

Position Paper on Rubella vaccines

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Selected references

Epidemiology of rubella and CRS

Gomwalk NE, Ahmad AA. Prevalence of rubella antibodies on the African continent. Rev Infect Dis. 1989 Jan-Feb;11(1):116-21.

Until recently, data on the epidemiology of rubella in Africa have been very scarce. However, several seroepidemiologic surveys within the last 10 years show that the virus is prevalent throughout Africa. In most of Africa rubella is contracted early in life; in areas such as the Gambia, Egypt, Zimbabwe, Mali, and parts of Kenya greater than 80% of children are immune to the virus by 10 years of age, and this level increases through adulthood. Most studies show that greater than 80% of pregnant women are immune to rubella.

Mellinger AK, Cragan JD, Atkinson WL, Williams WW, Kleger B, Kimber RG, Tavris D. High incidence of congenital rubella syndrome after a rubella outbreak. Pediatr Infect Dis J. 1995 Jul;14(7):573-8

Previous studies of the incidence of congenital rubella syndrome (CRS) after rubella outbreaks have been limited because most women with infection during the first trimester elected to have their pregnancies terminated. After a rubella outbreak in 1991 we measured prospectively the impact of maternal infection on CRS among the Amish in one county in Pennsylvania. We compared rubella serology of Amish women delivering before and after the outbreak and cord blood rubella IgM from Amish and non-Amish infants. Before the outbreak 20% of Amish women were susceptible to rubella; after the outbreak 4% were ($P = 0.001$). Of Amish infants 15% tested positive for rubella IgM; no non-Amish infants did ($P < 0.001$). This rubella outbreak in a largely unimmunized community led to a high rate of CRS. The annual CRS rate among the Amish was 2130/100,000 live births. Health care providers should promote immunization in all clients and intensify efforts among the Amish.

Miller E, Waight P, Gay N, Ramsay M, Vurdien J, Morgan-Capner P, Hesketh L, Brown D, Tookey P, Peckham C. The epidemiology of rubella in England and Wales before and after the 1994 measles and rubella vaccination campaign: fourth joint report from the PHLS and the National Congenital Rubella Surveillance Programme. Commun Dis Rep CDR Rev. 1997 Feb 7;7(2):R26-32.

The national immunisation campaign carried out in the United Kingdom in November 1994 was designed to give children aged 5 to 16 years of age a single dose of a combined measles and rubella vaccine. Its main objective was to prevent an epidemic of measles predicted in school age children. The rubella component of the vaccine was included in order to reduce the high level of susceptibility to rubella in young adult males and thus reduce the risk of transmission from this group to pregnant women. Susceptibility to rubella in children aged 5 to 16 years has fallen from 15.7% to 3.4% since the measles and rubella campaign. Despite this the incidence of laboratory confirmed rubella rose substantially in 1996, largely on account of cases among males aged 17 to 24 years, who were not vaccinated in the 1994 campaign and about 16% of whom are susceptible. The impact of the resurgence on the incidence of infection in pregnancy has been relatively limited, due to the low level of susceptibility in the antenatal population (2% in nulliparous and 1.2% in parous women for 1994/5). No cases of congenital rubella arising from administration of measles and rubella vaccine during the campaign have been identified. The numbers of babies born with congenital rubella and terminations of pregnancy for rubella arising from the 1996 resurgence are expected to be similar to those that followed the 1993 resurgence. The reduction in susceptibility in future cohorts of young men who received measles and rubella vaccine in the 1994 campaign should prevent future resurgences after the year 2000. If a second dose of measles, mumps, and rubella (MMR) vaccine had not been introduced, susceptibility levels in the school age population would have risen to about 12% in the future. The effect of the second dose of MMR vaccine introduced for children aged 4 to 5 years in October 1996 will be assessed through serological surveillance.

Cutts FT, Robertson SE, Diaz-Ortega JL, Samuel R. Control of rubella and congenital rubella syndrome (CRS) in developing countries, Part 1: Burden of disease from CRS. Bull World Health Organ. 1997;75(1):55-68.

