Burden of Suffering

Rubella is generally a mild illness; when contracted by pregnant women, however, especially those in the first 16 weeks of pregnancy, it frequently causes serious complications including miscarriage, abortion, stillbirth, and congenital rubella syndrome (CRS). The 1964 rubella pandemic in the U.S. caused over 12 million infections, 11,000 fetal losses, and 20,000 cases of CRS in infants. The most common manifestations of CRS are hearing loss, developmental delay, growth retardation, and cardiac and ocular defects. The lifetime costs of treating a patient with CRS were estimated in 1985 to exceed $220,000.

Since 1969, when rubella vaccine became available in the U.S. and universal childhood immunization was initiated, no major periodic rubella epidemics have occurred. The incidence of reported cases has declined dramatically, to an estimated incidence rate of 0.1/100,000 population (192 cases) and an indigenous CRS incidence rate of 0/100,000 live births (no cases reported) in 1993. Outbreaks of rubella infection have continued to occur, however; in 1991, for example, 1,401 rubella infections were reported.
reported (0.6/100,000), one third of which occurred among adolescents and young adults (ages 15–29 years), resulting in 31 cases of CRS (0.8/100,000).\textsuperscript{4,5} Most recent outbreaks have occurred in settings where many unvaccinated children and young adults are gathered (e.g., religious communities that refuse vaccination, colleges, prisons, and work places), and among persons in specific racial/ethnic groups (e.g., Asians/Pacific Islanders and Hispanics) who are often unvaccinated.\textsuperscript{4,6,7} The highest risk for CRS occurs in Amish women, for whom the rate in one Pennsylvania county was 14/1,000 live births in 1991, compared to 0.006/1,000 for the general U.S. population.\textsuperscript{4}

**Accuracy of Screening Tests**

One way to prevent rubella infection in adults is to screen for susceptibility, by serologic tests for antibodies or by vaccination history, and to administer vaccine to susceptible persons. Vaccine trials and cohort studies have shown that most patients with hemagglutination-inhibition (HI) antibody are protected from clinical disease.\textsuperscript{8–10} HI is a labor-intensive test, however, and it can be associated with both false-positive and false-negative results.\textsuperscript{1,8,11} Faster, more convenient laboratory methods (e.g., enzyme immunoassay and latex agglutination) have now replaced HI in most laboratories.\textsuperscript{1,12} Using HI as the comparison standard, these tests have sensitivities of 92–100% and specificities of 71–100%.\textsuperscript{11,13–15} The apparently low specificities of some newer methods are due to their ability to detect low levels of rubella antibody that are undetectable by HI methods and are therefore reported as “false positives.”\textsuperscript{1,16,17} There have been no controlled trials to determine if these low levels confer immunity against wild virus,\textsuperscript{1} but other clinical and in vitro evidence suggests that they are protective.\textsuperscript{16,18–22} These newer tests, therefore, appear to be both more accurate and more convenient than HI when performed in laboratories with demonstrated proficiency.

A history of rubella vaccination can identify many who may be protected. Despite a variety of design flaws in some of the available studies (such as selection biases and small sample sizes), most demonstrate that persons with a positive history of having received rubella vaccine are significantly more likely to be seropositive (median 92%, range 82–97%) than those without such a history (median 74%, range 62–83%).\textsuperscript{18,23–30} A positive rubella vaccination history documented by vaccination card, school record, or medical record is more likely to be associated with seropositivity than is an undocumented history (although this difference was not statistically significant in some studies),\textsuperscript{18,25–27} and it is therefore preferred. A positive history of rubella infection is substantially less likely to correctly predict rubella immunity than is a positive history of vaccina-
therefore, a history of infection is not adequate for determining susceptibility.

