Measles, Mumps, and Rubella -- Vaccine Use and Strategies for Elimination of Measles, Rubella, and Congenital Rubella Syndrome and Control of Mumps: Recommendations of the Advisory Committee on Immunization Practices (ACIP)

Recommendations and Reports

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SUMMARY

These revised recommendations of the Advisory Committee on Immunization Practices (ACIP) on measles, mumps, and rubella prevention supersede recommendations published in 1989 and 1990. This statement summarizes the goals and current strategies for measles, rubella, and congenital rubella syndrome (CRS) elimination and for mumps reduction in the United States. Changes from previous recommendations include

- Emphasis on the use of combined MMR vaccine for most indications;
- A change in the recommended age for routine vaccination to 12-15 months for the first dose of MMR, and to 4-6 years for the second dose of MMR;
- A recommendation that all states take immediate steps to implement a two dose MMR requirement for school entry and any additional measures needed to ensure that all school-aged children are vaccinated with two doses of MMR by 2001;
- A clarification of the role of serologic screening to determine immunity;
- A change in the criteria for determining acceptable evidence of rubella immunity;
- A recommendation that all persons who work in health-care facilities have acceptable evidence of measles and rubella immunity;
- Changes in the recommended interval between administration of immune globulin and measles vaccination; and
- Updated information on adverse events and contraindications, particularly for persons with severe HIV infection, persons with a history of egg allergy or gelatin allergy, persons with a history of thrombocytopenia, and persons receiving steroid therapy. INTRODUCTION

Since monovalent vaccines containing measles, rubella, and mumps vaccine viruses -- and subsequently combined measles-mumps-rubella (MMR) vaccine -- were licensed, the numbers of reported cases of measles, mumps, rubella, and congenital rubella syndrome (CRS) have decreased by more than 99%. In 1993, the Childhood Immunization Initiative established goals of eliminating indigenous transmission of measles and rubella in the United States by 1996. Subsequently, the goals of the initiative were extended to include reducing the number of reported mumps cases to less than or equal to 1600 by 1996. U.S. Public Health Service year 2000 objectives include eliminating measles, rubella, and congenital rubella syndrome, and reducing mumps incidence to less than 500 reported cases per year. Since 1995, fewer cases of measles, rubella, and mumps have been reported than at any time since nationwide disease reporting began, and elimination of indigenous transmission appears feasible. These recommendations are intended to hasten the achievement of these disease elimination goals. Measles Clinical Characteristics

The incubation period of measles (rubeola) averages 10-12 days from exposure to prodrome and 14 days from exposure to rash (range: 7-18 days). The disease can be severe and is most frequently complicated by diarrhea, middle ear infection, or bronchopneumonia. Encephalitis occurs in approximately one of every 1,000 reported cases; survivors of this complication often have permanent brain damage and mental retardation. Death occurs in 1-2 of every 1,000 reported measles cases in the United States. The risk for death from measles or its complications is greater for infants, young children, and adults than for older children and adolescents. The most common causes of death are pneumonia and acute encephalitis. In developing countries, measles is often more severe and the case-fatality rate can be as high as 25%.

Subacute sclerosing panencephalitis (SSPE) is a rare degenerative disease of the central nervous system associated with measles virus. Signs and symptoms of the disease appear years after measles infection. Widespread use of measles vaccine has essentially eliminated SSPE from the United States (1).

Measles illness during pregnancy leads to increased rates of premature labor, spontaneous abortion, and low birth weight among affected infants (2-5). Birth defects, with no definable pattern of malformation, have been reported among infants born to women infected with measles during pregnancy, but measles infection has not been confirmed as the cause of the malformations.

Measles can be severe and prolonged among immunocompromised persons, particularly those who have certain leukemias, lymphomas, or human immunodeficiency virus (HIV) infection. Among these persons, measles may occur without the typical rash and a patient may shed measles virus for several weeks after the acute illness (6,7). Measles Elimination

Before measles vaccine was licensed in 1963, an average of 400,000 measles cases were reported each year in the United States (8). However, because virtually all children acquired measles, the number of cases probably approached 3.5 million per year (i.e., an entire birth cohort).

Since measles vaccine became available, professional and voluntary medical and public health organizations have collaborated in vaccination programs that have reduced the reported incidence of measles by greater than 99%. During the late 1960s and early 1970s, the number of reported cases decreased to approximately 22,000-75,000 cases per year. Although measles incidence decreased substantially in all age groups, the greatest decrease occurred among children aged less than 10 years. A less marked decrease also occurred among older children.

During 1978, the Department of Health, Education, and Welfare (DHEW) initiated a Measles Elimination Program with the goal of eliminating indigenous measles from the United States by October 1, 1982. The three components of this program were a) maintenance of high levels of immunity with a single dose of measles vaccine, b) enhanced surveillance of disease, and c) aggressive outbreak control. As a result of this program, the number of cases reported annually decreased from 26,871 during 1978 to 1,497 during 1983. However, an average of 3,750 cases was reported each year during 1984-1988; 58% of these cases occurred among children aged greater than or equal to 10 years, most of whom had received only one dose of measles vaccine (9). Recurrent measles outbreaks among vaccinated school-aged children prompted both the Advisory Committee on Immunization Practices (ACIP) and the American Academy of Pediatrics (AAP) in 1989 to recommend that all children receive two doses of measles-containing vaccine, preferably as MMR. Although administration of the second dose was originally recommended either at entry to primary school (ACIP) or middle/ secondary school (AAP), ACIP, the AAP, and the American Academy of Family Physicians (AAFP) now recommend that a child receive the second dose before school entry, rather than delaying it until the child is aged 11-12 years.

During 1989-1991, a major resurgence of measles occurred in the United States. More than 55,000 cases and greater than 120 measles-related deaths were reported. The resurgence was characterized by an increasing proportion of cases among unvaccinated preschool-aged children, particularly those resident in urban areas (10-12).

Multiple barriers to timely vaccination of preschool-aged children were identified during investigation of the 1989-1991 measles resurgence. Efforts to increase vaccination coverage among preschool-aged children emphasized vaccination as close to the recommended age as possible. These efforts, coupled with ongoing implementation of the two-dose MMR recommendation, reduced reported measles cases from 2,237 in 1992 to 312 in 1993 (9). Although 963 measles cases were reported in 1994, measles incidence again declined in 1995, when 309 cases were reported (13). In 1996, 508 cases were reported, of which 65 were classified as international importations (14).

In 1993, the Childhood Immunization Initiative called for the elimination from the United States by 1996 of indigenous transmission of six childhood diseases, including rubella, congenital rubella syndrome (CRS), and measles (10). In September 1994, the Pan American Health Organization (PAHO) adopted a similar goal of eliminating measles throughout the Americas by 2000 (15). Both epidemiologic and laboratory evidence suggest that the transmission of indigenous measles was interrupted in the United States for the first time during 1993 (16,17).

However, even after indigenous measles transmission has been eliminated, measles cases caused by the importation of the virus from other countries will continue to occur. Sustaining measles elimination will require continuing efforts. Enhanced surveillance for measles must be maintained and disease control activities must be undertaken immediately when suspected cases of measles are reported. The major challenges to sustaining the elimination of measles from the United States are a) continuing to vaccinate all children aged 12-15 months with a first dose of MMR, b) ensuring that all school-aged children receive a second dose of MMR vaccine, and c) working with other countries to set and achieve national measles elimination goals. Rubella And Congenital Rubella Syndrome (CRS) Clinical Characteristics

Rubella is an exanthematous illness characterized by nonspecific signs and symptoms including transient erythematous and sometimes pruritic rash, postauricular or suboccipital lymphadenopathy, arthralgia, and low-grade fever. Clinically similar exanthematous illnesses are caused by parvovirus, adenoviruses, and enteroviruses. Moreover, 25%-50% of rubella infections are subclinical. The incubation period ranges from 12 to 23 days. Before rubella vaccine was available, the disease was common among children and young adults.

Among adults infected with rubella, transient polyarthralgia or polyarthritis occur frequently. These manifestations are particularly common among women (18). Central nervous system complications (i.e., encephalitis) occur at a ratio of 1 per 6,000 cases and are more likely to affect adults. Thrombocytopenia occurs at a ratio of 1 per 3,000 cases and is more likely to affect children.

The most important consequences of rubella are the miscarriages, stillbirths, fetal anomalies, and therapeutic abortions that result when rubella infection occurs during early pregnancy, especially during the first trimester. An estimated 20,000 cases of CRS occurred during 1964-1965 during the last U.S. rubella epidemic before rubella vaccine became available.

The anomalies most commonly associated with CRS are auditory (e.g., sensorineural deafness), ophthalmic (e.g., cataracts, microphthalmia, glaucoma, chorioretinitis), cardiac (e.g., patent ductus arteriosus, peripheral pulmonary artery stenosis, atrial or ventricular septal defects), and neurologic (e.g., microcephaly, meningoencephalitis, mental retardation). In addition, infants with CRS frequently exhibit both intrauterine and postnatal growth retardation. Other conditions sometimes observed among patients who have CRS include radiolucent bone defects, hepatosplenomegaly, thrombocytopenia, and purpuric skin lesions.

Infants who are moderately or severely affected by CRS are readily recognizable at birth, but mild CRS (e.g., slight cardiac involvement or deafness) may be detected months or years after birth, or not at all. Although CRS has been estimated to occur among 20%-25% of infants born to women who acquire rubella during the first 20 weeks of pregnancy, this figure may underestimate the risk for fetal infection and birth defects. When infants born to mothers who were infected during the first 8 weeks of gestation were followed for 4 years, 85% were found to be affected (19). The risk for any defect decreases to approximately 52% for infections that occur during the ninth to twelfth weeks of gestation. Infection after the twentieth week of gestation rarely causes defects. Inapparent (subclinical) maternal rubella infection can also cause congenital malformations. Fetal infection without clinical signs of CRS can occur during any stage of pregnancy. Rubella Elimination

Before rubella vaccine was licensed during 1969, rubella incidence was greatest among preschool and elementary school children. Therefore, vaccination campaigns initially targeted children in kindergarten and the early grades of elementary school, with the aim of interrupting circulation of the virus and eliminating the risk for exposure among susceptible pregnant women. The risks associated with administering a potentially teratogenic live virus vaccine to young women of childbearing age were not known. During 1969-1976, reported rubella cases decreased from 57,600 to 12,400. However, during 1975-1977, 62% of reported rubella cases occurred among persons aged greater than 15 years compared with 23% of cases occurring during 1966-1968, and serologic studies suggested that 10%-15% of adults remained susceptible to rubella (20).

The number of CRS cases reported nationwide decreased by 69% from 69 in 1970 to 22 in 1976. Rubella outbreaks continued to occur among older adolescents and young adults (e.g, in military camps, high schools, colleges, and universities). In 1977, ACIP modified its recommendations to include the vaccination of susceptible postpubertal girls and women. During the same year, the DHEW undertook the National Childhood Immunization Initiative, which sought to immunize greater than 90% of the nation's children against all vaccine-preventable diseases. Enforcement of requirements for vaccination before school entry was part of the initiative. The number of reported rubella and CRS cases decreased after these programs were implemented, from 20,395 rubella cases and 29 CRS cases in 1977 to 752 rubella cases and 2 CRS cases in 1984. In 1988, 225 cases of rubella were reported in the United States, the fewest since national reporting began.

However, because of outbreaks among unvaccinated adults (e.g., in prisons, colleges, and workplaces), greater than 1000 rubella cases were reported in 1990 and again in 1991. The largest outbreak and the greatest number of CRS cases occurred among children and adults in religious communities that do not accept vaccination. Since 1992, reported indigenous rubella and CRS have continued to occur at a low but relatively constant endemic level with an annual average of less than 200 rubella cases (128 cases in 1995 and 213 cases in 1996). Four confirmed CRS cases occurred in 1995 and 2 in 1996. However, in the United States, surveillance for CRS relies on a passive system. Consequently, the reported annual totals of CRS are regarded as minimum figures, representing an estimated 40%-70% of all cases (21,22).

During 1992-1997, 65% of reported cases of rubella occurred among persons aged greater than or equal to 20 years. In addition, recent evidence suggests that the risk for both rubella and CRS is increased among persons of Hispanic ethnicity, particularly those born outside the United States. Outbreaks of rubella in California (1990-1991), Massachusetts (1993-1994), Connecticut (1995), and North Carolina (1996 and 1997) have occurred primarily among persons of Hispanic origin. During 1985-1995, the ethnicity of a total of 89 children with laboratory-confirmed or clinically compatible cases of CRS was known; 35 (39%) were of Hispanic origin (23-27).

Recent data indicate that the rate of rubella susceptibility and risk for rubella infection are highest among young adults. During 1992-94, approximately 8% of persons aged 15-29 years were estimated to lack serologic evidence of immunity to rubella (CDC, unpublished data). Data from two recent studies indicate that vaccine-induced rubella antibody levels among adolescents may have decreased during the 9-14 years that had elapsed since they were initially vaccinated. However, recent rubella surveillance data do not indicate that rubella and CRS are increasing among vaccinated persons (28) (CDC, unpublished data).

The primary objective of the rubella immunization program is the prevention of CRS. The major components of the rubella and CRS elimination strategy are achieving and maintaining high immunization levels for children and adults, especially women of childbearing age; conducting accurate surveillance for rubella and CRS; and undertaking control measures promptly when a rubella outbreak occurs. Since the late 1970s, this strategy has effectively prevented major epidemics of rubella and CRS in the United States. Mumps Clinical Characteristics

Persons in whom "classical" mumps develops have bilateral or (less commonly) unilateral parotitis, with onset an average of 16-18 days after exposure. Parotitis may be preceded by fever, headache, malaise, myalgia, and anorexia. Only 30%-40% of mumps infections produce typical acute parotitis; 15%-20% of infections are asymptomatic and up to 50% of infections are associated with nonspecific or primarily respiratory symptoms (29,30). Inapparent infection may be more common among adults than children; parotitis occurs more commonly among children aged 2-9 years (30,31). Serious complications of mumps infection can occur without evidence of parotitis (29,32,33).

Most serious complications of mumps are more common among adults than among children (29,34). Although orchitis may occur among up to 38% of postpubertal men in whom mumps develops, sterility is thought to occur only rarely (35).

Aseptic meningitis affects 4%-6% of persons with clinical cases of mumps and typically is mild (29,36-38). However, mumps meningoencephalitis can cause permanent sequelae, including paralysis, seizures, cranial nerve palsies, aqueductal stenosis, and hydrocephalus (39-41). In the prevaccine era, mumps was a major cause of sensorineural deafness among children. Deafness may be sudden in onset, bilateral, and permanent (42-44).

Among women in whom mumps develops during the first trimester of pregnancy, an increased risk for fetal death has been observed (45). However, mumps infection during pregnancy is not associated with congenital malformations (46). Mumps Control

In the United States, the reported incidence of mumps decreased steadily after the introduction of live mumps vaccine in 1967 and the recommendation for its routine use in 1977. In 1995, 906 cases were reported, representing a 99% decrease from the 185,691 cases reported in 1968. The enactment and enforcement of state vaccination laws requiring that students be vaccinated before school entry has contributed more to reducing mumps incidence than any other measure (47). During the 1980s and early 1990s, mumps incidence was lowest in states where comprehensive vaccination laws were enforced. States where vaccination laws were less comprehensive reported intermediate mumps incidence, and the highest incidence was reported in states did not have such laws (47-51).

