or becomes pregnant within 1 month of vaccination, she should be counseled
about potential effects on the fetus. Wild-type varicella poses a low risk to the fetus (see Prenatal and Perinatal
Exposure). Because the virulence of the attenuated virus used in the vaccine is less than that of the wild-type virus, the risk to the fetus,
if any, should be even lower. In 1995, Merck and Co., Inc., in collaboration with CDC, established the VARIVAX
Pregnancy Registry to monitor the maternal-fetal outcomes of pregnant women who were inadvertently administered
varicella vaccine 3 months before or at any time during pregnancy (to report, call: 1-800-986-8999)
(186). During the first 10 years of the pregnancy registry no cases of congenital

varicella syndrome or birth defects compatible with congenital varicella syndrome have been documented (187,188). Among 131 live-born infants of prospectively reported seronegative women (82 of whom were born to mothers vaccinated during the highest risk period [i.e., the first or second trimester of pregnancy]), no birth defects consistent with congenital varicella syndrome have been documented (prevalence rate = 0; CI = 0--6.7%), and three major birth defects were reported (prevalence rate = 2.3%; CI = 0.5%--6.7%). The rate of occurrence of major birth defects from prospective reports in the registry was similar to the rate reported in the general U.S. population (3.2%), and the defects indicated no specific pattern or target organ. Although the study results do not exclude the possibility of risk for women who received inadvertent varicella vaccination before or during pregnancy, the potential risk, if any, is low.

Precautions

Illness

 Vaccination of persons who have acute severe illness, including untreated, active tuberculosis, should be postponed until recovery. The decision to delay vaccination depends on the severity of symptoms and on the etiology of the disease. No data are available regarding whether either single-antigen varicella or combination MMRV vaccines exacerbate tuberculosis.

Live attenuated measles, mumps, and rubella virus vaccines administered individually might result in a temporary depression

of tuberculin skin sensitivity. Therefore, if a tuberculin test is to be performed, it should be administered either any time

before, simultaneously with, or at least 4--6 weeks after combination MMRV vaccine. However, tuberculin skin testing is not

a prerequisite for vaccination with single-antigen varicella or combination MMRV vaccines.

Varicella vaccines may be administered to children without evidence of immunity who have mild illnesses, with or

without low-grade fever (e.g., diarrhea or upper-respiratory infection) (189). Physicians should be alert to the

vaccine-associated temperature elevations that might occur predominantly in the second week after vaccination, especially with

combination MMRV vaccine. Studies suggest that failure to vaccinate children with minor illnesses can impede

vaccination efforts (190).

Thrombocytopenia

Thrombocytopenia is not a contraindication for

single-antigen varicella vaccine. No clinical data are available regarding

the development or worsening of thrombocytopenia in persons vaccinated with combination MMRV vaccine. Cases

of thrombocytopenia have been reported after MMR vaccine and after varicella vaccination. Postmarketing experience with

live MMR vaccine indicates that persons with thrombocytopenia might develop more

severe thrombocytopenia after

vaccination. For vaccination of thrombocytopenic children with combination MMRV

vaccine, health-care providers should refer to

the ACIP recommendations on MMR vaccination

(160).

Recent Administration of Blood, Plasma, or Immune Globulin

Although passively acquired antibody is known to interfere with response to measles

and rubella vaccines

(191), the effect of the administration of immune globulin (IG) on the

response to varicella virus vaccine is unknown. The duration

of interference with the response to measles vaccination is dose-related and ranges

from 3--11 months. Because of the

potential inhibition of the response to varicella vaccination by passively transferred

antibodies, varicella vaccines should not

be administered for the same intervals as measles vaccine (3--11 months, depending

on the dosage) after

administration of blood (except washed red blood cells), plasma, or IG. Suggested

intervals between administration of antibody-containing

products for different indications and varicella vaccine have been published previously

(157). In addition, persons who received a varicella vaccine should not be administered

an antibody-containing product for 2 weeks after vaccination unless the

benefits exceed those of vaccination. In such cases, the vaccine recipient should either

be

revaccinated or tested for immunity at the appropriate intervals, depending on the dose

received, and then revaccinated if seronegative.

Use of Salicylates

No adverse events associated with the use of salicylates after varicella vaccination have been reported; however, the vaccine manufacturer recommends that vaccine recipients avoid using salicylates for 6 weeks after receiving varicella vaccines because of the association between aspirin use and Reye syndrome after varicella. Vaccination with subsequent close monitoring should be considered for children who have rheumatoid arthritis or other conditions requiring therapeutic aspirin. The risk for serious complications associated with aspirin is likely to be greater in children in whom natural varicella develops than it is in children who receive the vaccine containing attenuated VZV. No association has been documented between Reye syndrome and analgesics or antipyretics that do not contain salicylic acid.

