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Prevention of Congenital Rubella Syndrome—What Makes Sense in 2006?

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This review summarizes the practical aspects of rubella immunization programs in both developed and developing countries. Routine use of rubella vaccine is gradually resulting in the elimination of endemic rubella and congenital rubella syndrome (CRS) in the developed world, and routine use of vaccine in young children is now being implemented in many developing countries. However, such programs must achieve high immunization rates or be supplemented by the immunization of seronegative women of childbearing age to prevent a paradoxical increase in CRS as the burden of illness is shifted to an older age group. There are many successful prenatal screening programs for rubella immunity in developed countries, but screening prior to pregnancy could theoretically prevent even more cases of CRS. Enzyme-linked immunosorbent assay is the most commonly used laboratory test for screening, but the protective titer remains to be established. The need for reimmunization of women who serorevert or who remain seronegative following rubella vaccine has not been established. Surveillance for rubella cases and for CRS is vital in assessment of the ongoing success of rubella immunization programs.

antibodies, viral; immunization programs; rubella; rubella syndrome, congenital; rubella vaccine; rubella virus

Abbreviations: CRS, congenital rubella syndrome; ELISA, enzyme-linked immunosorbent assay; MMR, measles-mumps-rubella; WHO, World Health Organization.

INTRODUCTION

Congenital rubella syndrome (CRS) was first recognized in 1941 (1), shortly after the first isolation of the rubella virus. Viremia in the first 16 weeks of pregnancy can result in cellular deletion or endothelial damage in the developing fetus, with common manifestations being congenital cataracts, hearing impairment, patent ductus arteriosus, hepatosplenomegaly, thrombocytopenia, and mental retardation (2). Despite the introduction of an effective rubella vaccine in developed countries starting in 1969 and in selected developing countries starting in 1974, 836,356 cases of rubella from 123 countries were reported to the World Health Organization (WHO) in 2001 (3). The largest numbers of cases were reported from Belarus, Bulgaria, Kazakhstan, Poland, Ukraine, Argentina, Brazil, Mexico, and Venezuela, but it seems possible that some African and Asian countries with no rubella immunization or surveillance programs in place have higher incidence rates than do reporting countries. Cases of CRS continue to occur in the developing world (4), as does importation of rubella to developed countries where endemic disease has been eliminated. It is estimated by the WHO that a minimum of 100,000 cases of CRS occur annually worldwide (3), but it may be that the true incidence is more than double that estimate (5). Recognition of CRS is often hindered by its subtle or delayed manifestations, which contributes to the lack of data on the incidence of CRS in different WHO regions (4); only 50–181 cases were reported to the WHO annually for the years 2000–2004 (6). Rates of CRS as high as 3.5 per 1,000 livebirths (3) and 2.2 per 1,000 livebirths (4) have been described from outbreaks in the Russian Federation and Panama, respectively.

Our objective in this review is to describe 1) the rationale for and the efficacy of rubella immunization and screening

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strategies in developed and developing countries, 2) the appropriate postpartum management of women who are seronegative for rubella, and 3) the evaluation of programs designed to prevent CRS. To achieve this goal, we conducted a literature review of studies or review articles pertaining to rubella immunization programs, giving priority to those describing practical aspects of programs that could be applied outside the population under study.

RUBELLA IMMUNIZATION STRATEGIES

The historical perspective

Because the clinical features of rubella infection are often mild or nonspecific, making a clinical diagnosis of rubella infection can be difficult, and avoidance of infectious rubella cases during pregnancy is not practical. Therefore, ensuring that all pregnant women have natural or vaccine-induced immunity to rubella virus has become the prime strategy for the prevention of CRS. Many developed countries introduced a single dose of rubella vaccine for young children (United States) or adolescent girls (United Kingdom) shortly after the vaccine first became available, with the goal of preventing rubella infections in pregnant women. However, rubella virus continued to circulate in the community, since older children and/or boys had not been immunized and primary and secondary vaccine failures occurred (7, 8). A decade later, the primary strategy was changed to one of trying to eliminate endemic rubella by immunizing all children aged 12–15 months (there being evidence that vaccine can be given as early as 9 months of age without interference by passive maternal antibodies (9)), combined with variable campaigns for immunizing seronegative older children and women (10).