Mumps incidence is now very low in all areas of the United States. The substantial reduction in mumps incidence during the past few years may reflect the change in the recommendations for use of MMR vaccine. The implementation of the two-dose MMR vaccination schedule likely decreased mumps incidence further by immunizing children among whom the first dose of mumps antigen did not elicit an immune response (52,53). The principal strategy to prevent mumps is to achieve and maintain high immunization levels by routinely vaccinating all children with two doses of MMR. VACCINE PREPARATIONS

Measles, rubella, and mumps vaccines are available in monovalent measles (Attenuvax , Merck & Co., Inc.), rubella (Meruvax , Merck & Co., Inc.), or mumps (Mumpsvax , Merck & Co., Inc.) form and in combinations: measles-mumps-rubella (MMR) (M-M-R II , Merck & Co., Inc.), measles-rubella (MR) (M-R-Vax , Merck & Co., Inc.), and rubella-mumps (Biavax II , Merck & Co., Inc.) vaccines. Each dose of the combined or monovalent vaccines contains approximately 0.3 milligrams of human albumin, 25 micrograms of neomycin, 14.5 milligrams of sorbitol, and 14.5 milligrams of hydrolyzed gelatin (Merck & Co., Inc., manufacturer's package insert). Live measles vaccine and live mumps vaccine are produced in chick embryo cell culture. Live rubella vaccine is grown in human diploid cell culture. Measles Component

Since 1963, when both inactivated and live attenuated (Edmonston B strain) vaccines were licensed, the type of measles vaccine used in the United States has changed several times. Distribution of the inactivated and live Edmonston B vaccines ceased after 1967 and 1975, respectively. Distribution in the United States of a live, further attenuated vaccine (Schwarz strain) first introduced in 1965 has also ceased. A live, further attenuated preparation of the Enders-Edmonston virus strain that is grown in chick embryo fibroblast cell culture, licensed in 1968, is the only measles virus vaccine now available in the United States. This further attenuated vaccine (formerly called "Moraten") causes fewer adverse reactions than the Edmonston B vaccine.

Measles vaccine produces an inapparent or mild, noncommunicable infection. Measles antibodies develop among approximately 95% of children vaccinated at age 12 months and 98% of children vaccinated at age 15 months (CDC, unpublished data). Studies indicate that, if the first dose is administered no earlier than the first birthday, greater than 99% of persons who receive two doses of measles vaccine develop serologic evidence of measles immunity (54)(CDC, unpublished data). Although vaccination produces lower antibody levels than natural disease, both serologic and epidemiologic evidence indicate that the vaccine induces long-term -- probably lifelong -- immunity, in most persons (55). Most vaccinated persons who appear to lose antibody show an anamnestic immune response upon revaccination, indicating that they are probably still immune (56). Although revaccination elicits increased antibody levels in some persons, these increased levels may not be sustained (57). Findings of some studies indicate that immunity can wane after successful vaccination (secondary vaccine failure), but this phenomenon appears to occur rarely and to have little effect on measles transmission and the occurrence of outbreaks (55,58,59). Rubella Component

The live rubella virus vaccine currently distributed in the United States is prepared in human diploid cell culture. This vaccine, containing virus strain RA 27/3, was licensed in the United States in January, 1979 and replaced previous rubella vaccines (e.g., HPV-77 and Cendehill) because it induced an increased and more persistent antibody response and was associated with fewer adverse events.

In clinical trials, greater than or equal to 95% of susceptible persons aged greater than or equal to 12 months who received a single dose of strain RA 27/3 rubella vaccine developed serologic evidence of immunity (60-62). Clinical efficacy and challenge studies indicate that greater than 90% of vaccinated persons have protection against both clinical rubella and viremia for at least 15 years (63-66). Follow-up studies indicate that one dose of vaccine confers long-term -- probably lifelong -- protection (67). Although antibody titers induced by the vaccine are generally lower than those stimulated by rubella infection, vaccine-induced immunity protects, in nearly all instances, against both clinical illness and viremia after natural exposure (68,69). In studies that attempted artificial reinfection of persons who received RA 27/3 vaccine, resistance to reinfection was similar to the resistance that follows natural infection (70). However, several reports indicate that viremic reinfection following exposure may occur among vaccinated persons who have low levels of detectable antibody (64). The frequency and consequences of this phenomenon are unknown but it is believed to be uncommon. Clinical reinfection and fetal infection among persons who developed immunity as a consequence of infection with wild virus have been documented, but are apparently rare (71). Rarely, clinical reinfection and fetal infection have been reported among women with vaccine-induced immunity. Rare cases of CRS have occurred among infants born to mothers who had documented serologic evidence of rubella immunity before they became pregnant. Mumps Component

The only mumps vaccine now available in the United States is a live virus vaccine (Jeryl-Lynn strain) that is prepared in chick-embryo cell culture. The vaccine produces a subclinical, noncommunicable infection with very few side effects.

More than 97% of persons who are susceptible to mumps develop measurable antibody following vaccination and, in controlled clinical trials, one dose of vaccine was approximately 95% efficacious in preventing mumps disease (72-74). However, field studies have documented lower estimates of vaccine efficacy, ranging from 75% to 95% (47,75). Antibody levels induced by the vaccine are lower than antibody levels resulting from natural infection (72,76,77). The duration of vaccine-induced immunity is unknown, but serologic and epidemiologic data collected during 30 years of live vaccine use indicate both the persistence of antibody and continuing protection against infection (33,78,79). Vaccine Shipment and Storage

Administration of improperly stored vaccine may fail to provide protection against disease from measles, rubella, and/or mumps. These live virus vaccines are supplied in lyophilized form and should be stored at 2-8 C (35.6-46.4 F) or colder. They must be shipped at 10 C (50 F) or colder and may be shipped on dry ice. The vaccines must be protected from light, which may inactivate the vaccine viruses. Reconstituted vaccine also must be protected from light, must be stored at 2-8 C (35.6-46.4 F), and must not be frozen. Reconstituted vaccine must be discarded if not used within 8 hours. VACCINE USAGE

Two doses of MMR vaccine separated by at least 1 month (i.e., a minimum of 28 days) and administered on or after the first birthday are recommended for all children and for certain high-risk groups of adolescents and adults. The recommended 1 month interval between successive doses of MMR or other measles-containing vaccine is based on the principle that live virus vaccines not administered at the same time should be separated by at least 1 month (80).

MMR is the vaccine of choice when protection against any of these three diseases is required on or after the first birthday, unless any of its component vaccines is contraindicated. The purpose of the two-dose vaccination schedule is to produce immunity in the small proportion of persons who fail to respond immunologically to one or more of the components of the first dose. Studies indicate that two doses of measles vaccine are necessary to develop adequate population immunity to prevent measles outbreaks among school-aged and older persons. Mumps can occur in highly vaccinated populations; in these outbreaks, substantial numbers of cases have occurred among persons who had previously received a single dose of mumps-containing vaccine (33,81). Although primary rubella vaccine failure rarely occurs, the potential consequences of failure (i.e., CRS) are substantial.

Almost all persons who do not respond to the measles component of the first dose of MMR vaccine will respond to the second dose (82) (CDC, unpublished data). Few data regarding the immune response to the rubella and mumps components of a second dose of MMR vaccine are available, but most persons who do not respond to the rubella or mumps components of the first dose would be expected to respond to the second (82-84) (CDC, unpublished data). The second dose is not generally considered a booster dose because a primary immune response to the first dose provides long-term protection. Although some persons who develop normal antibody titers in response to a single dose of MMR vaccine will develop higher antibody titers to the three component vaccines when administered a second dose of vaccine, these increased antibody levels typically do not persist (57).

Use of combined MMR vaccine for both measles doses and all other indications should provide an additional safeguard against primary vaccine failures and facilitate elimination of rubella and CRS and continued reduction of mumps incidence. Data also indicate that the favorable benefit/cost ratio for routine measles, rubella, and mumps vaccination is even greater when the vaccines are administered as combined MMR vaccine (85,86). Dosage and Route of Administration

The lyophilized live MMR vaccine (and its component vaccines) should be reconstituted and administered as recommended by the manufacturer. All measles-, rubella-, or mumps-containing vaccines available in the United States should be administered subcutaneously in the recommended standard single-dose volume of 0.5 mL. Simultaneous Administration of Vaccines

In general, simultaneous administration of the most widely used live and inactivated vaccines does not impair antibody responses or increase rates of adverse reactions (80). The antibody responses of persons vaccinated with MMR are similar to those of persons vaccinated with single-antigen measles, mumps, and rubella vaccines at different sites or at different times.

ACIP encourages routine simultaneous administration of MMR, diphtheria and tetanus toxoids and acellular pertussis (DTaP) or diphtheria and tetanus toxoids and whole-cell pertussis (DTP) vaccine, Haemophilus influenzae type b (Hib) vaccine, and oral poliovirus vaccine (OPV) or inactivated poliovirus vaccine (IPV) to children who are at the recommended age to receive these vaccines. Antibody responses were equivalent and no clinically significant increases in the frequency of adverse events occurred when MMR vaccine, DTaP (or DTP), Hib vaccine, hepatitis B vaccine, and IPV or OPV were administered either simultaneously at different sites or at separate times (87). Likewise, seroconversion rates, antibody levels, and frequencies of adverse reactions were similar in two groups, one of which was administered MMR and varicella vaccines simultaneously at separate sites and the other of which received the vaccines 6 weeks apart (88)(Merck Research Laboratories, unpublished data).

Live measles and yellow fever vaccines can be administered simultaneously at separate anatomical sites in separate syringes (89). Limited data also indicate that the immunogenicity and safety of inactivated Japanese encephalitis vaccine are not compromised by simultaneous administration with live measles vaccine (90). Limited data exist concerning concurrent administration of MMR vaccine and other vaccines that are often recommended for international travelers (e.g., meningococcal vaccine, typhoid vaccines). However, neither theoretical considerations nor practical experience indicate that the simultaneous administration at separate anatomic sites of MMR and other live or inactivated vaccines will produce a diminished immune response or increase the incidence of adverse events among vaccinated persons.
DOCUMENTATION OF IMMUNITY

Only doses of vaccine 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 documentation. No health-care worker should provide a vaccination record for a patient unless that health-care worker has administered the vaccine or has seen a record that documents vaccination. Persons who may be immune to measles, mumps, or rubella but who lack either adequate documentation of vaccination or other acceptable evidence of immunity (Table_1) should be vaccinated. Vaccination status and date of administration of all vaccinations should be documented in the patient's permanent medical record.

Serologic screening for measles, rubella, or mumps immunity generally is neither necessary nor recommended if a person has other acceptable evidence of immunity to the disease (Table_1). Serologic screening can be a barrier to vaccination. With the exception of women who are known to be pregnant (see Women of Childbearing Age), persons who lack acceptable evidence of immunity generally should be vaccinated without serologic testing. Serologic screening is appropriate only when persons identified as susceptible are subsequently vaccinated in a timely manner. Screening is most applicable when the return and vaccination of those tested can be ensured (e.g., hiring of new health-care workers). If these conditions are not met, serologic screening is inappropriate (91). Likewise, during an outbreak of measles, rubella, or mumps, serologic screening before vaccination generally is not recommended because waiting for results, contacting, and then vaccinating persons identified as susceptible can impede the rapid vaccination needed to curb the outbreak.

Serologic screening for antibodies to measles, rubella, or mumps alone will not identify persons who are susceptible to the other diseases for which screening is not done. Post-vaccination serologic testing to verify an immune response to MMR or its component vaccines is not recommended.

The criteria for acceptable evidence of immunity to measles, rubella, and mumps (Table_1) provide presumptive rather than absolute evidence of immunity. Occasionally, a person who meets the criteria for presumptive immunity can contract and transmit disease. Specific criteria for documentation of immunity have been established for certain persons (e.g., health-care workers, international travelers, and students at post-high school educational institutions) who are at increased risk for exposure to measles, rubella, and mumps (Table_1). Criteria accepted as evidence of immunity for the purpose of meeting school or college entry requirements or other government regulations may vary among state and local jurisdictions. Measles

Persons generally can be presumed immune to measles (Table_1) if they have documentation of adequate vaccination, laboratory evidence of immunity to measles, documentation of physician-diagnosed measles, or were born before 1957. Criteria for adequate vaccination currently vary depending on state and local vaccination policy because of differences in the way states have implemented the two-dose measles vaccination schedule. All states are strongly encouraged to take immediate steps to implement the two-dose MMR vaccination schedule so that, by 2001, adequate vaccination of children will be defined in all 50 states as follows:

- For preschool-aged children: documentation of at least one dose of MMR vaccine administered on or after the first birthday.
- For children in kindergarten through grade 12: documentation of two doses of MMR vaccine separated by at least 28 days (i.e., 1 month), with the first dose administered no earlier than the first birthday.

Doses of MMR and other measles-containing vaccines administered before the first birthday should not be counted when determining adequacy of measles vaccination.

When measles virus is introduced into a community, persons who work in health-care facilities are at greater risk for acquiring measles than the general population (92). Because persons working in medical settings have been infected with and have transmitted measles to patients and coworkers, rigorous criteria for immunity among health-care workers have been established. For persons born during or after 1957 who work in health-care facilities, adequate vaccination consists of two doses of MMR or other live measles-containing vaccine separated by at least 28 days, with the first dose administered no earlier than the first birthday (Table_1). In addition, although birth before 1957 is generally considered acceptable evidence of measles immunity (Table 1), measles has occurred in some unvaccinated persons born before 1957 who worked in health-care facilities. Therefore, health-care facilities should consider recommending a dose of MMR vaccine for unvaccinated workers born before 1957 who lack a history of measles disease or laboratory evidence of measles immunity (see Health-Care Facilities).

The previously described criteria apply only to routine vaccination. During measles outbreaks, evidence of adequate vaccination for school-aged children, adolescents, and adults born during or after 1957 who are at risk for measles exposure and infection consists of two doses of measles-containing vaccine separated by at least 28 days, with the first dose administered no earlier than the first birthday (see Measles Outbreak Control). During outbreaks involving preschool-aged children, authorities should consider extending this criterion to all children aged greater than or equal to 12 months.

In the past, the most commonly used laboratory test for assessing immunity to measles was the hemagglutination-inhibition (HI) test but more sensitive assays (e.g., the enzyme immunoassay {EIA} or enzyme-linked immunosorbent assay {ELISA}) are now used in most laboratories. Persons who have measles-specific antibody that is detectable by any serologic test are considered immune. Persons with an "equivocal" test result should be considered susceptible unless they have other evidence of measles immunity (Table_1) or subsequent testing indicates they are immune. All new cases of suspected measles should be confirmed by laboratory testing (see Measles Case Investigation Laboratory Diagnosis). Rubella

Persons generally can be presumed immune to rubella (Table 1) if they have documentation of vaccination with at least one dose of MMR or other live rubella-containing vaccine administered on or after the first birthday, laboratory evidence of rubella immunity, or were born before 1957 (except women who could become pregnant). Birth before 1957 is not acceptable evidence of rubella immunity for women who could become pregnant because it provides only presumptive evidence of rubella immunity and does not guarantee that a person is immune (see Women of Childbearing Age). Rubella can occur among some unvaccinated persons born before 1957 and congenital rubella and CRS can occur among the offspring of women infected with rubella during pregnancy.