**Effectiveness of Early Detection**

Rubella vaccine, once administered, is efficacious. Efficacy studies in healthy vaccinees show that ≥90% have protection against clinical rubella illness, and seropositivity is long-lasting. After the initiation of universal child immunization in 1969, the incidence of both rubella and CRS dropped markedly (see above). Adverse reactions from the RA27/3 live attenuated rubella vaccine (the only rubella vaccine currently licensed in the U.S.) are generally mild in children. Joint symptoms after vaccination are common in adults but rarely persist; the incidence is higher in women than men and increases with increasing age at vaccination. Vaccination of persons who are already immune rarely induces the joint symptoms seen with primary immunization of susceptible adults.

Because an estimated 6–12% of the young adult population is seronegative, and because CRS continues to occur in the U.S. despite recommendations for universal childhood vaccination (see Chapter 65), it has been recommended by some authorities that clinicians also direct efforts toward vaccinating susceptible adolescents and young adults, particularly women of childbearing age. Several factors may reduce the effectiveness of a strategy to prevent CRS by screening (with history of vaccination or serology) and vaccinating susceptibles. The screening test may falsely identify some susceptible persons as immune; of 21 infants with CRS in 1990, 71% of their mothers had had a positive serologic test and 43% gave a history of vaccination. Persons correctly identified as susceptible may not be offered or accept the vaccine; vaccination rates after serologic screening in different populations have ranged from 37% to 88%.

Seronegative women are more likely than are seronegative men to accept immunization, with the highest rates of follow-up vaccination (78–87%) occurring in susceptible postpartum women. The effectiveness of a strategy of screening and follow-up vaccination to prevent CRS may be assessed by its effect on the incidence of CRS and of rubella infection and susceptibility in women of childbearing age. No controlled studies have evaluated the effectiveness of screening and vaccinating susceptible persons in reducing the incidence of CRS. CRS occurrence has decreased over time in some, but not all, countries that have employed selective vaccination of susceptible adolescent and adult females as their sole strategy to reduce CRS. Evidence that screening and follow-up vaccination can reduce the likelihood of rubella infection was provided by a severe rubella outbreak in Iceland, where identical rates of
protection from infection occurred in screened and immunized (98.5%) and in naturally immune (99%) schoolgirls.\textsuperscript{61} Evidence regarding rubella susceptibility is supplied by a cohort study from Scotland. Six to seven years after a screening program for schoolgirls took place, 98.7% of girls who had originally been naturally immune had circulating antibodies, compared to 95.1% of those who had been vaccinated as susceptibles and 42.8% of a small group of susceptibles who had refused vaccination.\textsuperscript{62} Case series from Iceland\textsuperscript{61,63} and cross-sectional studies from Great Britain\textsuperscript{52,64} also show a reduction in susceptibility among women of childbearing age using this strategy. There is thus fair evidence that screening and immunizing susceptible females of childbearing age reduces both rubella susceptibility and infection and, by inference, CRS.

An alternative strategy to prevent rubella infection in women of childbearing age is routine vaccination without screening. In addition to protecting those who have not been previously vaccinated, such a strategy would eliminate most susceptibility due to primary vaccine failure (failure to develop antibodies after initial vaccination). Primary vaccine failure occurs in 2–5% of RA27/3 vaccine recipients,\textsuperscript{65–70} and a second rubella vaccination results in seroconversion in most cases.\textsuperscript{9,18} Antibodies have been found in 99.2% of schoolchildren after two doses of rubella vaccine, compared to 94.6% after one dose.\textsuperscript{28} In Sweden and Finland, vaccine programs in which all adolescent girls are routinely immunized (as well as all children at age 14–18 months) have been associated with substantially reduced occurrence of both seronegativity and of rubella infection in female compared to male adolescents and adults.\textsuperscript{71,72} These data provide fair evidence for routine vaccination of all nonpregnant women of childbearing age to reduce rubella susceptibility and infection and, therefore, CRS.