Postexposure Prophylaxis

Healthy Persons

Prelicensure data from the United States and Japan on varicella exposures in children from household, hospital, and community settings indicate that single-antigen varicella vaccine is effective in preventing illness or modifying varicella severity if administered to unvaccinated children within 3 days, and possibly up to 5

days, of exposure to rash

(78,101,192). Vaccination within 3 days of exposure to rash was

>90% effective in preventing varicella whereas vaccination within 5 days

of exposure to rash was approximately 70% effective in preventing varicella and 100%

effective in modifying severe

disease (101,192). Limited postlicensure studies also have demonstrated that varicella

vaccine is highly effective in either preventing

or modifying disease if administered within 3 days of exposure

(193,194). Varicella vaccine is recommended for

postexposure administration for unvaccinated persons without other evidence of

immunity. If exposure to VZV does not cause

infection, postexposure vaccination should induce protection against subsequent

exposures. If the exposure results in infection,

no

evidence indicates that administration of single-antigen varicella vaccine during the

presymptomatic or prodromal stage

of illness increases the risk for vaccine-associated

adverse events. No data are available regarding the potential benefit

of administering a second dose to 1-dose vaccine recipients after exposure. However,

administration of a second dose should

be considered for persons who have previously received 1 dose to bring them

up-to-date. Studies on postexposure use of

varicella vaccine have been conducted exclusively in children. A higher proportion of

adults do not respond to the first dose of

varicella vaccine. Nevertheless, postexposure vaccination should be offered to adults

without evidence of immunity.

Although postexposure use of varicella vaccine has potential applications in hospital settings, vaccination is recommended routinely

for all HCP without evidence of immunity and is the preferred method for preventing varicella in health-care settings

(195). Preferably, HCP should be vaccinated when they begin employment. No data are available on the use of combination

MMRV raccine for postexposure prophylaxis.

Persons Without Evidence of Immunity Who Have Contraindications

for Vaccination and Who Are at Risk for Severe Disease and Complications

  Studies conducted in 1969 indicated that clinical varicella was prevented in nonimmune, healthy children by

the administration of zoster immune globulin (ZIG) (prepared from patients recovering from HZ) within 72 hours of

exposure (196). ZIG also lowered attack rates among immunocompromised persons if administered no later than 96 hours

after exposure (196). VZIG (prepared from plasma obtained from healthy, volunteer blood donors identified by routine

screening to have high antibody titers to VZV) became

available in 1978. Both serologic and clinical evaluations have demonstrated

that the product is equivalent to ZIG in preventing or modifying clinical illness in non-immune, immunocompromised

persons who are exposed to varicella

(197,198). In a study of immunocompromised children who were administered VZIG within

96 hours of exposure, approximately one in five exposures resulted in clinical varicella,

and one in 20 resulted in

subclinical disease (198). The severity of clinical varicella (evaluated by percentage of

patients with >100 lesions or complications)

was lower than expected on the basis of historic controls.

 The VZIG product currently used in the United States,

VariZIG™(Cangene Corporation, Winnipeg, Canada), is

available under an Investigational New Drug Application

Expanded Access protocol (available at

http://www.fda.gov/cber/infosheets/mphvzig020806.htm). A request for licensure in

the United States might be submitted to FDA in the

future. VariZIG is a lyophilized presentation which, when properly reconstituted, is

approximately a 5% solution of IgG that can be

administered intramuscularly (199). VariZIG can be

obtained 24 hours a day from the sole authorized U.S.

distributor (FFF Enterprises, Temecula, California) at 1-800-843-7477 or online at

http://www.fffenterprises.com.

Administration of VZIG

 VZIG provides maximum benefit when administered as soon as possible after

exposure, but it might be effective

if administered as late as 96 hours after exposure. The effectiveness of VZIG when

administered >96 hours after

initial exposure has not been evaluated. The duration of protection provided after

administration of VZIG is unknown,

but protection should last at least one half-life of the IG (i.e.,

approximately 3 weeks). Susceptible persons at high risk for

whom varicella vaccination is contraindicated and who are again exposed

>3 weeks after receiving a dose of VZIG should

receive another full dose of VZIG. Patients receiving monthly high-dose immune globulin intravenous (IGIV)

(>400 mg/kg) are likely to be protected and probably do not require VZIG if the last dose of IGIV was administered <3 weeks before

exposure (200). VZIG has not been proven to be useful in treating clinical varicella or HZ or in preventing disseminated zoster and

is not recommended for such use. VZIG might extend the incubation period of the virus from 10--21 days to

>28 days. This should be taken into account after exposures when VZIG is administered.