Persons who have an "equivocal" serologic test result should be considered susceptible to rubella unless they have evidence of adequate vaccination or a subsequent serologic test result indicates rubella immunity. Although only one dose of rubella-containing vaccine is required as acceptable evidence of immunity to rubella, children should receive two doses of MMR vaccine. The first dose is administered routinely when the child is aged 12-15 months and the second before the child enters school (i.e., at age 4-6 years)(see Routine Vaccination).

The clinical diagnosis of rubella is unreliable and should not be considered in assessing immune status. Because many rash illnesses may mimic rubella infection and many rubella infections are unrecognized, the only reliable evidence of previous rubella infection is the presence of serum rubella immunoglobulin G (IgG). Laboratories that regularly perform antibody testing generally provide the most reliable results because their reagents and procedures are more likely to be strictly standardized (see Rubella Case Investigation and Outbreak Control).

Postinfection immunity to rubella appears to be long-lasting and is probably lifelong. However, as with other viral diseases, re-exposure to natural rubella occasionally leads to reinfection without clinical illness or detectable viremia. The risk for CRS among infants born to women reinfected with rubella during pregnancy is minimal (93,94). Although data from several studies indicate that levels of vaccine-induced rubella antibodies may decline with time, data from surveillance of rubella and CRS suggest that waning immunity with increased susceptibility to rubella disease does not occur (28)(CDC, unpublished data).

HI antibody testing was formerly the method most frequently used to screen for rubella antibodies. However, the HI test has been supplanted by other assays of equal or greater sensitivity. EIAs are the most commonly used of these newer commercial assays, but latex agglutination, immunofluorescence assay (IFA), passive hemagglutination, hemolysis-in-gel, and virus neutralization tests are also available.

Any antibody level above the standard positive cutoff value of the assay with which it is measured can be considered evidence of immunity, if the assay is licensed. When serum specimens from adults who did not produce antibodies detectable by HI after vaccination were examined with an equivalently specific but more sensitive test, almost all had detectable antibody (95,96). A few children who initially developed antibody detectable by HI apparently "lost" this antibody during follow-up intervals of up to 16 years (77,97,98). However, almost all had antibody detectable by more sensitive tests. In several of these cases, immunity was confirmed by documenting a booster response (i.e., absence of IgM antibody and a rapid rise in IgG antibody) after revaccination (62,99).

Occasionally, persons with documented histories of rubella vaccination have rubella serum IgG levels that are not clearly positive by ELISA. Such persons can be administered a dose of MMR vaccine and need not be retested for serologic evidence of rubella immunity. Mumps

Persons generally can be presumed immune to mumps (Table_1) if they have documentation of vaccination with live mumps virus vaccine on or after the first birthday, laboratory evidence of mumps immunity, documentation of physician-diagnosed mumps, or were born before 1957.

The demonstration of mumps IgG antibody by any commonly used serologic assay is acceptable evidence of mumps immunity. Persons who have an "equivocal" serologic test result should be considered susceptible to mumps unless they have other evidence of mumps immunity (Table_1) or subsequent testing indicates they are immune. All new cases of suspected mumps should be confirmed by an appropriate serologic assay (see Mumps Case Investigation, Laboratory Diagnosis).

Live mumps vaccine was not used routinely before 1977. Before the vaccine was introduced, the age-specific incidence of the disease peaked among children aged 5-9 years. Therefore, most persons born before 1957 are likely to have been infected naturally between 1957 and 1977 and may be presumed immune, even if they have not had clinically recognizable mumps disease. However, birth before 1957 does not guarantee mumps immunity. Therefore, during mumps outbreaks, MMR vaccination should be considered for persons born before 1957 who may be exposed to mumps and who may be susceptible. Laboratory testing for mumps susceptibility before

vaccination is not necessary. ROUTINE VACCINATION Preschool-Aged Children

Children should receive the first dose of MMR vaccine at age 12-15 months (i.e., on or after the first birthday). In areas where risk for measles is high, initial vaccination with MMR vaccine is recommended for all children as soon as possible upon reaching the first birthday (i.e., at age 12 months). An area where measles risk is high is defined as:

- a county with a large inner city population,
- a county where a recent measles outbreak has occurred among unvaccinated preschool-aged children, or
- a county in which more than five cases of measles have occurred among preschool-aged children during each of the last 5 years.

These recommendations may be implemented for an entire county or only within defined areas of a county. This strategy assumes that the benefit of preventing measles cases among children aged 12-15 months outweighs the slightly reduced efficacy of the vaccine when administered to children aged less than 15 months. In addition, almost all children who do not respond immunologically to the first dose of MMR vaccine will develop measles immunity after receiving a second dose. HIV-infected children should receive MMR vaccine at age 12 months, if not otherwise contraindicated (see Special Considerations for Vaccination -- Persons Infected with Human Immunodeficiency Virus (HIV)). School-Aged Children and Adolescents

The second dose of MMR vaccine is recommended when children are aged 4-6 years (i.e., before a child enters kindergarten or first grade). This recommended timing for the second dose of MMR vaccine has been adopted jointly by ACIP, the American Academy of Pediatrics (AAP), and the American Academy of Family Physicians (AAFP). Evidence now indicates that a) the major benefit of administering the second dose is a reduction in the proportion of persons who remain susceptible because of primary vaccine failure, b) waning immunity is not a major cause of vaccine failure and has little influence on measles transmission, and c) revaccination of children who have low levels of measles antibody produces only a transient rise in antibody levels (55,57-59,100,101).

Because approximately 5% of children who receive only one dose of MMR vaccine fail to develop immunity to measles, ACIP recommends that all states implement a requirement that all children entering school have received two doses of MMR vaccine (with the first dose administered no earlier than the first birthday) or have other evidence of immunity to measles, rubella, and mumps (see Documentation of Immunity). In addition, to achieve complete immunization of all school-aged children and hasten progress toward measles elimination, states are strongly encouraged to take immediate steps to ensure that, by 2001, all children in grades kindergarten through 12 have received two doses of MMR vaccine.

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 should serve as an opportunity to evaluate vaccination status and administer MMR vaccine to all persons who have not received two doses at the recommended ages.

Children who do not have documentation of adequate vaccination against measles, rubella, and mumps or other acceptable evidence of immunity to these diseases (see Documentation of Immunity) should be admitted to school only after administration of the first dose of MMR vaccine. If required, the second MMR dose should be administered as soon as possible, but no sooner than 28 days after the first dose. Children who have already received two doses of MMR vaccine at least 1 month apart, with the first dose administered no earlier than the first birthday, do not need an additional dose when they enter school. Adults

Persons born in 1957 or later who are aged greater than or equal to 18 years and who do not have a medical contraindication should receive at least one dose of MMR vaccine unless they have

a. documentation of vaccination with at least one dose of measles-, rubella-, and mumps-containing vaccine or b) other acceptable evidence of immunity to these three diseases (Table_1). Persons born before 1957 generally can be considered immune to measles and mumps. In addition, persons born before 1957, except women who could become pregnant, generally can be considered immune to rubella.

MMR vaccine (one dose or two doses administered at least 28 days apart) may be administered to any person born before 1957 for whom the vaccine is not contraindicated. Adults who may be at increased risk for exposure to and transmission of measles, mumps, and rubella should receive special consideration for vaccination. These persons include international travelers, persons attending colleges and other post-high school educational institutions, and persons who work at health-care facilities. In addition, all women of childbearing age should be considered susceptible to rubella unless they have received at least one dose of MMR or other live rubella virus vaccine on or after the first birthday or have serologic evidence of immunity. Vaccination recommendations for these high-risk groups follow. Women of Childbearing Age

MMR vaccine should be offered to all women of childbearing age (i.e., adolescent girls and premenopausal adult women) who do not have acceptable evidence of rubella immunity whenever they make contact with the health-care system. Opportunities to vaccinate susceptible women include occasions when their children undergo routine examinations or vaccinations. The continuing occurrence of rubella among women of childbearing age indicates the need to continue vaccination of susceptible adolescent and adult women of childbearing age, and the absence of evidence of vaccine teratogenicity indicates that the practice is safe (102). Vaccination of susceptible women of childbearing age should

- be part of routine general medical and gynecologic outpatient care;
- take place in all family-planning settings; and
- be provided routinely before discharge from any hospital, birthing center, or other medical facility, unless a specific contraindication exists (see Precautions and Contraindications).

Outbreaks of rubella in the United States recently have occurred among women of Hispanic ethnicity, many of whom were born outside the fifty states. Efforts should be made to ensure that all susceptible women of childbearing age, especially those who grew up outside the fifty states in areas where routine rubella vaccination may not occur, are vaccinated with MMR vaccine or have other acceptable evidence of immunity (Table_1). Ascertainment of rubella-immune status of women of childbearing age and the availability of rubella vaccination should be components of the health-care program in places where the risks for disease exposure and transmission are substantial (e.g., day care facilities, schools, colleges, jails, and prisons).

No evidence indicates that administration of rubella-containing vaccine virus to a pregnant woman presents a risk for her fetus, although such a risk cannot be excluded on theoretical grounds. Therefore, women of childbearing age should receive rubella-containing vaccines (i.e., rubella, MR, or MMR vaccine) only if they state that they are not pregnant and only if they are counseled not to become pregnant for 3 months after vaccination. Because of the importance of protecting women of childbearing age against rubella, reasonable practices in any immunization program include a) asking women if they are pregnant, b) not vaccinating women who state that they are pregnant, c) explaining the potential risk for the fetus to women who state that they are not pregnant, and d) counseling women who are vaccinated not to become pregnant during the 3 months following MMR vaccination. Routine Vaccination of Women Who Are Not Pregnant. Women of childbearing age who do not have documentation of rubella vaccination or serologic evidence of rubella immunity should be vaccinated with MMR, if they have no contraindications to the vaccine. Birth before 1957 is not acceptable evidence of immunity for women who could become pregnant (Table_1). The use of MMR vaccine provides the potential additional benefit of protection against measles and mumps. Serologic testing before vaccination is not necessary and might present a barrier to timely vaccination. Routine testing for rubella antibody during clinic visits for routine health care, premarital evaluation, family planning, or diagnosis and treatment of sexually transmitted diseases may identify women who are not immune to rubella before they become pregnant. Such routine serologic testing is not useful unless it is linked to timely follow-up and vaccination of women who are susceptible (103). Prenatal Screening and Postpartum Vaccination. Prenatal serologic screening of women who have acceptable evidence of rubella immunity is generally not necessary, but is indicated for all pregnant women who lack acceptable evidence of rubella immunity (Table_1). Upon completion or termination of their pregnancies, women who do not have serologic evidence of rubella immunity or documentation of rubella vaccination should be vaccinated with MMR before discharge from the hospital, birthing center, or abortion clinic (104). They should be counseled to avoid conception for 3 months after vaccination. Postpartum rubella vaccination of all women not known to be immune could prevent up to half of CRS cases (105-108) (CDC, unpublished data). Colleges and Other Post-High School Educational Institutions

Risks for transmission of measles, rubella, and mumps at post-high school educational institutions can be high because these institutions may bring together large concentrations of persons susceptible to these diseases (109-113). Therefore, colleges, universities, technical and vocational schools, and other institutions for post-high school education should require that all undergraduate and graduate students have received two doses of MMR vaccine or have other acceptable evidence of measles, rubella, and mumps immunity (Table_1) before enrollment.

College entry requirements for measles immunity substantially reduce the risk for measles outbreaks on college campuses where they are implemented and enforced (111). State requirements for pre-enrollment vaccination ensure the best protection against widespread measles transmission among students at college campuses and other post-high school educational institutions. States are strongly encouraged to adopt such regulations. Students who do not have documentation of live measles, rubella, or mumps vaccination or other acceptable evidence of immunity at the time of enrollment (Table_1) should be admitted to classes only after receiving the first dose of MMR vaccine. These students should be administered a second dose of MMR vaccine 1 month (i.e., at least 28 days) later. Students who have documentation of

having received only one dose of measles-containing vaccine on or after the first birthday should receive a second dose of MMR before enrollment, provided at least 1 month has elapsed since the previous dose. Students who have a medical contraindication to receiving any of the components of MMR vaccine should be given a letter of explanation to present to the health officials of their educational institution. Health-Care Facilities

When measles virus is introduced into a community, persons who work in health-care facilities are at increased risk for acquiring measles compared with the general population (92,114,115). During 1985-1991, at least 795 measles cases (1.1% of all reported cases) occurred among adult health-care workers. Of these, 29% occurred among nurses, 15% among physicians, 11% among persons in other health-care occupations (e.g., laboratory and radiology technicians, etc.), 11% among clerks, 4% among nursing assistants, and 4% among medical and nursing students (115) (CDC, unpublished data). A general decline in measles incidence occurred after 1991. However, 15 of the 75 measles outbreaks reported during 1993-1996 involved transmission in a medical facility, and a total of 36 measles cases (1.8% of all reported cases) occurred among persons working in health-care facilities (CDC, unpublished data). Although similar surveillance data are not available for rubella, outbreaks have occurred in health-care settings, and health-care workers have transmitted rubella to patients (116) (CDC, unpublished data).

All persons who work in health-care facilities should be immune to measles and rubella (Table_1). Because any health-care worker (i.e., medical or nonmedical, paid or volunteer, full- or part-time, student or nonstudent, with or without patient-care responsibilities) who is not immune to measles and rubella can contract and transmit these diseases, all health-care facilities (i.e., inpatient and outpatient, private and public) should ensure that those who work in their facilities are immune to measles and rubella (Table_1) *.

Health-care workers have a responsibility to avoid transmitting these diseases and thereby causing harm to patients. Adequate vaccination for health-care workers born during or after 1957 consists of two doses of a live measles-containing vaccine and at least one dose of a live rubella-containing vaccine (Table_1). Health-care workers who need a second dose of measles-containing vaccine should be revaccinated 1 month (at least 28 days) after their first dose.

Although birth before 1957 is generally considered acceptable evidence of measles and rubella immunity (Table_1), health-care facilities should consider recommending a dose of MMR vaccine to unvaccinated workers born before 1957 who do not have a history of physician-diagnosed measles or laboratory evidence of measles immunity AND laboratory evidence of rubella immunity.

Rubella vaccination or laboratory evidence of rubella immunity is particularly important for female health-care workers who could become pregnant, including those born before 1957. In addition, during rubella outbreaks, health-care facilities should strongly consider recommending a dose of MMR vaccine to unvaccinated health-care workers born before 1957 who do not have serologic evidence of immunity. Serologic surveys of hospital workers indicate that 5%-9% of those born before 1957 do not have detectable measles antibody (117,118) and about 6% do not have detectable rubella antibody (119). In addition, during 1985-1992, 643 measles cases were reported among health-care workers whose year of birth was known; 27% of these persons were born before 1957 (CDC, unpublished data). Comparable surveillance data are not available for rubella.

Serologic screening need not be done before vaccinating for measles and rubella unless the medical facility considers it cost-effective (91,120,121). Serologic testing is appropriate only if persons who are identified as susceptible are subsequently vaccinated in a timely manner. Serologic screening ordinarily is not necessary for persons who have documentation of appropriate vaccination or other acceptable evidence of immunity (Table_1). During outbreaks of measles or rubella, serologic screening before vaccination is not generally recommended because rapid vaccination is necessary to halt disease transmission.

Transmission of mumps has occurred in medical settings (122). Therefore, immunity to mumps is highly desirable for all health-care workers (Table_1). Adequate mumps vaccination for health-care workers born during or after 1957 consists of one dose of live mumps-containing vaccine.