A second dose of combined vaccine (usually measles-mumps-rubella (MMR) vaccine but sometimes measles-rubella vaccine) was introduced in many countries during the late 1980s and early 1990s, mainly in response to measles outbreaks, with the main objective being to achieve immunity in patients with primary measles vaccine failure (10). Primary rubella vaccine failure appears to be rare; one study demonstrated a 100 percent seroconversion rate in 335 children given a single dose of vaccine at age 15 months (11), and a mean of 98 percent of 7,876 children and adults from six different older studies seroconverted following a single dose of vaccine (12). However, the efficacy of vaccine is of greater importance than the seroconversion rate, and efficacy was found to be 90 percent following a single dose administered during an outbreak at a US high school (8). Even if primary vaccine failure is rare, a second dose of rubella vaccine is potentially useful in the face of secondary vaccine failure. Although some investigators have described loss of immune titers in a small percentage of subjects during the years following a single dose of rubella vaccine (13–15) and asymptomatic reinfection appears to be very common in immunized subjects if they are exposed to rubella (7), it is not clear how frequently symptomatic rubella infection or CRS occurs secondary to waning immunity, nor is it clear that a second dose of vaccine would prevent these cases. Therefore, although two-dose strategies have resulted in the elimination of endemic rubella and have almost achieved elimination of CRS in many developed countries, the degree of benefit conferred by a second dose of rubella vaccine is still not clear (16).

The current perspective

Eradication of rubella and CRS is currently not a major global public health priority, because other diseases such as poliomyelitis and measles have historically resulted in more morbidity and mortality. However, eradication of rubella should be possible, since infection is limited to humans, prolonged shedding is limited to children with CRS, and vaccine efficacy is high (2). Rubella immunization has been shown to be cost-effective in both developed and developing countries if there is coadministration of measles vaccine and if coverage rates of more than 80 percent are achieved (17). However, the cost-effectiveness of a rubella immunization program has not been studied in the 48 countries classified as least developed by the WHO, where rates of CRS may be low because of high endemic rates of rubella infection and where low immunization rates could potentially shift rubella infections to an older age group (17). Despite the expected economic and medical benefits, only 116 (60 percent) of the 192 countries reporting to the WHO in 2004 had a rubella immunization program, accounting for 26 percent of the world birth cohort. The number of reported cases of rubella from each country is listed in the WHO vaccine-preventable diseases monitoring system (6). However, this is an impressive improvement from 1996, when only 78 countries had such a program (figure 1). Almost all countries offer the first dose of vaccine prior to age 24 months (18) and use live attenuated RA27/3 vaccine (5).

Despite the fact that most countries now rely on infant immunization to prevent CRS, this benefit will be achieved only if immunization rates are high; mathematical modeling predicts a possible paradoxical increase in CRS if childhood immunization rates are low, shifting infection to an older age group (19). Therefore, the WHO advises a minimum target rate of 80 percent for childhood immunization programs (20). In support of this theory, one study showed that immunization of teenage girls may be more effective than infant immunization for short-term prevention of CRS if vaccine uptake rates are suboptimal (21). Furthermore, increases in the incidence of CRS occurred in Greece and Brazil during the 1990s when childhood immunization rates were low (22, 23). Paradoxically, the availability of rubella vaccine to the private sector in developing countries that lack rubella immunization programs could increase the incidence of CRS (3).

It is interesting to consider that with 100 percent immunization rates, eradication of CRS would take 30–40 years with infant immunization alone and 10–20 years with adolescent female immunization alone, yet it is immediately attainable with the much less practical strategy of immunizing all women of childbearing age (24). Therefore, despite the fact that most rubella immunization strategies target children, immunization of seronegative women of childbearing age would prevent more cases of CRS in the immediate future. Thus, the goal of all countries should be