Congenital rubella syndrome (CRS) can lead to deafness, heart disease, and cataracts, and a variety of other permanent manifestations. In developing countries, the burden of CRS has been assessed as follows: by surveillance of CRS; by surveillance of acquired rubella; by age-stratified serosurveys; and by serosurveys documenting the rubella susceptibility of women of childbearing age. During rubella outbreaks, rates of CRS per 1000 live births were at least 1.7 in Israel, 1.7 in Jamaica, 0.7 in Oman, 2.2 in Panama, 1.5 in Singapore, 0.9 in Sri Lanka, and 0.6 in Trinidad and Tobago. These rates are similar to those reported from industrialized countries during the pre-vaccine era. Special studies of CRS have been reported from all WHO regions. Rubella surveillance data show that epidemics occur every 4-7 years, similar to the situation in Europe during the pre-vaccination era. In developing countries, the estimated average age at infection varies from 2-3 years to 8 years. For 45 developing countries we identified serosurveys of women of childbearing age that had enrolled > or = 100 individuals. The proportion of women who remained susceptible to rubella (e.g. seronegative) was < 10% in 13 countries, 10-24% in 20 countries, and > or = 25% in 12 countries. Discussed are methods to improve the surveillance of rubella and CRS in developing countries.

Rubella immunization policy

Hinman AR, Bart KJ, Orenstein WA, Preblud SR. Rational strategy for rubella vaccination. Lancet. 1983 Jan 1;1(8314-5):39-40

Current rubella vaccination programmes, devised when knowledge of vaccine characteristics was still incomplete, have not been fully successful in protecting those at maximum risk of the sequelae of rubella infection. Now that more is known of vaccine characteristics and the impact of the initially chosen strategies has been assessed, it is time to modify immunisation strategies, the priorities being first to protect women of childbearing age, and then to interrupt transmission of rubella.

Robertson SE, Cochi SL, Bunn GA, Morse DL, Preblud SR. Preventing rubella: assessing missed opportunities for immunization. Am J Public Health. 1987 Oct;77(10):1347-9

Cases of rubella continue to occur among adults in the United States because 10-20 per cent of persons in this age group remain susceptible. To evaluate the potential preventability of these cases, we present a method for assessing missed opportunities for rubella immunization, based on immunization recommendations of the Immunization Practices Advisory Committee (ACIP) of the US Public Health Service (PHS). Immunization programs faced with limited resources can use analysis of missed opportunities to focus on those gaps in implementation contributing most to the remaining rubella cases.

Robertson SE, Cutts FT, Samuel R, Diaz-Ortega JL. Control of rubella and congenital rubella syndrome (CRS) in developing countries, Part 2: Vaccination against rubella. Bull World Health Organ. 1997;75(1):69-80

In 1995-96 we conducted a review of rubella immunization strategies. Worldwide, 78 countries (more than one-third) reported a national policy of using rubella vaccine. This was closely related to country economic status. Based on the United Nations country classification, rubella vaccine is used in 92% of industrialized countries, 36% of those with economies-in-transition, and 28% of developing countries. Cases of congenital rubella syndrome (CRS) may be prevented as follows: by providing direct protection to women and/or schoolgirls (a selective vaccination strategy); by vaccinating boys and girls to provide indirect protection by reducing the transmission of rubella virus (a childhood vaccination strategy); or by a combination of these approaches (a combined strategy). A combined strategy was most commonly reported (60% of countries); seven countries (9%) reported a selective strategy; and 24 countries (31%) reported only childhood immunization. Experience has shown that it is essential to include vaccination of women of childbearing age in any rubella control strategy. Childhood vaccination alone may pose a risk of an increase in CRS cases. Although many countries have introduced

rubella vaccine, few report any data on the impact of vaccination. Countries using rubella vaccine need to establish surveillance for rubella and CRS and monitor coverage in each of the target groups.

Rubella vaccines

Lerman SJ, Bollinger M, Brunken JM. Clinical and serologic evaluation of measles, mumps, and rubella (HPV-77:DE-5 and RA 27/3) virus vaccines, singly and in combination. Pediatrics. 1981 Jul; 68(1):18-22.

A double-blind, placebo-controlled comparison of single component and combination measles, mumps, and rubella (HPV-77:DE-5 and RA 27/3) virus vaccines involving 502 young children was conducted. The rubella antibody response was similar with RA 27/3 rubella and measles-mumps-rubella (RA 27/3) vaccines, but was diminished with the combination vaccine that incorporated HPV-77:DE-5 rubella. There was no evidence of enhanced clinical reactivity with either of the measles-mumps-rubella vaccines.