MMR vaccine generally should be used whenever any of its component vaccines is indicated. However, if the prospective vaccinee has acceptable evidence of immunity to one or two of the components of MMR vaccine (Table_1), a monovalent or bivalent vaccine can be used. International Travel

Measles, rubella, and mumps are endemic in many countries. Protection against measles is especially important for persons planning foreign travel, including adolescents and adults who have not had measles disease and have not been adequately vaccinated, and infants aged 6-11 months. Similarly, protection against rubella is especially important for women of childbearing age who are not immune to the disease. Although proof of vaccination is not required for entry into the United States, persons traveling or living abroad should ensure that they are immune to measles, rubella, and mumps.

Persons who travel or live abroad and who do not have acceptable evidence of measles, rubella, and mumps immunity (Table_1) should be vaccinated with MMR. Children who travel or live abroad should be vaccinated at an earlier age than recommended for children remaining in the United States. Before their departure from the United States, children aged greater than or equal to 12 months should have received two doses of MMR vaccine separated by at least 28 days, with the first dose administered on or after the first birthday. Children aged 6-11 months should receive a dose of monovalent measles vaccine before departure. If monovalent measles vaccine is not available, no specific contraindication exists to administering MMR to children aged 6-11 months. However, because the risk for serious disease from either mumps or rubella infection among infants is relatively low and because children aged less than 12 months are less likely to develop serologic evidence of immunity when vaccinated with measles, mumps, and rubella antigens than are older children, mumps vaccine and rubella vaccine generally are administered only to children aged greater than or equal to 12 months. Children administered monovalent measles vaccine or MMR before the first birthday should be considered potentially susceptible to all three diseases and should be revaccinated with two doses of MMR, the first of which should be administered when the child is aged 12-15 months (12 months if the child remains in an area where disease risk is high) and the second at least 28 days later.

Parents who travel or reside abroad with infants aged less than 12 months should have acceptable evidence of immunity to rubella and mumps (Table_1), as well as measles, so they will not become infected if their infants contract these diseases. Infants aged less than 6 months are usually protected against measles, rubella, and mumps by maternally derived antibodies and ordinarily do not require additional protection unless the infant's mother is diagnosed with measles (see Use of Vaccine and Immune Globulin Among Persons Exposed to Measles, Rubella, or Mumps). SPECIAL CONSIDERATIONS FOR VACCINATION Persons Infected with Human Immunodeficiency Virus (HIV)

Although the risk for measles exposure is currently low in most areas of the United States and the Western Hemisphere, this risk remains high in many other regions and measles continues to be imported into the United States. HIV-infected persons are at increased risk for severe complications if infected with measles (126,127). Among HIV-infected persons who did not have evidence of severe immunosuppression (Table_2), no serious or unusual adverse events have been reported after measles vaccination (123-126). Therefore, MMR vaccination is recommended for all asymptomatic HIV-infected persons who do not have evidence of severe immunosuppression and for whom measles vaccination would otherwise be indicated. MMR vaccination should also be considered for all symptomatic HIV-infected persons who do not have evidence of severe immunosuppression (Table_2) (128,129). Testing asymptomatic persons for HIV infection is not necessary before administering MMR or other measles-containing vaccine (130).

Transient increases in HIV viral load have been observed after administration of other vaccines to HIV-infected persons (131,132). The clinical significance of these increases is not known. Theoretically, a similar increase also may occur after MMR vaccination of HIV-infected persons.

Because the immunologic response to live and killed-antigen vaccines may decrease as HIV disease progresses, vaccination early in the course of HIV infection may be more likely to induce an immune response (133). Therefore, HIV-infected infants without severe immunosuppression should routinely receive MMR vaccine as soon as possible upon reaching the first birthday (i.e., at age 12 months)(130). Consideration should be given to administering the second dose of MMR vaccine as soon as 28 days (i.e., 1 month) after the first dose rather than waiting until the child is ready to enter kindergarten or first grade. In addition, if at risk for exposure to measles, HIV-infected infants who are not severely immunocompromised should be administered single-antigen measles vaccine or MMR vaccine at age 6-11 months. These children should receive another dose, administered as MMR vaccine, as soon as possible upon reaching the first birthday, provided at least 1 month has elapsed since the administration of the previous dose of measles-containing vaccine. An additional dose of MMR vaccine can be administered as early as 1 month after the second dose. If otherwise indicated, newly diagnosed HIV-infected children and adults without acceptable evidence of measles immunity (Table_1) should receive MMR vaccine as soon as possible after diagnosis, unless they have evidence of severe immunosuppression (Table_2). Data indicate that, of the HIV-infected infants born in the United States annually, approximately 5% (i.e., 50 children per year) would be classified as severely immunocompromised at age 12 months, when the first dose of MMR vaccine is recommended.

Measles vaccine is not recommended for HIV-infected persons with evidence of severe immunosuppression (Table_2) for several reasons:

- a case of progressive measles pneumonitis occurred in a person with AIDS and severe immunosuppression to whom MMR vaccine was administered (134);
- evidence indicates a diminished antibody response to measles vaccine among severely immunocompromised HIV-infected persons (133);
- morbidity related to measles vaccination has been reported among persons with severe immunosuppression unrelated to HIV infection (135-138); and
- in the United States, the incidence of measles is presently very low.

Serious illness associated with administration of rubella or mumps vaccines to HIV-infected persons has not been reported. MMR vaccine is not contraindicated for the

close contacts of immunocompromised persons. All family and other close contacts of HIV-infected persons should be vaccinated with MMR vaccine, unless they have acceptable evidence of measles immunity.

Severely immunocompromised patients and other symptomatic HIV-infected patients who are exposed to measles should receive immune globulin (IG) prophylaxis regardless of vaccination status because they may not be protected by the vaccine. For patients receiving intravenous immune globulin (IGIV) therapy, a standard dose of 100-400 mg/kg should be sufficient to prevent measles infection after exposures occurring within 3 weeks after administration of IGIV; for patients exposed to measles greater than 3 weeks after receiving a standard IGIV dose, an additional dose should be considered. Although no data are available concerning the effectiveness of IGIV in preventing measles, high dose IGIV may be as effective as immune globulin administered intramuscularly. Persons receiving regular (e.g., monthly) IGIV therapy for HIV infection or other indications may not respond to MMR or its component vaccines because of the continued presence of high levels of passively acquired antibody (see Precautions and Contraindications, Recent Administration of Immune Globulin). If indicated, MMR vaccine should be administered at least 2 weeks before beginning IGIV therapy. Use of Vaccine and Immune Globulin Among Persons Exposed to Measles, Rubella, or Mumps Use of Vaccine

Exposure to measles is not a contraindication to vaccination. MMR or measles vaccine, if administered within 72 hours of initial measles exposure, may provide some protection (139-143). For most persons aged greater than or equal to 12 months who are exposed to measles in most settings (e.g., day care facilities, schools, colleges, health-care facilities), administration of MMR or measles vaccine is preferable to using immune globulin (IG). For susceptible persons aged greater than or equal to 6 months who are 0household contacts of measles patients, use of vaccine within 72 hours of initial exposure is also acceptable. However, measles often is not recognized as such until greater than 72 hours after onset. Therefore, administration of IG to susceptible household contacts who are not vaccinated within 72 hours of initial exposure is recommended (see Use of Immune Globulin). Infants vaccinated before age 12 months must be revaccinated on or after the first birthday with two doses of MMR vaccine separated by at least 28 days (see Routine Vaccination). Measles-containing vaccine is not recommended for postexposure measles prophylaxis in immunocompromised persons or pregnant women (see Contraindications).

Postexposure MMR vaccination does not prevent or alter the clinical severity of rubella or mumps. However, widespread vaccination during a mumps outbreak may help terminate such outbreaks (144).

If exposure to measles, rubella, or mumps does not cause infection, postexposure vaccination with MMR should induce protection against subsequent infection. If the exposure results in infection, no evidence indicates that administration of MMR vaccine during the presymptomatic or prodromal stage of illness increases the risk for vaccine-associated adverse events. Use of Immune Globulin

If administered within 6 days of exposure, IG can prevent or modify measles in a nonimmune person. However, any immunity conferred is temporary unless modified or typical measles occurs (139). The usual recommended dose of IG is 0.25 mL/kg (0.11 mL/lb) of body weight (maximum dose = 15 mL). However, the recommended dose of IG for immunocompromised persons is 0.5 mL/kg of body weight (maximum dose = 15 mL). For persons receiving IGIV therapy, administration of at least 100 mg/kg within 3 weeks before measles exposure should be sufficient to prevent measles infection.

IG is indicated for susceptible household contacts of measles patients, particularly those for whom the risk for complications is increased (i.e., infants aged less than or equal to 12 months, pregnant women, or immunocompromised persons). Infants less than 6 months of age are usually immune because of passively acquired maternal antibodies. However, if measles is diagnosed in a mother, unvaccinated children of all ages in the household who lack other evidence of measles immunity should receive IG. IG prophylaxis is not indicated for household contacts who have received a dose of measles vaccine on or after the first birthday, unless they are immunocompromised. Only if administered within 72 hours of initial measles exposure is MMR vaccine acceptable for postexposure prophylaxis in household contacts aged greater than or equal to 6 months except pregnant women, immunocompromised patients, and others for whom vaccine is contraindicated (see Use of Vaccine). IG should not be used to control measles outbreaks.

Any person exposed to measles who lacks evidence of measles immunity (Table_1) and to whom IG is administered should subsequently receive MMR vaccine, which should be administered no earlier than 5-6 months after IG administration, provided the person is then aged greater than or equal to 12 months and the vaccine is not otherwise contraindicated. Passively acquired measles antibodies can interfere with the immune response to measles vaccination (see Recent Administration of Immune Globulins). The interval required to avoid such interference varies (Table_3).

IG does not prevent rubella or mumps infection after exposure and is not recommended for that purpose. Although administration of IG after exposure to rubella will not prevent infection or viremia, it may modify or suppress symptoms and create an unwarranted sense of security. Therefore, IG is not recommended for routine postexposure prophylaxis of rubella in early pregnancy or any other circumstance. Infants with congenital rubella have been born to women who received IG shortly after exposure. Administration of IG should be considered only if a pregnant woman who has been exposed to rubella will not consider termination of pregnancy under any circumstances. In such cases, intramuscular administration of 20 mL of immune globulin within 72 hours of rubella exposure may reduce -- but will not eliminate -- the risk for rubella (145,146). Revaccination of Persons Vaccinated According to Earlier Recommendations

Some persons vaccinated according to earlier recommendations for use of measles, rubella, mumps, and MMR vaccines should be revaccinated to ensure that they are adequately protected. Unless one of its component vaccines is contraindicated, MMR vaccine should be used for this purpose. Previous vaccination with live measles, rubella, and mumps vaccines. Persons vaccinated with live measles, rubella, or mumps vaccines before the first birthday who were not revaccinated on or after the first birthday should be considered unvaccinated. Unless they have other acceptable evidence of immunity to measles, rubella, and mumps (Table_1), these persons should be revaccinated with MMR.

Live attenuated Edmonston B measles vaccine (distributed from 1963 to 1975) was usually administered with IG or high-titer measles immune globulin (MIG; no longer available in the United States). Vaccination with this product, administered on or after the first birthday, is considered an effective first dose of vaccine. If indicated, a second dose of MMR vaccine should be administered (see Documentation of Immunity).

IG or MIG administered simultaneously with further attenuated measles vaccines (i.e., vaccines containing the Schwarz or Moraten virus strains) may have impaired the immune response to vaccination. Persons who received measles vaccine of unknown type or further attenuated measles vaccine accompanied by IG or MIG should be considered unvaccinated and should be administered two doses of MMR vaccine. Persons vaccinated with other previously licensed live rubella vaccines that were not administered with IG or MIG (i.e., HPV-77 or Cendehill vaccines) need not be revaccinated against rubella.

Previous vaccination with inactivated measles vaccine or measles vaccine of unknown type. Inactivated (killed) measles vaccine was available in the United States only from 1963 to 1967 but was available through the early 1970s in some other countries. It was frequently administered as a series of two or three injections. Because persons who received inactivated vaccine are at risk for developing severe atypical measles syndrome when exposed to the natural virus, they should receive two doses of MMR or other live measles vaccine, separated by at least 28 days (147). Persons who received inactivated vaccine followed within 3 months by live virus vaccine should also be revaccinated with two more doses of MMR or other live measles vaccine. Revaccination is particularly important when the risk for exposure to natural measles virus is increased (e.g., during international travel).

Persons vaccinated during 1963-1967 with vaccine of unknown type may have received inactivated vaccine and also should be revaccinated. Persons who received a vaccine of unknown type after 1967 need not be revaccinated unless the original vaccination occurred before the first birthday or was accompanied by IG or MIG. However, such persons should receive a second dose before entering college, beginning work in a health-care facility, or undertaking international travel.

Some recipients of inactivated measles vaccine who were later revaccinated with live measles vaccine have had adverse reactions to the live vaccine; the percentage who reported adverse reactions ranges from 4% to 55% (148). In most cases, these reactions were mild (e.g., local swelling and erythema, low-grade fever lasting 1-2 days), but rarely more severe reactions (e.g., prolonged high fevers, extensive local reactions) have been reported. However, natural measles infection is more likely to cause serious illness among recipients of inactivated measles vaccine than is live measles virus vaccine.

Previous vaccination with inactivated mumps vaccine or mumps vaccine of unknown type. A killed mumps virus vaccine was licensed for use in the United States from 1950 through 1978. Although this vaccine induced antibody, the immunity was transient. The number of doses of killed mumps vaccine administered between licensure of live attenuated mumps vaccine in 1967 until the killed vaccine was withdrawn in 1978 is unknown but appears to have been limited.

Revaccination with MMR should be considered for certain persons vaccinated before 1979 with either killed mumps vaccine or mumps vaccine of unknown type who are at high risk for mumps infection (e.g., persons who work in health-care facilities during a mumps outbreak). No evidence exists that persons who have had mumps disease or who have previously received mumps vaccine (killed or live) are at increased risk for local or systemic reactions upon receiving MMR or live mumps vaccine. ADVERSE EVENTS AFTER MMR VACCINATION

Adverse events associated with administration of MMR vaccine range from local pain, induration, and edema to rare systemic reactions such as anaphylaxis. Side effects tend to occur among vaccine recipients who are nonimmune and therefore are very rare after revaccination (see Revaccination). Expert committees at the Institute of Medicine (IOM) recently reviewed all evidence concerning the causal relationship between MMR vaccination and various adverse events (149,150). The IOM determined that evidence establishes a causal relation between MMR vaccination and anaphylaxis, thrombocytopenia, febrile seizures, and acute arthritis. Although vasculitis, otitis media, conjunctivitis, optic neuritis, ocular palsies, Guillain-Barre syndrome, and ataxia have been reported after administration of MMR or its component vaccines and are listed in the manufacturer's package insert, no causal relationship has been established between these events and MMR vaccination.

Evidence does not support a causal association of administration of measles-containing vaccine with risk for Crohn disease, a hypothesis proposed by some researchers in the United Kingdom and Sweden (151-156). Other researchers have been unable to replicate the laboratory findings that were reported to support this hypothesized association (157,158). Concerns also have been raised about the methods used in the epidemiologic studies that suggested an association between Crohn disease and measles vaccination (159-163). Other data do not support an association between measles vaccination and risk for Crohn disease or other inflammatory bowel disease (164,165).