The rubella vaccine is contraindicated during pregnancy because of the theoretical possibility of teratogenicity, although there have been no reported cases of rubella vaccine-related birth defects in the United States after inadvertent vaccination of 321 susceptible pregnant women within 3 months of conception.\textsuperscript{1} Similarly reassuring results have been reported from Great Britain and Germany.\textsuperscript{73,74} Based on reported data, the true risk for CRS in susceptible women vaccinated during pregnancy using the RA27/3 vaccine may be zero, and the probability is 95% that the true risk is less than 1.7%.\textsuperscript{75} Because a measurable iatrogenic risk cannot be excluded, however, vaccination of susceptible women who are known to be pregnant should be postponed until the postpartum period.\textsuperscript{75} The virus has been isolated in breast milk and in breast-fed infants after postpartum vaccination,\textsuperscript{76} but no adverse consequences from such exposure have been reported.\textsuperscript{76,77} A greater disadvantage of postpartum immunization is that it often occurs too late to prevent CRS; 61% of reported cases have occurred with the first live birth.\textsuperscript{78}
In settings where large numbers of young adults are gathered (e.g., military bases and colleges), outbreaks of rubella are not uncommon, and males and females are infected at similar rates. Rubella screening or routine vaccination of young men in such settings might reduce the risk of spreading rubella to susceptible pregnant women. There is weak evidence from a single before-after study that universal rubella screening and follow-up vaccination of military recruits is effective in preventing rubella infection and eliminating epidemic rubella. A small cohort study using the older Cendehill vaccine found that routine vaccination of young male military recruits reduced rubella susceptibility, clinical disease, and viral shedding. In a before-after study of 256 college athletes (62% male) screened serologically with follow-up vaccination of susceptibles, the proportion with documented immunity by serology increased from 93% to 96%, and 8 of the remaining 9 seronegative students were vaccinated but did not receive follow-up testing. There is, however, no direct evidence that either screening or routine vaccination of males in these settings reduces CRS. For young men not living in such settings, no evidence was found to support either screening or routine vaccination in reducing susceptibility, infection, or CRS.

There are few data concerning rubella screening or vaccination in older men or in women past childbearing age. Because men ages 40 years and older and postmenopausal women account for only a small proportion (<10%) of recent rubella cases, have a high rate of natural immunity (85–95%), have a greater likelihood of postvaccine joint reactions, and are at little direct risk if they do become infected, routine screening or vaccination of this population does not seem to be justified despite the fact that these persons might, on rare occasions, transmit rubella to susceptible women of childbearing age.

**Recommendations of Other Groups**

The American Academy of Pediatrics (AAP), American College of Obstetricians and Gynecologists (ACOG), American College of Physicians, and Advisory Committee for Immunization Practices (ACIP) recommend vaccinating all adolescents and adults (particularly women and persons in colleges, health care settings, and military institutions) who have no contraindications and who lack documented evidence of either rubella immunization or after the first birthday or of serologic evidence of immunity. Routine serologic testing of men and nonpregnant women is not recommended by these organizations. The American Medical Association and Bright Futures recommend rubella vaccination (as measles-mumps-rubella [MMR]) for all adolescents who have not had two previous MMR vaccinations. The American Academy of Family Physicians recom-
mends rubella antibody testing in all women of childbearing age who lack evidence of immunity. AAP, ACOG, and ACIP recommend routine prenatal or antepartum serologic screening of all pregnant women not known to be immune, and postpartum vaccination of those found to be susceptible. The Canadian Task Force on the Periodic Health Examination recommends serologic screening of women of childbearing age, with vaccination of seronegative nonpregnant women immediately and seronegative pregnant women after delivery. They also recommend universal vaccination of women of childbearing age without screening as an acceptable alternative. The Canadian Task Force does not recommend for or against universal vaccination of young men in settings where large numbers of young persons are gathered.

Discussion

When administered to children, the current rubella vaccine is efficacious in the induction of rubella immunity and in the prevention of rubella infection and CRS. Recent cases of rubella and CRS have been associated with outbreaks among groups of unvaccinated persons, leading to infections of unvaccinated pregnant women. The added coverage provided by the two MMR vaccinations many will receive during childhood to meet current recommendations for measles immunization (see Chapter 65) should eliminate most primary vaccine failures, and will increase the rate of primary immunization among women of childbearing age. Therefore, the incidence of CRS will probably decline as the current cohort of highly immunized female children and adolescents enters its childbearing years.