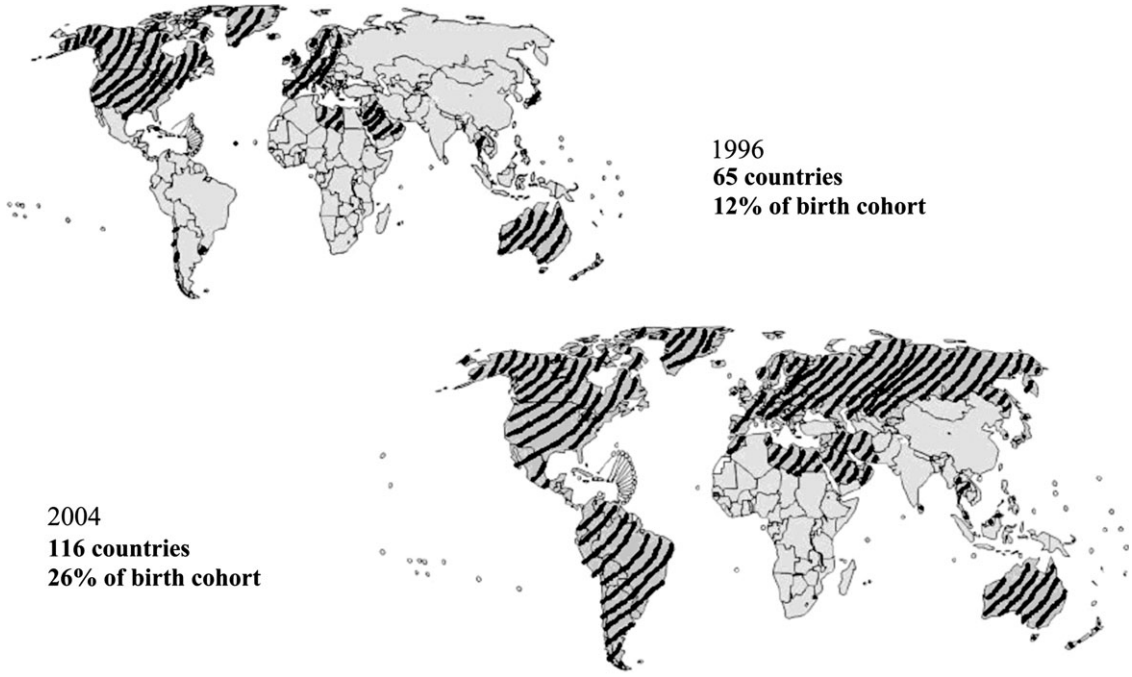

FIGURE 1. Countries reporting to the World Health Organization that have national rubella immunization programs. (Based on reports from 192 World Health Organization member countries, September 2005 (18).)

to ensure that all women with childbearing potential or all children have received at least one dose of measles-rubella or MMR vaccine, but caution should be exercised in introducing childhood immunization programs in places where uptake could be less than 80 percent. Eradication of rubella is not currently an attainable goal, but a marked reduction in the incidence of CRS should be possible with more widespread immunization programs (2).

Use of measles-rubella vaccine in programs designed primarily to prevent CRS has had a favorable effect on the incidence of measles infection (25). Despite the lack of data in the least developed countries, it is recommended that all immunization programs use MMR or measles-rubella vaccine, since the incremental cost of the second or third vaccine is low and the methods of achieving measles elimination mirror the methods of eliminating rubella and CRS (2, 25).

Profits from the manufacture of a vaccine that has been available for over 35 years and is no longer under patent are limited, so rubella vaccine shortages can occur (2). In March 2006, Chiron Corporation (Emeryville, California) withdrew its MMR vaccine from the market because of a possible association with fever and lymphadenopathy (26).

SCREENING FOR RUBELLA IMMUNITY

What screening strategy is most feasible in developed countries?

Determination of immunoglobulin G titers to rubella virus at the first prenatal care visit to assess immunity to rubella and determine the need for postpartum immunization is the most common screening strategy in developed countries, with screening rates of over 95 percent being reported in US studies (27, 28). The rubella seropositivity rate in developed countries ranges from less than 90 percent in an ethnically diverse population in Canada (29) to 99 percent in Australia (30). The success of screening is dependent on the number of women who seek prenatal care and is undoubtedly improved if rubella serologic analysis is part of routine prenatal blood work. Lower compliance with screening occurs if the clinician has to order specific tests (31), so the aim should be to use preprinted requisitions. One problem with screening pregnant women at the first prenatal care visit is that rubella infection may have already occurred in the pregnancy, resulting in an ''immune'' titer being reported (32). Screening with an immunoglobulin M assay would detect some of these cases but is not recommended, as it would add considerable cost to current screening programs. Furthermore, when rubella disease prevalence is low, the positive predictive value of a rubella immunoglobulin M result is poor, and thus false-positive findings resulting from cross-reacting antibodies are possible (33, 34). Positive immunoglobulin M results in a pregnant woman should always be further confirmed using additional laboratory testing, such as 1) a significant rise in immunoglobulin G titer between acute and convalescent paired sera, 2) virus isolation or detection, or 3) rubella immunoglobulin G avidity testing, with low avidity being indicative of recent primary infection (34, 35). Because of the important clinical management implications of rubella

infection in a pregnant woman, all laboratory, epidemiologic, and clinical data should be taken into account. Centralization of prenatal screening for a large population in a single laboratory allows for the comparison of rubella immunoglobulin G results from previous pregnancies to trigger investigation of cases with seroconversion in the absence of intercurrent rubella vaccine.