Infection with mumps virus may trigger the onset of diabetes mellitus in some persons. However, no association has been established between vaccination with MMR or other mumps virus vaccine and pancreatic damage or subsequent development of diabetes mellitus (150). Fever, Rash, Lymphadenopathy, or Parotitis

Measles, rubella, and mumps vaccines may cause fever after vaccination; the measles component of MMR vaccine is most often associated with this adverse event. Approximately 5% of children develop a temperature of greater than or equal to 103 F (greater than or equal to 39.4 C) after MMR vaccination. Such febrile reactions usually occur 7-12 days after vaccination and generally last 1-2 days (166). Most persons with fever are otherwise asymptomatic.

Measles- and rubella-containing vaccines (including MMR) can cause transient rashes, which usually appear 7-10 days after vaccination, in approximately 5% of vaccinated persons. Transient lymphadenopathy sometimes occurs following administration of MMR or other rubella-containing vaccine, and parotitis has been reported rarely following administration of MMR or other mumps-containing vaccine. Allergic Reactions

Hypersensitivity reactions, usually consisting of urticaria or a wheal and flare at the injection site, occur rarely after administration of MMR or any of its component vaccines. Immediate anaphylactic reactions to these vaccines are very rare. More than 70 million doses of MMR vaccine have been distributed in the United States since the Vaccine Adverse Events Reporting System (VAERS) was implemented in 1990. The reported rate of possible anaphylaxis after vaccination with measles-containing vaccine is less than 1 case per 1 million doses distributed (CDC, unpublished data). Allergic reactions including rash, pruritus, and purpura have been temporally associated with mumps vaccination but are uncommon, usually mild, and of brief duration. Thrombocytopenia

Surveillance of adverse reactions in the United States and other countries indicates that MMR vaccine can, in rare instances, cause clinically apparent thrombocytopenia within 2 months after vaccination. In prospective studies, the reported frequency of clinically apparent thrombocytopenia after MMR vaccination ranged from 1 case per 30,000 vaccinated children in Finland and Great Britain (167,168) to 1 case per 40,000 in Sweden (169), with a temporal clustering of cases occurring 2-3 weeks after vaccination. Based on passive surveillance, the reported frequency of thrombocytopenia was approximately 1 case per 100,000 vaccine doses distributed in Canada (170) and France (171), and approximately 1 case per 1 million doses distributed in the United States (172). The clinical course of these cases was usually transient and benign, although hemorrhage occurred rarely (172). The risk for thrombocytopenia during rubella or measles infection is much greater than the risk after vaccination (173). Based on case reports, the risk for MMR-associated thrombocytopenia may be increased for persons who have previously had immune thrombocytopenic purpura, particularly for those who had thrombocytopenic purpura after an earlier dose of MMR vaccine (150,174,175). Neurological Events

Adverse neurological events after administration of MMR vaccine are rare. Reports of nervous system illness following MMR vaccination do not necessarily denote an etiologic relationship between the illness and the vaccine. Although several cases of sensorineural deafness have been reported after administration of MMR vaccine, evidence from these case reports (e.g., timing of onset and other features) is inadequate to accept or reject a causal relation between MMR vaccination and sensorineural deafness. Aseptic Meningitis

Aseptic meningitis has been clearly associated with administration of the Urabe strain mumps vaccine virus but not with the Jeryl Lynn strain, which is the only mumps vaccine used in the United States (176-178). Sentinel surveillance laboratories in the United Kingdom identified thirteen aseptic meningitis cases (91 cases per 1 million doses distributed) that occurred after administration of the Urabe strain vaccine during 1988-1992 (168). Since the United Kingdom switched to Jeryl Lynn strain vaccine in 1992, no mumps vaccine-associated aseptic meningitis cases have been reported by the surveillance laboratories (178). Subacute Sclerosing Panencephalitis (SSPE)

Measles vaccination substantially reduces the occurrence of SSPE as evidenced by the near elimination of SSPE cases after widespread measles vaccination. SSPE has been reported rarely among children who had no history of natural measles infection, but who had received measles vaccine. Evidence indicates that at least some of these children had unrecognized measles infection before they were vaccinated and that the SSPE was directly related to the natural measles infection. The administration of live measles vaccine does not increase the risk for SSPE, even among persons who have previously had measles disease or received live measles vaccine (150,179). Encephalopathy/Encephalitis

Encephalitis with resultant residual permanent central nervous system (CNS) impairment (encephalopathy) develops in approximately 1 per 1,000 persons infected with measles virus. Whether attenuated live viral measles vaccine can also produce such a syndrome has been a concern since the earliest days of measles vaccine use. In 1994, the IOM noted that most data were from case reports, case series, or uncontrolled observational studies, and concluded that the evidence was inadequate to accept or reject a causal relation (150).

The British National Childhood Encephalopathy Study (NCES) identified a fourfold elevation in risk for encephalopathy or convulsions among children who received measles vaccine during 1976-1979, compared with the risk for these conditions among unvaccinated children (180). Among previously normal children, the attributable risk for acute encephalopathy or convulsions was 1 case per 87,000 vaccinations. Findings of a subsequent 10-year follow-up study of persons diagnosed with convulsions or acute encephalopathy in the NCES indicated little difference in risk for persisting neurological abnormality among those who had received measles vaccine compared with those who had not (E. Miller, personal communication).

Although cases of encephalopathy have been reported after administration of measles-containing vaccine (181), lack of a unique clinical syndrome or specific laboratory test has hampered causality assessment. However, four independent passive surveillance systems in the United States (i.e., CDC measles surveillance from 1963 to 1971, the Monitoring System for Adverse Events Following Immunizations {MSAEFI} from 1979 to 1990, the Vaccine Adverse Event Reporting System {VAERS} from 1991 to 1996, and the Vaccine Injury Compensation Program {VICP}) have reported cases of encephalopathy in which a similar timing of reported events following vaccine administration is apparent. In all four case series, onset of encephalopathies follows a non-random distribution with onset approximately 10 days after vaccination, a timing consistent with onset of encephalopathy after infection with wild measles virus (182). Although this pattern may be in part attributable to consistent biases of these passive surveillance systems, it is also consistent with a causal relationship between measles vaccine and encephalopathies (183). During the period these four systems have collected data, 166 cases of encephalopathy occurring 6-15 days after vaccination have been identified and an estimated 313 million doses of measles-containing vaccines have been distributed (i.e., approximately 1 case per 2 million doses distributed). Thus, encephalopathy occurs much less frequently after administration of measles vaccine than after measles infection. Febrile Seizures and Personal and Family History of Convulsions

MMR vaccination, like other causes of fever, may cause febrile seizures. The risk for such seizures is approximately 1 case per 3,000 doses of MMR vaccine administered (168). Studies have not established an association between MMR vaccination and residual seizure disorders (150). Although children with personal or family histories of seizures are at increased risk for idiopathic epilepsy, febrile seizures after vaccinations do not increase the probability that epilepsy or other neurologic disorders will subsequently develop in these children. Most convulsions that occur after measles vaccination are simple febrile seizures, which affect children who do not have other known risk factors for seizure disorders.

Antipyretics may prevent febrile seizures after MMR vaccination if administered before the onset of fever and continued for 5-7 days. However, antipyretics are difficult to use for this purpose because the onset of fever is often sudden and occurs unpredictably. Seizures can occur early in the course of fever. Parents should be vigilant for fever that occurs after vaccination and should be counseled regarding its appropriate treatment. Use of aspirin during some illnesses in childhood is associated with the occurrence of Reye syndrome. Therefore, aspirin generally should not be used to prevent or control fever among children and adolescents.

The 5%-7% of children who have either a personal history of convulsions or a parent or sibling with history of convulsions may be at increased risk for febrile convulsions after MMR vaccination (184). The precise risk has not been measured, but appears to be minimal. On the other hand, febrile seizures occur commonly among children in whom measles disease develops, and the risk for acquiring measles is substantial. Therefore, the benefits of administering MMR vaccine to children with a personal or family history of convulsions substantially outweigh the risks and these children should be vaccinated following the recommendations for children who have no contraindications.

Children who are being treated with anticonvulsants should continue to take them after measles vaccination. Because protective levels of most currently available anticonvulsant drugs (e.g., phenobarbital) are not achieved for some time after therapy is initiated, prophylactic use of these drugs is not feasible.

The parents of children who have either a personal or family history of seizures should be advised of the benefits of vaccination and the minimal increased risk for seizures, which generally occur 5-14 days after measles vaccination. Guillain-Barre Syndrome (GBS)

Cases of GBS occurring after administration of MMR or its component vaccines have been reported, but the IOM judged the evidence insufficient to accept or reject a causal relationship (150). Recent studies provide evidence against this potential association (185,186). After recent mass vaccination campaigns that involved approximately eight million doses of measles-rubella vaccine in the United Kingdom and greater than 70 million doses of measles vaccine in Latin America, evaluations of GBS incidence demonstrated no increases over background rates. Arthralgia, Arthritis, and Persistent or Recurrent Arthropathy

Joint symptoms are associated with the rubella component of MMR. Among susceptible persons who receive rubella vaccine, arthralgia and transient arthritis occur more

frequently among adults than among children and more frequently among postpubertal females than among males. Acute arthralgia or arthritis are rare among children who receive RA 27/3 vaccine (187). By contrast, arthralgia develops among approximately 25% of susceptible postpubertal females after RA 27/3 vaccination and approximately 10% have acute arthritis-like signs and symptoms (188,189). Although rare reports of transient peripheral neuritic complaints have occurred, insufficient evidence exists to indicate a causal relation between RA 27/3 vaccine and peripheral neuropathies (149,190). When acute joint symptoms occur, or when pain and/or paresthesias not associated with joints occur, they generally begin 1-3 weeks after vaccination, persist for 1 day to 3 weeks, and rarely recur. Adults who experienced acute joint symptoms after rubella vaccination usually have not had to disrupt work activities (189,190,191).

A 1991 report by the IOM stated that although some data were consistent with a causal relation between RA27/3 rubella vaccine and chronic arthritis among adult women, the evidence was limited in scope and confined to reports from a single institution (149). Several more recently published studies have found no evidence of increased risk for new onset of chronic arthropathies among women vaccinated with RA 27/3 vaccine (192-194). In addition, data from a recent prospective, randomized, placebo-controlled trial by the same group that initially reported chronic arthropathy after rubella vaccination demonstrated only a small excess risk for persistent joint symptoms among persons who received rubella vaccine (relative risk {RR} = 1.58; 95% confidence interval = 1.01-2.45) (195). Neither the duration of arthropathy nor timing of onset was reported. The occurrence of arthropathy described as moderate or severe did not differ between vaccine and placebo recipients and was rare in both groups. Interference with Tuberculin Skin Tests

Tuberculin testing is not a prerequisite for vaccination with MMR or any of its component vaccines. MMR vaccine may interfere with the response to a tuberculin test (196-198). Therefore, tuberculin testing, if otherwise indicated, can be done either on the same day MMR vaccine is administered or 4-6 weeks later. Revaccination

No evidence indicates that administration of live measles, mumps, or rubella vaccine increases the risk for adverse reactions among persons who are already immune to these diseases as a result of previous vaccination or natural disease. Data indicate that only persons who are not immune when vaccinated tend to have postvaccination side effects similar to the disease symptoms (139). No evidence exists that persons who have previously received killed mumps vaccine or had mumps disease are at increased risk for local or systemic reactions from receiving live mumps vaccine. Some recipients of inactivated measles vaccine who were later revaccinated with live measles vaccines have had adverse reactions to the live vaccine (see Revaccination of Persons Vaccinated According to Earlier Recommendations). REPORTING ADVERSE EVENTS

Reporting of serious adverse events that occur after administration of MMR or its component vaccines helps identify adverse events that may be caused by these vaccines. The National Childhood Vaccine Injury Act of 1986 requires health-care providers to report serious adverse events that occur after vaccination with MMR and its component vaccines to the Vaccine Adverse Events Reporting System (VAERS). Persons other than health-care workers can also report adverse events to VAERS. Events that must be reported after MMR vaccination are listed in the reportable events table within the Act and include anaphylaxis or anaphylactic shock occurring within 7 days of vaccination, encephalopathy (or encephalitis) occurring within 7 days of vaccination, and any events described in the manufacturer's package insert as contraindications to additional doses of vaccine (199). Other adverse events occurring after administration of a vaccine, especially events that are serious or unusual, also should be reported to VAERS, regardless of the provider's opinion of the causality of the association. VAERS reporting forms and information are available 24 hours a day by calling 1-800-822-7967 or via the World Wide Web at http:\\www.cdc.gov/nip/vaers.htm. VACCINE INJURY COMPENSATION

The National Vaccine Injury Compensation Program, established by the National Childhood Vaccine Injury Act of 1986, is a system under which compensation may be paid on behalf of a person thought to have been injured or to have died as a result of receiving a vaccine covered by the program. The program is intended as an alternative to civil litigation under the traditional tort system because negligence need not be proven.

The Act establishes a) a Vaccine Injury Compensation Table that lists the vaccines covered by the program; b) the injuries, disabilities, and conditions (including death) for which compensation may be paid without proof of causation; and c) the period after vaccination during which the first symptom or substantial aggravation of the injury must appear. Modifications to the Vaccine Injury Table became effective March 24, 1997 (199). Persons may be compensated for an injury listed in the established table or one that can be demonstrated to result from administration of a listed vaccine. Additional information about the program is available. * PRECAUTIONS AND CONTRAINDICATIONS Pregnancy

MMR and its component vaccines should not be administered to women known to be pregnant. Because a risk to the fetus from administration of these live virus vaccines cannot be excluded for theoretical reasons, women should be counseled to avoid becoming pregnant for 30 days after vaccination with measles or mumps vaccines and for 3 months after administration of MMR or other rubella-containing vaccines. Routine precautions for vaccinating postpubertal women with MMR should be followed in all vaccination programs (see Routine Vaccination -- Women of Childbearing Age). If a pregnant woman is vaccinated or if she becomes pregnant within 3 months after vaccination, she should be counseled about the theoretical basis of concern for the fetus, but MMR vaccination during pregnancy should not ordinarily be a reason to consider termination of pregnancy. Rubella-susceptible women who are not vaccinated because they state they are or may be pregnant should be counseled about the potential risk for CRS and the importance of being vaccinated as soon as they are no longer pregnant.

Because birth defects are noted in 3%-5% of all births, confusion about the etiology of birth defects may result if vaccine is administered during pregnancy. Although of theoretical concern, no cases of congenital rubella syndrome or abnormalities attributable to infection with measles, rubella, or mumps vaccine virus infection have been observed among infants born to susceptible mothers who received any of these vaccines during pregnancy. From January 1971 through April 1989, CDC followed to term 321 known rubella-susceptible pregnant women who had been vaccinated with live rubella vaccine within 3 months before or 3 months after conception. Ninety-four women received HPV-77 or Cendehill vaccines, one received vaccine of unknown strain, and 226 received RA 27/3 vaccine (the only rubella vaccine presently used in the United States). None of the 324 infants born to these mothers had malformations compatible with congenital rubella infection. This total included five infants who had serologic evidence of subclinical infection; three of the infants were exposed to HPV-77 or Cendehill vaccine and two were exposed to RA 27/3 vaccine. Based on these data, the estimated risk for serious malformations attributable to RA 27/3 rubella vaccine ranges from zero to 1.6%. If the infants exposed to other rubella vaccines are included, the estimated risk is zero to 1.2%, substantially less than the greater than or equal to 20% risk for CRS associated with maternal infection during the first trimester of pregnancy (200). Moreover, the observed risk for CRS with both the HPV-77 or Cendehill and RA 27/3 strains of vaccine is zero.