In the intervening years, however, many women of childbearing age will remain unimmunized and, therefore, susceptible to rubella infection. Universal screening and follow-up vaccination of susceptible females would reduce rubella susceptibility, infections, and CRS; however, the effectiveness of this strategy in the clinical setting may be limited by incomplete screening, imperfect screening tests, and failure to vaccinate susceptibles. Routine vaccination of all women of childbearing age, without screening, also seems to be effective in reducing rubella infections; it avoids the problem of noncompliance with return visits, and if given as MMR also provides immunity to other infectious diseases, but it results in vaccination of many women who are already immune. Because the adverse effects of vaccinating immune persons appear to be minimal, cost and convenience are likely to be the determining factors in deciding which strategy should be used. In one study, the most cost-effective strategy was record review followed by vaccination, if at least 75% of patients had records available; otherwise, vaccination of all persons without screening was most cost-effective. On the other hand, a study from Iceland found that serologic screening of females
ages 12–40 followed by vaccination of seronegatives and follow-up retesting was more cost-effective than routine vaccination.\textsuperscript{94} These estimates are sensitive to the prevalence of immunity, compliance with follow-up, and the costs of screening, vaccine, and follow-up.

Whether either strategy (screening for susceptibility or routine vaccination of women of childbearing age) is justified by expected benefits compared to costs is not clear. An analysis of a premarital rubella screening program found that costs did not justify benefits unless at least 85% of seronegatives were vaccinated.\textsuperscript{95,96} Variation in the cost of the screening tests and vaccines, the prevalence of immunity, and the likelihood of rubella exposure will influence these results, however. The impact and benefit-cost ratio of strategies to reduce rubella susceptibility are likely to be greatest in settings where many women are unvaccinated (and are therefore at higher risk for acquiring rubella), such as certain religious communities and communities with many unimmunized immigrants from developing countries. Cost-benefit analyses concerning rubella screening and vaccination of women in various settings are needed.

**CLINICAL INTERVENTION**

All children without contraindications should receive MMR vaccine at age 12-15 months and again at age 4-6 years (see Chapter 65). To reduce further the incidence of CRS, screening for rubella susceptibility by history of vaccination or by serology is recommended for all women of childbearing age at their first clinical encounter ("B" recommendation). A documented history of vaccination is more accurate than an undocumented history in determining rubella immunity and is therefore preferred. All susceptible nonpregnant women of childbearing age should be offered vaccination. Susceptible pregnant women should be vaccinated in the immediate postpartum period. An equally acceptable alternative for nonpregnant women of childbearing age is to offer vaccination against rubella without screening ("B" recommendation). The decision of which strategy to use should be tailored to the individual clinician’s practice population, depending on the availability of vaccination records, the reliability of the vaccination history, the rate of immunity, the cost of serologic testing, and the cost and likelihood of follow-up vaccination for susceptible persons identified by serologic testing.

There is insufficient evidence to recommend for or against routine screening or vaccination of young men to prevent CRS in settings where large numbers of susceptible young adults of both sexes congregate, such as military bases and colleges ("C" recommendation). Recommendations to give MMR vaccine in these settings may be made on other grounds, however, such as prevention of measles (see Chapter 66). Routine screening or
vaccination of other young men, of older men, or of postmenopausal women, is not recommended ("D" recommendation).

Guidelines for the administration of MMR vaccine, and its contraindications, have been published by ACIP. The National Childhood Vaccine Injury Act requires that the date of administration, the manufacturer and lot number, and the name, address, and title of the person administering the vaccine be recorded in the patient’s permanent medical record (or in a permanent office log or file).97

The draft update of this chapter was prepared for the U.S. Preventive Services Task Force by Carolyn DiGuiseppi, MD, MPH.

REFERENCES


Chapter 32: Rubella