Dosage

 VariZIG is supplied in 125-U vials. The recommended dose is 125 units/10 kg of body weight, up to a maximum of

625 units (five vials). The minimum dose is 125 U. The human IgG content is 60--200 mg per 125 units dose of VariZIG.

Indications for the Use of VZIG for Postexposure Prophylaxis

 The decision to administer VZIG depends on three factors: 1) whether the patient lacks evidence of immunity, 2)

whether the exposure is likely to result in infection, and 3) whether the patient is at greater risk for complications than the

general population.

Both healthy and immunocompromised children and adults who have verified positive histories of varicella (except for bone-marrow transplant recipients) may be considered immune (see Evidence of Immunity). The association between positive histories of varicella in bone-marrow donors and susceptibility to varicella in recipients after transplants has not been studied adequately. Thus, persons who receive bone-marrow transplants should be considered nonimmune, regardless of previous history of varicella disease or varicella vaccination in themselves or in their donors. Bone-marrow recipients in whom varicella or HZ develops after transplantation should subsequently be considered immune.

VZIG is not indicated for persons who received 2 doses of varicella vaccine and became immunocompromised as a result of disease or treatment later in life. These persons should be monitored closely; if disease occurs, treatment with acyclovir should be instituted at the earliest signs or symptoms. For patients without evidence of immunity and on steroid therapy doses >2 mg/kg of body weight or a total of 20 mg/day of prednisone or equivalent, VariZIG is indicated.

Types of Exposure

Certain types of exposure can place persons without evidence of immunity at risk for varicella. Direct contact exposure is defined as face-to-face contact with an infectious person while indoors. The duration of face-to-face contact that

warrants administration of VZIG is not certain. However, the contact should not be transient. Certain experts suggest a contact of

>5 minutes as constituting significant exposure for this purpose, whereas others define close contact as >1 hour

(200). Substantial exposure for hospital contacts consists of sharing the same hospital room with an infectious patient or direct,

face-to-face contact with an infectious person (e.g., HCP). Brief contacts with an infectious person (e.g., contact with x-ray technicians

or housekeeping personnel) are less likely than more

prolonged contacts to result in VZV transmission.

  Persons with continuous exposure to household members who have varicella or disseminated HZ are at greatest risk

for infection. Varicella occurs in approximately 85% (range: 65%--100%) of susceptible household contacts exposed to

VZV. Localized HZ is much less infectious than varicella or disseminated HZ

(52). Transmission from localized HZ is more

likely after close contact, such as in household settings. Physicians may consider recommending postexposure prophylaxis

with VZIG in such circumstances. After household exposure to varicella, attack rates among immunocompromised children

who were administered VZIG were up to 60%

(197). No comparative data are available for immunocompromised

children without evidence of immunity who were not administered VZIG. However, the incidence of severe disease

(defined as >100 skin lesions) was less than that predicted from the natural history of disease in normal children (27% and 87%,

respectively), and the incidence of pneumonia was less than that described in children

with neoplasm (6% and 25%, respectively)

(201). The risk for varicella after close contact (e.g., contact with playmates) or hospital exposure is estimated to be

approximately 20% of the risk occurring from household exposure.

The attack rate in healthy neonates who were exposed in utero within 7 days of delivery and who received VZIG after

birth was 62%, which does not differ substantially from rates reported for neonates who were similarly exposed but not treated

with VZIG (49). However, the occurrence of complications and fatal outcomes was substantially lower for neonates who

were treated with VZIG than for those who were not.

In a study of pregnant women without immunity to VZV who were exposed to varicella and administered VZIG,

the infection rate was 30%. This is substantially lower than the expected rate of >70% in unimmunized women exposed

to varicella (199,202).

Recommendations for the Use of VZIG

The following patient groups are at risk for severe disease and complications from varicella and should receive VZIG:

Immunocompromised patients. VZIG is used primarily for passive immunization of immunocompromised

persons without evidence of immunity after direct exposure to varicella or disseminated HZ patients, including persons who 1)

have primary and acquired immune-deficiency disorders, 2) have neoplastic diseases, and 3) are receiving

immunosuppressive

treatment. Patients receiving monthly high-dose IGIV

(>400 mg/kg) are likely to be protected and probably do not

require VZIG if the last dose of IGIV was administered

<3 weeks before exposure (200).

 Neonates whose mothers have signs and symptoms of varicella around the time of

delivery. VZIG is indicated for neonates whose mothers have signs and symptoms of

varicella from 5 days before to 2 days after delivery. VZIG is

not necessary for neonates whose mothers have signs and symptoms of varicella more

than 5 days before delivery, because

those infants should be protected from severe varicella by transplacentally acquired

maternal antibody. No evidence suggests

that infants born to mothers in whom varicella occurs >48 hours after delivery are at

increased risk for serious complications

(e.g., pneumonia or death).