Rubella vaccine virus has been isolated from the aborted fetus of one (3%) of 35 rubella-susceptible women who received RA 27/3 strain vaccine during pregnancy. In contrast, vaccine virus was isolated from the fetuses of 17 (20%) of 85 women to whom HPV-77 or Cendehill vaccines were administered (201). This finding provides additional evidence that the RA 27/3 vaccine poses no greater risk for teratogenicity than did the HPV-77 or Cendehill vaccines.

Breast feeding is not a contraindication to vaccination. Although a woman can excrete rubella vaccine virus in breast milk and transmit the virus to her infant, the infection remains asymptomatic (202-205). Otherwise, persons who receive MMR or its component vaccines do not transmit measles, rubella, or mumps vaccine viruses (206,207). Thus, MMR vaccine can be administered safely to susceptible children or other persons with household contacts who are pregnant to help protect these pregnant women from exposure to wild rubella virus.

All suspected cases of CRS, whether presumed to be due to wild-virus or vaccine-virus infection, should be reported to state and local health departments. Suspected or confirmed cases of CRS can also be reported to the VAERS (see Reporting Adverse Events). Severe Illness

Because of the importance of protecting susceptible children against measles, mumps, and rubella, medical personnel should use every opportunity to vaccinate susceptible persons. The decision to vaccinate or postpone vaccination of a person who currently has or recently has had an acute febrile illness depends largely on the cause of the illness and the severity of symptoms. Minor illnesses, with or without fever (e.g., diarrhea, upper respiratory infection, otitis media) are not contraindications for vaccination and vaccination should not be postponed because of them. Data indicate that seroconversion rates for each component of MMR vaccine among persons with mild febrile illness are similar to those among healthy persons (208,209). Similarly, performing routine physical examinations or measuring temperatures are not prerequisites for vaccinating persons who appear to be in good health. In childhood vaccination programs, appropriate procedures include a) asking the parent or guardian if the child is ill, b) postponing vaccination of children who have moderate or severe febrile illnesses, and c) vaccinating children who do not have other contraindications.

Vaccination of persons with moderate or severe febrile illnesses should generally be deferred until they have recovered from the acute phase of their illness. This wait avoids superimposing adverse effects of vaccination on the underlying illness or mistakenly attributing a manifestation of the underlying illness to the vaccine. Data are generally not available regarding the safety and immunogenicity of MMR vaccine among persons with moderate or severe febrile illness.

Persons under treatment for tuberculosis have not experienced exacerbations of the disease when vaccinated with MMR. Although no studies have been reported concerning the effect of MMR vaccine on persons with untreated tuberculosis, a theoretical basis exists for concern that measles vaccine might exacerbate tuberculosis. Consequently, before administering MMR to persons with untreated active tuberculosis, initiating antituberculous therapy is advisable. Tuberculin testing is not a pre-requisite for routine vaccination with MMR or other measles-containing vaccines. Allergies

Among persons who are allergic to eggs, the risk for serious allergic reactions such as anaphylaxis following administration of measles- or mumps-containing vaccines is extremely low and skin-testing with vaccine is not predictive of allergic reaction to vaccination (210-212). Therefore, skin testing is not required before administering MMR (or other measles- and mumps-containing vaccines) to persons who are allergic to eggs. Similarly, the administration of gradually increasing doses of vaccine is not required. In the past, persons with a history of anaphylactic reactions (i.e., hives, swelling of the mouth or throat, difficulty breathing, hypotension, and shock) following egg ingestion were considered to be at increased risk for serious reactions after administration of measles- or mumps-containing vaccines, which are produced in chick

embryo fibroblasts. Although protocols have been developed for skin testing and vaccination of persons who experience anaphylactic reactions to egg ingestion, data indicate that most anaphylactic reactions to measles- and mumps-containing vaccines are not associated with hypersensitivity to egg antigens but to other components of the vaccines (213-217).

The literature contains several case reports of persons with an anaphylactic sensitivity to gelatin who had anaphylactic reactions after receiving MMR vaccine (218-220). MMR and its component vaccines contain hydrolyzed gelatin as a stabilizer. Therefore, extreme caution should be exercised when administering MMR or its component vaccines to persons who have a history of an anaphylactic reaction to gelatin or gelatin-containing products. Before administering MMR or its component vaccines to such persons, skin testing for sensitivity to gelatin can be considered. However, no specific protocols for this purpose have been published.

Because MMR and its component vaccines contain trace amounts of neomycin (25 ug), persons who have experienced anaphylactic reactions to topically or systemically administered neomycin should not receive these vaccines. However, neomycin allergy is most often manifested as a delayed or cell-mediated immune response (i.e., a contact dermatitis), rather than anaphylaxis. In persons who have such a sensitivity, the adverse reaction to the neomycin in the vaccine is an erythematous, pruritic nodule or papule appearing 48-96 hours after vaccination. A history of contact dermatitis to neomycin is not a contraindication to receiving MMR vaccine. MMR vaccine does not contain penicillin and therefore a history of penicillin allergy is not a contraindication to MMR vaccination.

Although anaphylaxis after vaccination is extremely rare and no anaphylaxis deaths associated with administration of MMR vaccine have been reported, this adverse event can be life threatening (150). Epinephrine should be available for immediate use at any site where vaccines are administered in case symptoms of anaphylaxis occur. Thrombocytopenia

Children who have a history of thrombocytopenia or thrombocytopenic purpura may be at increased risk for developing clinically significant thrombocytopenia after MMR vaccination (172,175). Although thrombocytopenia can be life threatening, no deaths have been reported as a direct consequence of vaccine-induced thrombocytopenia. The decision to vaccinate with MMR should depend on the benefits of immunity to measles, mumps, and rubella and the risks for recurrence or exacerbation of thrombocytopenia after vaccination or during natural infection with measles or rubella. The benefits of primary immunization are usually greater than the potential risks, and administration of MMR vaccine is justified, particularly with regard to the even greater risk for thrombocytopenia after measles or rubella disease. However, avoiding a subsequent dose of MMR vaccine may be prudent if an episode of thrombocytopenia occurred within approximately 6 weeks after a previous dose of the vaccine. Serologic evidence of measles immunity among such persons may be sought in lieu of MMR vaccination.

Recent Administration of Immune Globulins Recent evidence indicates that high doses of immune globulins can inhibit the immune response to measles and rubella vaccine for 3 or more months (221, 222). The duration of this interference with the immune response depends on the dose of immune globulin administered. The effect of immune globulin preparations on the response to mumps vaccine is unknown. Blood (e.g., whole blood, packed red blood cells, and plasma) and other antibody-containing blood products (e.g., IG, specific immune globulins, and IGIV) can reduce the immune response to MMR or its component vaccines. Therefore, these vaccines should be administered to persons who have received an immune globulin preparation only after the recommended intervals have elapsed (Table_3) (80). However, postpartum administration of MMR or rubella vaccine to women who are susceptible to rubella should not be delayed because anti-Rho(D) immune globulin (human) or any other blood product was received during the last trimester of pregnancy or at delivery. Such rubella-susceptible women should be vaccinated immediately after delivery and tested at least 3 months later to ensure that they are immune to rubella and measles.

Immune globulin preparations generally should not be administered simultaneously with MMR or its component vaccines. If administration of an immune globulin preparation becomes necessary because of imminent exposure to disease, MMR or its component vaccines can be administered simultaneously with the IG preparation, although vaccine-induced immunity may be compromised. Usually, vaccine virus replication and stimulation of immunity will occur 1-2 weeks after vaccination. Thus, if the interval between administration of any of these vaccines and administration of an IG preparation is less than 14 days, vaccination should be repeated after the recommended interval (Table_3), unless serologic testing indicates that the vaccinated person's immune system has produced antibodies to each vaccine component (i.e., measles, rubella, and mumps). The vaccine should be administered at an anatomic site remote from that chosen for the IG injection. Altered Immunocompetence

Enhanced replication of vaccine viruses may occur in persons who have immune deficiency diseases and in other persons who are immunosuppressed. Severe immunosuppression may be caused by many disease conditions (e.g., congenital immunodeficiency, HIV infection, hematologic or generalized malignancy) and by therapy with immunosuppressive agents, including large doses of corticosteroids. For some of these conditions, all affected persons are severely immunocompromised. For other conditions (e.g., HIV infection), the degree to which the immune system is compromised depends on the severity of the condition, which in turn depends on the disease or treatment stage. Ultimately, the patient's physician must assume responsibility for determining whether the patient is severely immunocompromised based on clinical and laboratory assessment.

Case reports have linked vaccine-associated measles infection to the deaths of some severely immunocompromised persons (150,223). Therefore, MMR vaccine should not be administered to severely immunocompromised persons. To reduce the risk for measles, rubella, and mumps exposure of immunocompromised patients, their susceptible close contacts should be vaccinated with MMR. No case reports exist linking MMR or mumps- or rubella-containing vaccines with clinically significant infection caused by mumps or rubella vaccine virus among immunocompromised vaccine recipients. HIV-Infected Persons

Among asymptomatic and symptomatic HIV-infected patients who are not severely immunosuppressed, MMR vaccination has been associated with variable antibody responses but not with severe or unusual adverse events. Asymptomatic persons do not need to be evaluated and tested for HIV infection before MMR and other measles-containing vaccines are administered. MMR vaccine is recommended for all asymptomatic HIV-infected persons who are not severely immunosuppressed and who lack evidence of measles immunity. MMR vaccination of symptomatic HIV-infected persons should be considered if they a) do not have evidence of severe immunosuppression and b) lack evidence of measles immunity. MMR and other measles-containing vaccines are not recommended for HIV-infected persons with evidence of severe immunosuppression (see Special Considerations for Vaccination -- Persons Infected with Human Immunodeficiency Virus {HIV}) (Table_2). Steroids

Systemically absorbed corticosteroids can suppress the immune system of an otherwise healthy person. However, neither the minimum dose nor the duration of therapy sufficient to cause immune suppression are well defined. Most experts agree that steroid therapy usually does not contraindicate administration of live virus vaccines such as MMR and its component vaccines when therapy is: a) short term (i.e., less than 14 days) low-to-moderate dose; b) low-to-moderate dose administered daily or on alternate days; c) long term alternate day treatment with short-acting preparations; d) physiologic maintenance doses (replacement therapy); or e) administered topically (skin or eyes), by aerosol, or by intra-articular, bursal, or tendon injection. Although the immunosuppressive effects of steroid treatment vary, many clinicians consider a steroid dose that is equivalent to or greater than a prednisone dose of 2 mg/kg of body weight per day or a total of 20 mg per day sufficiently immunosuppressive to raise concern about the safety of administration of live virus vaccines. Persons who have received systemic corticosteroids in these or greater doses daily or on alternate days for an interval of greater than or equal to 14 days should avoid vaccination with MMR and its component vaccines for at least 1 month after cessation of steroid therapy. Persons who have received prolonged or extensive topical, aerosol, or other local corticosteroid therapy that causes clinical or laboratory evidence of systemic immunosuppression should also avoid vaccination with MMR for at least 1 month after cessation of therapy. Persons who receive doses of systemic corticosteroids equivalent to a prednisone dose of greater than or equal to 2 mg/kg of body weight or greater than or equal to 20 mg total daily or on alternate days during an interval of less than 14 days generally can receive MMR or its component vaccines immediately after cessation of treatment, although some experts prefer waiting until 2 weeks after completion of therapy. MMR or its component vaccines generally should not be administered to persons who have a disease that, in itself, suppresses the immune response and who are receiving either systemic or locally administered corticosteroids. Leukemia

Persons with leukemia in remission who were not immune to measles, rubella, or mumps when diagnosed with leukemia may receive MMR or its component vaccines. At least 3 months should elapse after termination of chemotherapy before administration of the first dose of MMR vaccine. Management of Patients with Contraindications to Measles Vaccine

If immediate protection against measles is required for persons with contraindications to measles vaccination, 0.25 mL/kg (0.11 mL/lb) of body weight (maximum dose = 15 mL) of IG should be administered as soon as possible after known exposure (See Use of Vaccine and Immune Globulin Among Persons Exposed to Measles, Rubella, or Mumps). Exposed symptomatic HIV-infected and other immunocompromised persons should receive IG regardless of their previous vaccination status. Because IG in usual doses may not be effective for immunocompromised persons, the recommended dose is 0.5 mL/kg of body weight if IG is administered intramuscularly (maximum dose = 15 mL). This corresponds to a dose of IgG protein of approximately 82.5 mg/kg (maximum dose = 2,475 mg). Intramuscular IG may not be needed if a patient is receiving at least 100-400 mg/kg IGIV at regular intervals and exposure occurs within 3 weeks after administration of the last dose of IGIV. Because the amounts of protein administered are similar, high-dose IGIV may be as effective as intramuscular IG. However, no data are available concerning the effectiveness of IGIV in preventing measles.

The effectiveness of IG or IGIV for preventing mumps or rubella is unknown. These products should not be used for prophylaxis among immunocompromised persons exposed to these diseases. SURVEILLANCE AND OUTBREAK CONTROL

Surveillance for vaccine preventable diseases has four primary purposes: a) to provide important data on program progress and long term trends, b) to provide the basis for changes in disease prevention strategies, c) to help define groups in greatest need of vaccination, and d) to evaluate vaccine safety and effectiveness (e.g., protective efficacy, duration of vaccine-induced immunity, and occurrence of adverse effects). As the incidence of measles, rubella, and mumps declines in the United States, enhanced surveillance becomes increasingly important.

Any person aware of a suspected or known cases of measles, rubella, congenital rubella syndrome, or mumps should report the case to the local or state health department. The designated public health authorities should investigate the case immediately. The purpose of the investigation is to classify the case, identify the characteristics of the case and the source of exposure, and prevent further spread.

Cases of measles, rubella, and congenital rubella syndrome are reportable in all states, and mumps is reportable in most states. Data from measles, rubella, congenital rubella syndrome, and mumps cases are routinely reported by state and local health departments to CDC and published weekly in the Morbidity and Mortality Weekly Report. Measles Case Investigation and Outbreak Control Case Definition

A suspected measles case is defined as any febrile illness accompanied by rash. Suspected and known cases of measles should be reported immediately to the local or state health department. The designated public health authorities should quickly initiate an investigation of the reported case. Rapid case reporting and investigation can help limit further transmission.

A clinical case of measles is defined as an illness characterized by

- a generalized rash lasting greater than or equal to 3 days, and
- a temperature of greater than or equal to 38.3 C (greater than or equal to 101 F), and
- cough, coryza, or conjunctivitis. A probable case of measles
- meets the clinical case definition for measles, and
- is not epidemiologically linked to a confirmed case, and
- has not been serologically or virologically tested or has noncontributory serologic or virologic results. A confirmed case of measles
- meets the laboratory criteria for measles or
- meets the clinical case definition and is epidemiologically linked to a confirmed case.