Greaves WL, Orenstein WA, Hinman AR, Nersesian WS. Clinical efficacy of rubella vaccine. Pediatr Infect Dis. 1983 Jul-Aug;2(4):284-6.

In the period October 10, 1980, to January 19, 1981, 83 cases of rash illness compatible with rubella were reported in Sanford, ME. Twenty-two (27%) were confirmed serologically. Forty cases (48%) occurred in Sanford High School students; the overall attack rate was 3.2%. A case-control study was undertaken to determine the effectiveness of rubella vaccine in preventing clinical rubella. Bayes' theorem was used to calculate the attack rates in the vaccinated population (ARV) and the unvaccinated population (ARU). Vaccine efficacy (VE), calculated with use of the formula $VE (\%) = [(ARU - ARV)/ARU] \times 100$, was 90%. These results indicate that rubella vaccine is highly effective in preventing clinical rubella and do not support proposals for routine revaccination.

Deforest A, Long SS, Lischner HW, Girone JA, Clark JL, Srinivasan R, Maguire TG, Diamond SA, Schiller RP, Rothstein EP, et al. Simultaneous administration of measles-mumps-rubella vaccine with booster doses of diphtheria-tetanus-pertussis and poliovirus vaccines. Pediatrics. 1988 Feb;81(2):237-46

The safety and efficacy of simultaneous administration of measles-mumps-rubella (MMR), diphtheria-tetanus-pertussis (DTP), and trivalent oral poliovirus (OPV) vaccines in a test group of 405 children were compared with the safety and efficacy of sequential administration of the same vaccines in a control group of 410 children given MMR followed by booster doses of DTP and OPV 2 months later. The study was double blind and placebo controlled with respect to DTP and OPV. Seroconversion rates to measles, mumps, and rubella exceeded 96% in both groups. Geometric mean titers to measles ($P = .05$) and rubella ($P = .004$) were

higher in the test group, and titers of antibodies to the other seven antigens were similar in both groups. Clinical reaction data were analyzed in 248 of 405 test children and 249 of 410 control children. The rates of serious vaccine-associated reactions were low and similar in the two groups. Some minor side effects were reported more frequently in the test group, but these differences were judged to be related to study design rather than to differences in the safety of the two vaccine schedules. The results indicate that the safety and serologic efficacy of administering MMR simultaneously with reinforcing doses of DTP and OPV in the second year of life is equivalent to the safety and efficacy observed after administering these antigens separately.

Schoub BD, Johnson S, McAnerney JM, Wagstaff LA, Matsie W, Reinach SG, Vandevoorde D, Andre FE, Teuwen DE. Measles, mumps and rubella immunization at nine months in a developing country. *Pediatr Infect Dis J.* 1990 Apr;9(4):263-7.

The antibody responses and reactogenicity of a measles, mumps and rubella vaccine in 9-month-old and 15-month-old black children in South Africa were compared. The antibody response to the measles component was marginally better in the older group, but no differences were observed in the response to the mumps and rubella components. Reactogenicity was similar in the two age groups. Therefore it is possible that a trivalent measles, mumps and rubella vaccine can safely and effectively replace routine measles immunization at 9 months of age in this population. Whether routine immunization policy should incorporate such a vaccine depends on the extent of acceptance of measles vaccination. In urban populations of developing countries with high rates of measles immunization, routine vaccination at 9 months might interrupt circulating wild type rubella and provide sufficient herd immunity to protect susceptible women of childbearing age. It also should decrease significantly the complications associated with wild type mumps infection. The replacement of measles vaccine by a trivalent vaccine may be very cost-effective.

Singh R, John TJ, Cherian T, Raghupathy P. Immune response to measles, mumps & rubella vaccine at 9, 12 & 15 months of age. *Indian J Med Res.* 1994 ct;100: 155-9.