  Premature neonates exposed postnatally. Transmission of varicella in the hospital

nursery is rare because the majority

of neonates are protected by maternal antibody. Premature

infants who have substantial postnatal exposure should be

evaluated on an individual basis. The risk for complications of postnatally acquired

varicella in premature infants is

unknown. However, because the immune system of premature infants is not fully

developed, administration of VZIG to premature infants born

at >28 weeks of gestation who are exposed during the neonatal period and whose

mothers do not have evidence of immunity

is indicated. Premature infants born at <28 weeks of gestation or who weigh

<1,000 g at birth and were exposed during

the neonatal period should receive VZIG regardless of maternal immunity because such infants might not have acquired

maternal antibody. The majority of premature infants born at

>28 weeks of gestation to immune mothers have enough

acquired maternal antibody to protect them from severe disease and complications.

Although infants are at higher risk than older children for serious and fatal complications, the risk for healthy, full-term infants who have varicella after postnatal exposure

is substantially less than that for infants whose mothers were infected

5 days before to 2 days after delivery. VZIG is

not recommended for healthy, full-term infants who are exposed postnatally, even if their mothers have no history of

varicella infection.

 Pregnant women. Because pregnant women might be at higher risk for severe varicella and complications

(37,42,203), VZIG should be strongly considered for pregnant women without evidence of immunity who have been

exposed. Administration of VZIG to these women has not been found to prevent viremia, fetal infection, congenital varicella

syndrome, or neonatal varicella. Thus, the primary indication for VZIG in pregnant women is to prevent complications of

varicella in the mother rather than to protect the fetus.

Neonates born to mothers who have signs and symptoms of varicella from 5

days before to 2 days after delivery should receive VZIG, regardless of whether the mother received VZIG.

Interval Between Administration of VZIG and Varicella Vaccine

Any patient who receives VZIG to prevent varicella should receive varicella vaccine
subsequently, provided the vaccine is
not contraindicated. Varicella vaccination should be delayed until 5 months after VZIG
administration. Varicella vaccine is
not needed if the patient has varicella after administration of VZIG.

Antiviral Therapy

Because VZIG might prolong the incubation period by
>1 week, any patient who receives VZIG should be observed
closely for signs or symptoms of varicella for 28 days after exposure. Antiviral therapy
should be instituted immediately if signs
or symptoms of varicella disease occur. The route and duration of antiviral therapy
should be determined by specific host
factors, extent of infection, and initial response to therapy. Information regarding how
to obtain VariZIG is available at
http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5508a5.htm
(204).

economic analysis. Jessica Leung, MPH, Division of Viral Diseases, National Center for Immunization and Respiratory Diseases, CDC, helped

with the graphs, tables, and references.

References

† In this report, efficacy refers to the extent to which a specific intervention produces a beneficial result under ideal conditions.

§ The en dash in numeric ranges is used to represent inclusive years, hours, days, ages, dosages, or a sequence of numbered items.

¶ In this report, effectiveness refers to the extent to which a specific intervention, when deployed in the field, does what it is intended to do for a

defined population.

Prenatal assessment of women for evidence of varicella

immunity is recommended. Upon completion or termination

of pregnancy, women who do not have evidence of varicella immunity should be vaccinated.

Vaccination of HIV-Infected Persons

Vaccination should be considered for HIV-infected children with age-specific CD4+ T-lymphocyte percentage

>15% and may be considered for adolescents and adults in with CD4+ T-lymphocyte count

>200 cells/μL.

Outbreak Control

All states should require that students at all grade levels

(including college) and those in child care centers

receive varicella vaccine unless they have other evidence of immunity of varicella.

Evidence of Immunity to Varicella

Evidence of immunity to varicella includes any of the

following:

* For children who received their first dose at age <13 years and for whom the interval between the 2 doses was

>28 days, the second dose is considered valid.

† Commercial assays can be used to assess disease-induced immunity, but they lack sensitivity to always detect vaccine-induced immunity (i.e., they might

yield false-negative results).

§ For health-care personnel, pregnant women, and immunocompromised persons, birth before 1980 should not be considered evidence of immunity.

¶ Verification of history or diagnosis of typical disease can be provided by any health-care provider (e.g., school or occupational clinic nurse, nurse

practitioner, physician assistant, or physician). For persons reporting a history of, or

reporting with, atypical or mild cases, assessment by a physician or their designee

is recommended, and one of the following should be sought: 1) an epidemiologic link to

a typical varicella case or to a laboratory-confirmed case or 2)

evidence of laboratory confirmation if it was performed at the time of acute disease.

When such documentation is lacking, persons should not be considered as having

a valid history of disease because other diseases might mimic mild atypical varicella.

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