Confirmed measles cases are routinely reported to CDC by state health departments. Laboratory Diagnosis

The laboratory criteria for measles diagnosis are:

- a positive serologic test for measles IgM antibody, or
- a significant rise in measles antibody level by any standard serologic assay, or
- isolation of measles virus from a clinical specimen.

A laboratory-confirmed case need not meet the clinical case definition. Serologic confirmation should be attempted for every suspected case of measles and is particularly important for any case that cannot be epidemiologically linked through a chain of transmission to a confirmed case. However, reporting of suspected or probable cases, investigation of cases, and the implementation of control activities should not be delayed pending laboratory results.

Blood for serologic testing should be collected during the first clinical encounter with a person who has suspected or probable measles. The serum should be tested for measles IgM antibody as soon as possible using an assay that is both sensitive and specific (e.g., direct-capture IgM EIA method). Correct interpretation of serologic data depends on the timing of specimen collection in relation to rash onset and on the characteristics of the antibody assay used. This timing is especially important for interpreting negative results because IgM antibody may not be detectable with some less sensitive assays until at least 72 hours after rash onset. Measles IgM may be detectable at the time of rash onset, peaks approximately 10 days after rash onset, and is usually undetectable 30-60 days after rash onset. In general, if measles IgM is not detected in a serum specimen obtained in the first 72 hours after rash onset from a person whose illness meets the clinical case definition for measles, another specimen should be obtained at least 72 hours after rash onset and tested for measles IgM antibody. Measles IgM is detectable for at least 1 month after rash onset. Persons with febrile rash illnesses who are seronegative for measles should be tested for rubella.

As measles becomes rare in the United States, the likelihood of obtaining false positive serologic results from measles IgM antibody testing increases. False positive results have been obtained by using a commercially available ELISA assay for measles IgM in persons with parvovirus infection (fifth disease) (224). Confirmatory testing by using an assay that is both sensitive and specific (e.g., direct-capture IgM EIA method) should be considered when IgM is detected in a patient with suspected measles who has no identified source of infection and no epidemiologic linkage to another confirmed case. The Measles Virus Laboratory of CDC's National Center for Infectious Diseases has provided training to all state public health laboratories to perform such testing.

Serologic diagnosis of measles can also be confirmed by a significant rise in antibody titer between acute- and convalescent-phase serum specimens. Typically, the acute-phase serum specimen is obtained within 1-3 days after rash onset and the convalescent-phase specimen is obtained approximately 2-4 weeks later. This method has been largely supplanted by IgM assays which can be done on a single serum specimen obtained soon after rash onset.

Asymptomatic measles reinfection can occur among persons who have previously developed antibodies from vaccination or from natural disease. Symptomatic reinfections accompanied by rises in measles antibody titers are rare, and those resulting in detectable measles IgM antibody occur even more rarely.

Molecular characterization of measles virus isolates has become an important tool for defining the epidemiologic features of measles during periods of low disease incidence and for documenting the impact of measles elimination efforts (16). In addition to serologic confirmation, a specimen (e.g., urine or nasopharyngeal mucus) for measles virus isolation and genetic characterization should be collected as close to the time of rash onset as possible. Delay in collection of these clinical specimens reduces the chance of isolating measles virus. Clinicians who have a patient with suspected measles should immediately contact their local or state health departments concerning additional information about collecting and shipping urine and nasal specimens for measles virus isolation. Molecular characterization of the measles virus isolated from urine or nasopharyngeal specimens requires considerable time and cannot be used for diagnosis of measles. Use of oral fluid in tests for detecting measles IgM and IgG antibodies is being investigated (225). Measles Outbreak Control

The local or state health department should be contacted immediately when suspected cases of measles occur in a community. All reports of suspected measles cases should be investigated promptly. Because of the potential for rapid spread of the disease, one confirmed case of measles in a community is an urgent public health situation. Once a case is confirmed, prompt vaccination of susceptible persons at risk for exposure may help prevent dissemination of measles. Control activities should not be delayed pending the return of laboratory results from persons with suspected or probable cases. Persons who cannot readily provide acceptable evidence of measles immunity (Table_1) should be vaccinated or excluded from the setting of the outbreak (e.g., school, day care facility, hospital, clinic). Almost all persons who are excluded from an outbreak area because they lack acceptable evidence of immunity quickly comply with vaccination requirements. Persons exempted from measles vaccination for medical, religious, or other reasons should be excluded from involved institutions in the outbreak area until 21 days after the onset of rash in the last case of measles. Mass revaccination of entire communities generally is not necessary. Staff of the National Immunization Program, CDC, are available to assist health departments in developing an outbreak control strategy. Measles Outbreaks Among Preschool-Aged Children

Although most infants are protected from measles by maternal antibody, the disease is often more severe when it affects children aged less than 12 months. If cases are occurring among infants aged less than 12 months, measles vaccination of infants aged as young as 6 months may be undertaken as an outbreak control measure. Monovalent measles vaccine is preferred, but MMR vaccine may be administered if the monovalent vaccine is not readily available (see Routine Vaccination -- International Travel). Children vaccinated with measles or MMR vaccine before the first birthday should be revaccinated at age 12-15 months and again before entering school.

Passive immunization with IG may be preferred for infants aged less than 12 months who are household contacts of measles patients, both because it is likely they will have been exposed greater than 72 hours before diagnosis of the disease in the household member and because they are at highest risk for complications from the disease (see Use of Vaccine and Immune Globulin Among Persons Exposed to Measles, Rubella, or Mumps). IG should not be used to control measles outbreaks. Measles Outbreaks in Day Care Facilities, Schools, and Other Educational Institutions

During an outbreak in a day care facility, revaccination with MMR is recommended for all attendees and their siblings who have not received two doses of measles-containing vaccine on or after the first birthday and who do not have other evidence of measles immunity. Facility personnel (e.g., employees, volunteers, service providers) who cannot provide acceptable evidence of immunity (Table_1) also should be vaccinated with MMR. Revaccination also should be considered for unaffected child care facilities in the community that may be at risk for measles exposure and transmission.

During outbreaks in schools (elementary, middle, junior and senior high schools, colleges and other institutions of higher education), a program of revaccination with MMR vaccine is recommended in the involved schools. Revaccination of students and personnel of unaffected schools in the same geographic area who may be at risk for measles transmission also should be considered. Revaccination should include all students and their siblings and all school personnel born during or after 1957 who cannot provide documentation of adequate measles vaccination or other acceptable evidence of measles immunity. For persons born in 1957 or later, adequate vaccination consists of two doses of measles-containing vaccine separated by at least 28 days with the first dose administered no earlier than the first birthday (Table_1) (see Documentation of Immunity). Persons who cannot readily provide documentation of acceptable evidence of measles immunity should be vaccinated or excluded from the day care facility, school, or other educational institution. Revaccinated persons, as well as persons who receive their first dose as part of the outbreak control program, may be readmitted to school immediately. Persons exempted from measles vaccination for medical, religious, or other reasons, and those who refuse vaccination for any reason, should be excluded from the day care facility, school, or other educational institution until 21 days after the onset of rash in the last case of measles. Measles Outbreaks in Health-Care Settings

If a measles outbreak occurs within a health-care facility (e.g., hospital, clinic, physician office) or in the areas served by the facility, all persons working at the facility who cannot provide documentation of two doses of measles-containing vaccine separated by at least 28 days with the first dose administered on or after the first birthday, or who do not have other evidence of measles immunity (Table_1), should receive a dose of MMR vaccine. If indicated, health-care workers born during or after 1957 should receive a second dose of MMR vaccine at least 28 days after the previous dose (see Documentation of Immunity). Some health-care workers born before 1957 have acquired measles in health-care facilities and have transmitted the disease to patients or coworkers (see Health-care Facilities). Therefore, during outbreaks, health-care facilities also should strongly consider recommending a dose of MMR vaccine to unvaccinated health-care workers born before 1957 who do not have serologic evidence of immunity or a history of measles disease.

Serologic testing of health-care workers before vaccination is not generally recommended during an outbreak because arresting measles transmission requires rapid vaccination of susceptible health-care workers. The need to screen, wait for results, and then contact and vaccinate susceptible persons can impede the rapid vaccination needed to curb the outbreak.

Susceptible health-care workers (Table_1) exposed to measles should receive a dose of MMR vaccine and should be removed from all patient contact and excluded from the facility from the fifth to the 21st day after the exposure. They may return to work on the 22nd day after exposure. However, susceptible health-care workers who are not vaccinated after exposure should be removed from all patient contact and excluded from the facility from the fifth day after their first exposure to the 21st day after the last exposure, even if they receive postexposure IG. Personnel who become ill with prodromal symptoms or rash should be removed from all patient contact and excluded immediately from the facility until 4 days after the onset of their rash. Use of Quarantine

Imposing quarantine measures for outbreak control is usually both difficult and disruptive to schools and other organizations. Under special circumstances (i.e., during outbreaks in schools attended by large numbers of persons who refuse vaccination), restriction of an event or other quarantine measures might be warranted (226). However, such action is not recommended as a routine measure for control of most outbreaks. Rubella Case Investigation and Outbreak Control Case Definition

A suspected rubella case is any generalized rash illness of acute onset. A clinical case of rubella is defined as an illness characterized by all of the following clinical features:

- acute onset of generalized maculopapular rash; and
- a temperature of greater than 37.2 C (greater than 99 F), if measured; and
- arthralgia/arthritis, or lymphadenopathy, or conjunctivitis.

Cases meeting the measles case definition are excluded, as are cases with serologic findings compatible with recent measles virus infection.

A probable case of rubella

- meets the clinical case definition for rubella, and
- has no or noncontributory serologic or virologic testing, and
- is not epidemiologically linked to a laboratory-confirmed case.

A confirmed rubella case

- meets the laboratory criteria for rubella, or
- meets the clinical case definition and is epidemiologically linked to a laboratory confirmed case.

Suspected and known rubella cases should be reported immediately to local health departments. Aggressive case finding and intensified surveillance for CRS should follow. Rubella surveillance is complicated by the nonspecific nature of the symptoms of the clinical disease. Rubella can be confused with other illnesses, including measles. Thus, all rubella cases, particularly isolated cases that do not occur as part of an outbreak, should be confirmed by laboratory testing. Confirmed rubella cases are reported to the CDC by state health departments. Cases of febrile rash illness that are laboratory-negative for rubella may be measles (rubeola) and the patients should be tested for measles IgM.

Laboratory confirmation of suspected cases of CRS also is necessary because the constellation of findings of CRS varies. Case reports of indigenous congenital rubella syndrome are sentinel events, indicating the presence of rubella infections in the community that may previously have been unrecognized. The diagnosis of one or more indigenous CRS cases in a community should trigger intensified rubella and CRS surveillance.

A confirmed case of CRS has laboratory confirmation of rubella infection and at least one defect in each of the two following categories: a) cataracts/congenital glaucoma (either or both count as one), congenital heart disease, loss of hearing, pigmentary retinopathy; and, b) purpura, splenomegaly, jaundice, microcephaly, mental retardation, meningoencephalitis, radiolucent bone disease.

A probable case of CRS has any two conditions listed in category a) or one from category a) and one from category b) and lacks evidence of any other etiology. A case with laboratory evidence of rubella infection but no clinical symptoms or signs of CRS is classified "infection only." Laboratory Diagnosis

The criteria for laboratory diagnosis of rubella are

- a positive serologic test for rubella IgM antibody; or
- a significant rise between acute- and convalescent-phase titers in serum rubella IgG antibody level by any standard serologic assay; or
- the isolation of rubella virus from an appropriately collected clinical specimen.

The clinical diagnosis of acute rubella should be confirmed by laboratory testing (230). The demonstration of rubella-specific IgM antibody is the most commonly used method to obtain serologic confirmation of acute rubella infection. Rubella-specific IgM antibody usually becomes detectable shortly after rash onset. The IgM antibody peaks approximately 7 days after rash onset and remains detectable for 4-12 weeks, although it is more likely to be detectable if the serum specimen is obtained within 4-5 weeks after rash onset. Occasionally, rubella-specific IgM antibody can be detected up to 1 year after acute infection.

To test for IgM, one serum specimen can be obtained as early as 1-2 days after rash onset. If IgM is not detectable in this first specimen, a second serum specimen should be collected 5 days after the onset of rash or as soon as possible thereafter. False-negative rubella IgM antibody test results may sometimes occur even if the specimen is appropriately drawn. False-positive IgM test results may occur among persons with certain viral infections (e.g., acute infectious mononucleosis, cytomegalovirus, or parvovirus) and among persons who are rheumatoid factor positive.

For IgG assays, the criteria for a significant rise in rubella antibody level vary by type of assay and by laboratory. For HI assays, a fourfold rise in the titer of antibody indicates recent infection. The acute-phase serum specimen should be obtained as soon after rash onset as possible, preferably within 7 days. The convalescent-phase serum specimen should be drawn at least 10 days after the acute-phase serum specimen. The acute- and convalescent-phase serum specimens should be tested simultaneously in the same laboratory. If the acute-phase serum specimen is drawn greater than 7 days (and occasionally even if obtained within 7 days) after rash onset, a significant rise in antibody titer may not be detected by most commonly used IgG assays.

In the absence of rash illness, the diagnosis of subclinical cases of rubella can be facilitated by obtaining the acute-phase serum specimen as soon as possible after

exposure. The convalescent-phase specimen should be drawn at least 28 days after exposure. If acute- and convalescent-phase paired sera provide inconclusive results, rubella-specific IgM antibody testing can be performed. Expert consultation may be necessary to interpret the data.

Among pregnant women of unknown immune status who experience a rash illness or who are exposed to rubella, laboratory confirmation of rubella infection may be difficult. A serum specimen should be obtained as soon as possible. Unfortunately, serologic results are often nonconfirmatory. Such situations can be avoided by performing routine prenatal serologic screening of women who do not have acceptable evidence of rubella immunity (see Documentation of Immunity and Women of Childbearing Age). In addition, health-care providers should request that laboratories performing prenatal serologic screening retain such specimens until delivery, in case retesting is necessary. Congenital Rubella

Suspected cases of CRS should be managed with contact isolation (228). While diagnostic confirmation is pending, children with suspected CRS should be cared for only by personnel known to be immune to rubella. Confirmation of diagnosis by virus isolation can be done by culturing nasopharyngeal and urine specimens. Serologic confirmation can be obtained by testing cord blood for the presence of rubella-specific IgM antibodies. An alternative method for infants aged greater than or equal to 3 months is to document rubella-specific antibody levels that do not decline at the rate expected from passive transfer of maternal antibody (i.e., the equivalent of a twofold decline in HI titer per month). However, some infected infants may have low antibody levels because of agammaglobulinemia or dysgammaglobulinemia.

In some infants with CRS, rubella virus can persist and can be isolated from nasopharyngeal and urine cultures throughout the first year of life or longer (229). Children with CRS should be presumed infectious at least through the first year of life unless nasopharyngeal and urine cultures are negative for virus after age 3 months (230). Some authorities suggest that an infant who has CRS should be considered infectious until two cultures of clinical specimens obtained 1 month apart are negative for rubella virus (230). Precautions should be taken to ensure that infants with CRS do not cause additional rubella outbreaks. Specifically, all persons who have contact with a child with CRS (e.g., care givers, household contacts, medical personnel, laboratory workers) should be immune to rubella (Table_1) (see Documentation of Immunity and Routine Vaccination). Rubella Outbreak Control

Outbreak control is important for eliminating CRS. Aggressive responses to outbreaks may interrupt chains of transmission and can increase vaccination coverage among persons who might not be protected otherwise. Although methods for controlling rubella outbreaks are evolving, the main strategy should be to define target populations for rubella vaccination, ensure that susceptible persons within the target populations are vaccinated rapidly (or excluded from exposure if a contraindication to vaccination exists), and maintain active surveillance to permit modification of control measures as needed.