Recognition of rubella susceptibility prior to pregnancy is a useful addition to prenatal screening, since it allows for immunization of seronegative women. Most countries have abandoned premarital screening programs (which were implemented primarily for detection of syphilis) as common-law relationships have become more prevalent, so there is no longer a ''golden opportunity'' to do such screening. However, the majority of women would be identified if it were standard practice to confirm that rubella screening had been performed in all women of a certain age (such as 12–30 years) seen for the first time by a physician or when women first sought advice about birth control. Increasing use of electronic health records will facilitate confirmation that such screening has been performed and that seronegative women have received vaccine. Immigrant women of childbearing age from the developing world should be offered MMR at their first encounter with the health care system, since they account for a large number of CRS cases and waiting for results of serologic screening may result in a missed opportunity to vaccinate them (9, 10, 36, 37).

The need for rescreening of women who were previously immunoglobulin-G-seropositive for rubella virus remains controversial. As with many other viruses, a secondary immune response and replication in the respiratory tract can frequently be documented upon reexposure to wild rubella virus (7), but prior immunity usually prevents viremia and CRS can only occur in the face of viremia. There are reports of CRS occurring in infants born to women who had natural or vaccine-induced immunity to rubella prior to pregnancy but were reinfected with rubella during pregnancy (32). However, it is not known whether waning titers in early pregnancy were the risk factor for viremia in these cases. Unexpectedly, some of these women had neutralizing antibodies prior to the pregnancy in which the CRS occurred and a normal rubella-specific lymphoproliferative response to infection (38), suggesting that a complex immune defect may predispose them to reinfection. Rescreening early in pregnancy would not have prevented the CRS in these reported cases, since vaccine would not have been administered until postpartum. Although postpartum reimmunization of women with waning titers could potentially prevent CRS in subsequent pregnancies, there is insufficient evidence to support rescreening of previously seropositive women and no data to support or refute the value of offering rubella vaccine to women who serorevert.

How should screening be done in developing countries and the least developed countries?

Seropositivity rates in women of childbearing age have varied markedly in recent surveys, with rates of over 95 percent being reported from Haiti (39) and rates of 55 percent being reported from parts of India (40). A study of seropositivity in 45 developing countries from 1965 to 1997 showed that seropositivity was greater than 90 percent in 13 countries, 76–90 percent in 20 countries, and less than or equal to 75 percent in 12 countries (4). Screening should only be implemented if rubella immunization will be offered to seronegative women. Further studies will be required in order to determine whether limited health care dollars would be better spent on expanding rubella immunization programs or on prenatal screening in developing countries with variable seropositivity rates in pregnant women. A study from Thailand indicated that offering rubella vaccine to all girls in high school would be more cost-effective than implementing routine prenatal screening (41), and WHO policy is that given the safety of rubella vaccine and the cost of rubella serologic analysis, there is no role for serologic analysis prior to immunization in developing countries (20).

What method and cutoff should be used for screening for immunity?

Seropositivity is generally used as a marker of immunity to rubella, because the role of cell-mediated immunity remains unclear. Rubella serologic analysis was initially performed with hemagglutination inhibition, with a titer of 8 (1:8) being considered protective on the basis of studies in which subjects were exposed to wild rubella virus (42). Laboratories now perform an enzyme-linked immunosorbent assay (ELISA), with less frequent use of passive latex agglutination tests, immunofluorescent assays, radial hemolysis tests, and virus neutralization assays. ELISAs are generally considered more sensitive than hemagglutination inhibition tests (43, 44); ELISA titers of 15 IU/ml correspond to hemagglutination inhibition titers of 8–10 and so are considered indicative of immunity (42). However, run-to-run variability can occur with ELISA, and results are not necessarily transferable between assays, with one major manufacturer of rubella reagents (Abbott Laboratories, Chicago, Illinois) and the US Clinical and Laboratory Standards Institute using 10 IU/ml as a breakpoint (42, 45). When challenged with rubella vaccine, patients with titers below 15 IU/ml often have an immune response that is indicative of previous immunity, yet reinfection with viremia has been documented in patients with titers above 15 IU/ml (42), suggesting that antibodies measured by ELISA are not always functional. Therefore, uncertainty remains as to the appropriate breakpoint, since there have been no studies in which large numbers of subjects with various titers were exposed to wild rubella virus (42).