Control measures should be implemented as soon as a case of rubella is confirmed in a community. This approach is especially important in any outbreak setting involving pregnant women (e.g., obstetric-gynecologic and prenatal clinics). All persons at risk who cannot readily provide laboratory evidence of immunity or a documented history of vaccination on or after the first birthday should be considered susceptible and should be vaccinated unless vaccination is contraindicated (Table_1) (see Documentation of Immunity). Rubella Outbreaks in Schools or Other Educational Institutions

An effective means of terminating rubella outbreaks and increasing rates of vaccination quickly is to exclude from possible contact persons who cannot provide valid evidence of immunity. Experience with measles outbreak control indicates that almost all students who are excluded from school because they lack evidence of immunity quickly comply with vaccination requirements and are promptly readmitted to school. Persons exempted from rubella vaccination for medical, religious, or other reasons should also be excluded from attendance. Exclusion should continue for 3 weeks after the onset of rash of the last reported case in the outbreak setting. Less rigorous approaches (e.g., voluntary appeals for vaccination) have not been effective in terminating outbreaks. Rubella Outbreaks in Health-Care Settings

During rubella outbreaks in health-care settings where pregnant women may be exposed, mandatory exclusion and vaccination of health-care workers who lack evidence of rubella immunity (Table_1) should be practiced. Exposed health-care workers who lack evidence of immunity should be excluded from duty from the seventh day after first exposure through the twenty-first day after their last exposure or until 5 days after the rash appears. In addition, because birth before 1957 does not guarantee rubella immunity, health-care facilities should strongly consider recommending a dose of MMR vaccine to unvaccinated health-care workers born before 1957 who do not have serologic evidence of immunity. Although rubella vaccination during an outbreak has not been associated with substantial personnel absenteeism (116,191), vaccination of susceptible persons before an outbreak occurs is preferable because vaccination causes far less absenteeism and disruption of routine work activities than does rubella infection. Mumps Case Investigation and Outbreak Control Case Definition

A clinical case of mumps is defined as an illness characterized by acute onset of unilateral or bilateral tender, self-limited swelling of the parotid or other salivary gland lasting greater than or equal to 2 days, and without other apparent cause (as reported by a health professional).

A probable case of mumps

- meets the clinical case definition of mumps, and
- is not epidemiologically linked to a confirmed or probable case, and
- has noncontributory or no serologic or virologic testing.

A confirmed case of mumps

- meets the laboratory criteria for mumps, or
- meets the clinical case definition and is epidemiologically linked to a confirmed or probable case.

A laboratory-confirmed case need not meet the clinical case definition. Two probable cases that are epidemiologically linked are considered confirmed, even in the absence of laboratory confirmation.

Reporting of mumps often has been based solely on clinical diagnosis without laboratory confirmation. However, parotitis may have other infectious and noninfectious causes. Therefore, serologic confirmation of the diagnosis is preferred. Use of criteria for clinical diagnosis that are both stricter and more reliable, combined with laboratory confirmation, can be expected to decrease the number of false positive mumps cases reported and allow a more accurate assessment of mumps incidence.

Probable or confirmed cases of mumps should be reported immediately to state and local health departments. Recommended procedures to enhance the comprehensiveness of reporting include identification of all contacts, follow-up of susceptible contacts, and serologic testing of all probable cases to confirm the diagnosis. Laboratory Diagnosis

The laboratory criteria for the diagnosis of mumps are

- isolation of the mumps virus from a clinical specimen, or
- a significant rise between acute and convalescent-phase titers in serum mumps IgG antibody level by any standard serologic assay, or
- a positive serologic test for mumps IgM antibody.

In a prospective study in the practices of family practitioners in a Canadian community, one-third of persons with clinically diagnosed cases of mumps had no serologic evidence of recent mumps infection (28). Serum mumps IgM IFA tests are commercially available. However, until more data are available concerning the use and interpretation of these tests, laboratory confirmation of mumps should be based on tests of demonstrated reliability. State health department laboratories can provide guidance when testing for acute mumps infection is necessary. Mumps Outbreak Control

The strategy for outbreak control includes three main elements. The target population (transmission setting) must be defined. Persons within the population who are susceptible to mumps must be identified and vaccinated. Consideration should be given to excluding susceptible persons who are exempt from vaccination (for medical, religious, or other reasons) from the affected institution or setting until the outbreak is terminated. Active surveillance for mumps should be conducted until two incubation periods (i.e., 5-6 weeks) have elapsed since onset of the last case. School-based Mumps Outbreaks

Exclusion of susceptible students from schools affected by a mumps outbreak (and other, unaffected schools judged by local public health authorities to be at risk for transmission of the disease) should be considered among the means to control mumps outbreaks. Excluded students can be readmitted immediately after they are vaccinated. Experience with outbreak control for other vaccine-preventable diseases indicates that almost all students who are excluded from the outbreak area because they lack evidence of immunity quickly comply with requirements and can be readmitted to school. Pupils who have been exempted from mumps vaccination for medical, religious, or other reasons should be excluded until at least 26 days after the onset of parotitis in the last person with mumps in the affected school. Mumps Outbreaks in Health-Care Settings

Sporadic nosocomial cases of mumps have occurred in long-term care facilities housing adolescents and young adults (122). However, mumps virus is less transmissible

than measles and other respiratory viruses. The low level of mumps transmission in the community results in a low risk for introduction of the disease into health-care facilities. Because mumps is shed by infected persons before clinical symptoms become evident and because infected persons often remain asymptomatic, an effective routine MMR vaccination program for health-care workers is the best approach to prevent nosocomial transmission.

To prevent droplet transmission of the disease, respiratory isolation precautions for persons with mumps should be maintained for 9 days after onset of symptoms (e.g., parotitis). If exposed to mumps, health-care workers who lack acceptable evidence of immunity (Table_1) should be excluded from the health-care facility from the 12th day after the first exposure through the 26th day after the last exposure. Workers in whom the disease develops should be excluded from work until 9 days after the onset of symptoms.

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* Facilities that provide care exclusively for elderly patients who are at minimal risk for measles and rubella and complications of these diseases are a possible exception.

National Vaccine Injury Compensation Program, Health Resources and Services Administration, Parklawn Building, Room 8-05, 5600 Fishers Lane, Rockville MD 20857, Telephone: (800) 338-2382 (24-hour recording). Internet Home Page: "http://www.hrsa.dhhs.gov/ bhpr/vicp/new.htm." Persons wishing to file a claim for vaccine injury should write to: U.S. Court of Federal Claims, 717 Madison Place, NW, Washington DC 20005. Telephone: (202) 219-9657.

Table_1

Note: To print large tables and graphs users may have to change their printer settings to landscape and use a small font size.

TABLE 1. Acceptable presumptive evidence of immunity to measles, rubella, and mumps

	Routine	Persons who work in health-care facilities*	International travelers	Students at post-high school educational institutions
Measles	(1) documentation of adequate vaccination+: - preschool-aged children and adults not at high risk: 1 dose - school-aged children (grades K-12): 2 doses&,or (2) laboratory evidence of immunity,or (3) born before 1957,or (4) documentation of physician-diagnosed measles	(1) documented administration of 2 doses of live measles virus vaccine+@,or (2) laboratory evidence of immunity,or (3) born before 1957&,or (4) documentation of physician-diagnosed measles	(1) documented administration of 2 doses of live measles virus vaccine+**,or (2) laboratory evidence of immunity,or (3) born before 1957,or (4) documentation of physician-diagnosed measles	(1) documented administration of 2 doses of live measles virus vaccine+,or (2) laboratory evidence of immunity,or (3) born before 1957,or (4) documentation of physician-diagnosed measles
Rubella	(1) documented administration of one dose of live rubella virus, vaccine+,or (2) laboratory evidence of immunity,or (3) born before 1957 (except women of childbearing age who could become pregnant++)	(1) documented administration of one dose of live rubella virus vaccine+,or (2) laboratory evidence of immunity,or (3) born before 1957 (except women of childbearing age who could become pregnant++)	(1) documented administration of one dose of live rubella virus vaccine+,or (2) laboratory evidence of immunity, or (3) born before 1957 (except women of childbearing age who could become pregnant++)	(1) documented administration of one dose of live rubella virus vaccine+,or (2) laboratory evidence of immunity,or (3) born before 1957 (except women of childbearing age who could become pregnant++)
Mumps	(1) documented	(1) documented	(1) documented	(1) documented

	administration of one dose of live mumps virus vaccine+,or (2) laboratory evidence of immunity,or (3) born before 1957,or (4) documentation of physician-diagnosed mumps	administration of one dose of live mumps virus vaccine+ (2) laboratory evidence of immunity,or (3) born before 1957,or (4) documentation of physician-diagnosed mumps	administration of one dose of live mumps virus vaccine+ (2) laboratory evidence of immunity,or (3) born before 1957,or (4) documentation of physician-diagnosed mumps	administration of one dose of live mumps virus vaccine+ (2) laboratory evidence of immunity,or (3) born before 1957,or (4) documentation of physician-diagnosed mumps

* Health care workers include all persons (i. e., medical or nonmedical, paid or volunteer, full- or part-time, student or nonstudent, with or without patient- care responsibilities) who work in facilities that provide health care to patients (i. e., inpatient and outpatient, private and public). Facilities that provide care exclusively for elderly patients who are at minimal risk for measles and rubella and complications of these diseases are a possible exception.

\+ The first dose should be administered on or after the first birthday; the second dose of measles-containing vaccine should be administered no earlier than one month (i. e., minimum of 28 days) after the first dose. Combined measles- mumps- rubella (MMR) vaccine generally should be used whenever any of its component vaccines is indicated.

& May vary depending on current state or local requirements.

@ Health- care facilities should consider recommending a dose of MMR vaccine for unvaccinated workers born before 1957 who are at risk for occupational exposure to measles and who do not have a history of measles disease or laboratory evidence of measles immunity.

** Children aged 6- 11 months should receive a dose of monovalent measles vaccine (or MMR, if monovalent vaccine is not available) before departure. Children who receive a dose of measles- containing vaccine before their first birthdays should be revaccinated with two doses of MMR vaccine, the first of which should be administered when the child is aged 12- 15 months (12 months if the child remains in a high- risk area) and the second at least 28 days later.

++ Women of childbearing age are adolescent girls and premenopausal adult women. Because rubella can occur in some persons born before 1957 and because congenital rubella and congenital rubella syndrome can occur in the offspring of women infected with rubella virus during pregnancy, birth before 1957 is not acceptable evidence of rubella immunity for women who could become pregnant.

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Table_2

Note: To print large tables and graphs users may have to change their printer settings to landscape and use a small font size.

TABLE 2. Age-specific CD4+ T-lymphocye count and percent of total lymphocytes as criteria for severe immunosuppression in persons infected with human immunodeficiency virus (HIV)

	Age			
	<12 mos	1-5 yrs	6-12 yrs	>=13 yrs
Total CD4+ T-lymphocytes I OR CD4+ T-lymphocytes (as % of total lymphocytes)	<750/ uL OR <15%	<500/uL OR <15%	<200/uL OR <15%	<200/uL OR <14%

Sources:
CDC. 1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR 1992;41(RR-17):1-19. (125)
CDC. 1994 Revised classification system for human immunodeficiency virus infection in children less than 13 years of age; official authorized addenda: human immunodeficiency virus infection codes and official guidelines for coding and reporting ICD-9-CM. MMWR 1994; 43(RR-12):1-19. (126)

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Table_3

Note: To print large tables and graphs users may have to change their printer settings to landscape and use a small font size.

TABLE 3. Suggested intervals between administration of immune globulin prep- arations for various indications and vaccines containing live-measles virus *

Indications	Dose (mg IgG/kg)	Interval (mos) before measles vaccination
Tetanus prophylaxis (TIG)	250 units (10 mg IgG/kg) IM	3
Hepatitis A prophylaxis (IG) -	0.02 mL/kg (3.3 mg IgG/kg) IM	3
Contact prophylaxis - International travel	0.06 mL/kg (10 mg IgG/kg) IM	3
Hepatitis B prophylaxis (HBIG)	0.06 mL/kg (10 mg IgG/kg) IM	3
Rabies prophylaxis (HRIG)	20 IU/kg (22 mg IgG/kg) IM	4

Varicella prophylaxis (VZIG)	125 units/10 kg (20-40 mg IgG/kg) IM (maximum 625 units)	5
Measles prophylaxis (IG) -	0.25 mL/kg (40 mg IgG/kg) IM	5
Standard (i.e. nonimmuno-	0.50 mL/kg (80 mg IgG/kg) IM	6
compromised contact) -		
Immunocompromised contact		
Blood transfusion: - Red blood	10 mL/kg (negligible IgG/kg) IV	0
cells (RBCs), washed - RBCs,	10 mL/kg (10 mg IgG/kg) IV	3
adenine-saline added - Packed	10 mL/kg (60 mg IgG/kg) IV	6
RBCs (Hct 65%)+ - Whole blood	10 mL/kg (80-100 mg IgG/kg) IV	6
cells (Hct 35%-50%)+ -	10 mL/kg (160 mg IgG/kg) IV	7
Plasma/platelet products		
Replacement therapy for immune deficiencies&	300-400 mg/kg IV (as IVIG)	8
Respiratory syncytial virus prophylaxis	750 mg/kg IV (as RSV-IGIV)	9
Immune thrombocytopenic	400 mg/kg IV (as IGIV)	8
purpura(ITP)	1000 mg/kg IV (as IGIV)	10
Kawasaki disease	2 g/kg IV (as IGIV)	11

* This table is not intended for determining the correct indications and dosage for the use of IG preparations. Unvaccinated persons may not be fully protected against measles during the entire suggested time interval, and additional doses of immune globulin and/or measles vaccine may be indicated after measles exposure. The concentration of measles antibody in a particular immune globulin preparation can vary by lot. The rate of antibody clearance after receipt of an immune globulin preparation can vary. The recommended intervals are extrapo-lated from an estimated half life of 30 days for passively acquired antibody and an observed interference with the immune response to measles vaccine for 5 months after a dose of 80 mg IgG/kg. (See Mason W, Takahashi M, Schneider T. Persisting passively acquired measles antibody following gamma globulin therapy for Kawaski disease and response to live virus vaccination. In: Program and abstracts of the 32nd meeting of the Interscience Conference on Antimicrobial Agents and Chemotherapy {Abstract} Los Angeles CA, October 1992.

+ Assumes a serum IgG concentration of 16 mg/mL.

& Measles vaccination is recommended for HIV-infected children aged 36 months who do not have evidence of severe immunosuppression, but is contraindicated for patients who have congenital disorders of the immune system (Table 2).

Abbreviations: HBIG=hepatitis B immune globulin; Hct=hematocrit; HRIG=human rabies immune globulin; IG=serum immune globulin; IGIV=immunoglobulin, intravenous; IM=intramuscular; IV=intravenous, RBCs=red blood cells; RSV-IGIV=respiratory syncytial virus immune globulin, intravenous; TIG=tetanus immune globulin; VZIG=varicella zoster immune globulin.

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