RUBELLA IMMUNIZATION IN SPECIFIC CIRCUMSTANCES

What approach should be taken to postpartum immunization and follow-up serology?

Even in jurisdictions with excellent prenatal screening programs, in-hospital postpartum immunization rates for seronegative women are variable, with recently reported rates of 66 percent (28) and 76 percent (27) in the United

States and 85 percent (46) and 94 percent (47) in the United Kingdom. Rates are presumably lower following induced or spontaneous abortion. Missed opportunities for postpartum or postabortal rubella immunization were documented in 12 of 21 cases of CRS in California (37). In one study from 2000, only 21 percent of US hospitals had a policy for postpartum rubella immunization (28). Barriers to postpartum or postabortal immunization include lack of clinician access to rubella serologic results, misunderstandings about contraindications for rubella vaccine (the only established contraindications being receipt of intravenous gamma globulin within the preceding 3 months, immunosuppression, and hypersensitivity to vaccine components), failure of health care workers to process postpartum immunization orders prior to hospital discharge, and failure to order vaccine if further pregnancies are considered unlikely. Introduction of preprinted orders increased postpartum immunization rates from 12 percent to 82 percent at one Canadian hospital (48). The benefit of having rubella vaccine available in outpatient clinics for postpartum immunization and the effects of early discharge on compliance with postpartum rubella immunization orders require further study.

TABLE 1. Research priorities in the field of prevention of congenital rubella syndrome (CRS)

Epidemiology
Establish the incidence of rubella and CRS worldwide.
Immunization
1. Determine whether a routine second dose of rubella vaccine would be cost-effective.
2. Ascertain the cost-effectiveness of rubella and combined measles-rubella vaccines in the least developed countries.
3. For developing countries, determine the most cost-effective timing of routine immunization for ensuring that pregnant women are protected from rubella.
4. For developed countries, develop a systematic method of screening women for rubella immunity prior to their first pregnancy.
5. Establish improved methods of ensuring that seronegative women are immunized postpartum.
6. Ascertain the risk of CRS in women with primary or secondary vaccine failure, including those with primary failure after two doses of vaccine.
Screening for immunity
Confirm the protective rubella titer with enzyme-linked immunosorbent assays.

What should be done if women remain seronegative following immunization?

As with women who serorevert, the vast majority of women who have received one or more doses of rubella vaccine are thought to be at minimal risk of developing viremia upon exposure to wild rubella virus, even if they remain seronegative. Approximately two thirds of unselected seronegative adults had a secondary immune response with reimmunization, indicating that they were immune to rubella despite being seronegative (45). One theory is that these subjects have neutralizing antibodies that are not measured by ELISA but inhibit the replication of vaccine virus, resulting in no detectable ELISA response to vaccine (45). Therefore, the value of a second dose of rubella vaccine in women who have been previously immunized is unclear. Pending more sophisticated assays for rubella immunity, it would seem reasonable to administer a second dose of vaccine, especially since failure to respond to a live viral vaccine can be due to improper cold-chain maintenance. However, it seems unlikely that a third dose of vaccine would confer additional immunity in a woman who remained seronegative after two doses.

What are the potential risks of administering vaccine to seronegative women of childbearing age?

Fever and lymphadenopathy can result from the viremia induced by rubella vaccine, and there have been rare reports of encephalitis and thrombocytopenia (10). Rubella vaccine was implicated in cases of chronic arthritis in the 1980s with isolation of virus from joint tissue, but it now appears that this association was not causal (9). Acute transient arthritis occurs in approximately 25 percent of immunized women but is also common after rubella infection, and this is the only common adverse event attributable to rubella vaccine (2, 9).

Prolonged shedding of the vaccine strain of the virus has been documented in an infant infected in utero following administration of rubella vaccine to a pregnant woman (49). However, to date there have been no documented cases of CRS attributable to immunization prior to or during pregnancy in mass immunization campaigns (16). A 2001 review of available registries in the United States, the United Kingdom, Sweden, and Germany by the Advisory Committee on Immunization Practices revealed that there were no cases of CRS among 680 children born to women who inadvertently received rubella vaccine during the 3 months prior to or during pregnancy (50). It is possible that the vaccine strain of the virus is sufficiently attenuated that CRS cannot result from fetal infection (2). However, it is still recommended that pregnancy be delayed for 28 days following vaccine administration (50).

Is vaccine-induced immunity equivalent to natural immunity?

As with other viruses, vaccine-induced immunity to rubella is not as durable as natural immunity. Peak vaccine-induced titers in children generally are lower and wane faster than titers following natural infection (13, 14), although one study showed a parallel decrease in titers (15). In a Finnish study, after administration of two doses of vaccine at 14–18 months and 6 years of age, titers were maintained at more than 15 IU/ml for 10 years in all 132 children but waned to 5–15 IU/ml at 15 years postvaccine in approximately one third of the children (51). In Sweden, vaccine-induced immunity (as indicated by a hemagglutination inhibition titer of 1:8 or greater) was shown to persist for 16 years in 94 percent of 190 girls immunized with a single dose at age 12 years (52). Another study showed

that the 5 percent of subjects who lacked immune hemagglutination inhibition titers 11 years postimmunization all had neutralizing antibodies, suggesting that they might have had immunity to rubella despite being seronegative (42). Reinfection following exposure to wild rubella virus is documented more commonly in patients with vaccine-induced immunity than in those with natural immunity, with one study showing the difference to be 80 percent versus 3 percent (7). Most cases of reinfection are thought to be asymptomatic, with viremia being rare. The clinical importance of waning immunity as measured by current assays is not clear, and to date there is no evidence of outbreaks of rubella or CRS in subjects with remote rubella immunization, suggesting that almost all of these subjects remain protected against clinical rubella and rubella viremia (10). However, it is conceivable that increasing numbers of women with vaccine-induced immunity alone will be identified as rubella-seronegative as compared with an era when most women had natural immunity, potentially increasing the public health burden for follow-up of seronegative women.

EVALUATION OF RUBELLA IMMUNIZATION PROGRAMS

As the goal of a rubella program shifts from outbreak control to the elimination phase, rubella surveillance shifts from outbreak detection to case-by-case investigation of possible cases of acquired rubella or CRS. The goal of such programs should be to decrease the incidence of CRS to less than 1 per 100,000 livebirths (53). Rubella immunoglobulin M in serum is typically used as a marker of recent infection for surveillance purposes, although false-positive results can occur (33), as explained above. Surveillance for acquired rubella requires investigation of all measles/rubella-like rashes with an immunoglobulin M assay for both viruses, as studies have shown that at least 20 percent of measles-like rashes are actually due to rubella (2, 9). Surveillance for CRS requires investigation of all infants with unexplained microcephaly, hearing impairment, cataracts, glaucoma, pigmentary retinopathy, patent ductus arteriosus, hepatosplenomegaly, thrombocytopenia, or radiolucent bone disease, even if maternal immunity to rubella was documented prior to or during pregnancy. If the most sensitive assays are used, rubella immunoglobulin M in serum can be found in almost 100 percent of children under 3 months of age with CRS (5). However, half of children with CRS have lost immunoglobulin M by age 12 months (54). Diagnosis may then depend upon persistence of serum immunoglobulin G beyond approximately 6 months of age (when maternal antibodies are no longer present) in the absence of rubella immunization (54) or detection of rubella virus in urine, blood, or nasopharyngeal secretions by culture or by reverse transcription polymerase chain reaction. Although prolonged shedding of virus in infants with CRS is a well-recognized phenomenon, virus can be cultured from only 50–60 percent of infants with CRS at 3 months of age and from 3 percent at 13–20 months of age (55). Because reverse transcription polymerase chain reaction is more sensitive than culture, it may be possible to detect shedding for a longer period of time.

Research priorities in the study of rubella virus are outlined in table 1. Prevention of CRS is best achieved through widespread immunization, resulting in a high seropositivity rate in pregnant women. The optimal method of achieving this goal is dependent upon both the local epidemiology of rubella infection and the local availability of public health services. Success can only be assured in the face of ongoing monitoring for vaccine coverage and surveillance for rubella infection and CRS.

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