Seroconversion rates to measles, mumps and rubella (MMR) in children given MMR vaccine at 9, 12 and 15 months of age were assessed so as to recommend the optimum age for vaccination. A total of 164 infants were recruited, of whom 123 completed the study. Sera were tested pre-immunization and 4 wk after MMR vaccine, for the presence and titres of antibodies by the haemagglutination inhibition (HI) test and by enzyme-linked immunosorbant assay (ELISA). The pre-immunization results showed that levels of maternal antibody detectable by HI had disappeared by 9 months in all infants in the case of measles, but not in the

case of mumps or rubella. Evidence for subclinical infection with the three viruses was found in 19 to 31 per cent of infants by 15 months of age. The responses to measles antigen by both HI test and ELISA were better (> 95%) at 12 or 15 months than at 9 months (80%). Vaccine failure was low at 12 or 15 months. The response to mumps antigen by HI antigen was also higher (92%) at 12 months than at 9 months (75%). Vaccine failure was less frequent at 12 months than at 9 months. The ELISA was found to be unreliable for mumps virus antibody testing. Rubella vaccine evoked good seroresponse (> 92%) at 9, 12 and 15 months, both by HI test and ELISA. Thus a better response to the MMR vaccine was obtained at or after 12 months of age than earlier. Hence, a dose of MMR may be given optimally at 12 months for children not previously immunized with measles vaccine. For those already given measles vaccine, the MMR may be given at 12 or 15 months.

Peltola H, Heinonen OP, Valle M, Paunio M, Virtanen M, Karanko V, Cantell K. The elimination of indigenous measles, mumps, and rubella from Finland by a 12-year, two-dose vaccination program. N Engl J Med. 1994 Nov 24;331(21):1397-402

BACKGROUND. In the 1970s measles, mumps, and rubella were rampant in Finland, and rates of immunization were inadequate. In 1982 a comprehensive national vaccination program began in which two doses of a combined live-virus vaccine were used. **METHODS.** Public health nurses at 1036 child health centers administered the vaccine to children at 14 to 18 months of age and again at 6 years, and also to selected groups of older children and young adults. Vaccination was voluntary and free of charge. In follow-up studies, we focused on rates of vaccination, reasons for noncompliance, adverse reactions, immunogenicity, persistence of antibody, and incidence of the three diseases. Since 1987, paired serum samples have been collected from all patients with suspected cases of measles, mumps, or rubella. **RESULTS.** Over a period of 12 years, 1.5 million of the 5 million people in Finland were vaccinated. Coverage now exceeds 95 percent. The vaccine was efficient and safe, even in those with a history of severe allergy. No deaths or persistent sequelae were attributable to vaccination. The most frequent complication requiring hospitalization was acute thrombocytopenic purpura, which occurred at a rate of 3.3 per 100,000 vaccinated persons. The 99 percent decrease in the incidence of the three diseases was accompanied by an increasing rate of false positive clinical diagnoses. In 655 vaccinated patients with clinically diagnosed disease, serologic studies confirmed the presence of measles in only 0.8 percent, mumps in 2.0 percent, and rubella in 1.2 percent. The few localized outbreaks were confined to patients in the partially vaccinated age groups. There are now fewer than 30 sporadic cases of each of the three diseases per year, and those are probably imported. **CONCLUSIONS.** Over a 12-year period, an immunization program using two doses of combined live-virus vaccine has eliminated indigenous measles, mumps, and rubella from Finland. Serologic studies show that most reported sporadic cases are now due to other causes, but a continued high rate of vaccination coverage is essential to prevent outbreaks resulting from exposure to imported disease.

Watson BM, Laufer DS, Kuter BJ, Staehle B, White CJ, Starr SE. Safety and immunogenicity of a combined live attenuated measles, mumps, rubella, and varicella vaccine (MMR(II)V) in healthy children. J Infect Dis. 1996 Mar;173(3):731-4. Erratum in: J Infect Dis 1996 Jun;173(6):1529.

An investigational tetravalent combined measles, mumps, rubella, and varicella vaccine and measles-mumps-rubella and varicella vaccines at separate injection sites given at the same visit were evaluated with respect to safety and cell-mediated and humoral immune responses at 6 weeks and 1 year after vaccination. Varicella seroconversion rates and lymphocyte proliferation responses were 100% for both vaccine groups at 6 weeks and 1 year. However, the antibody titer to varicella was lower in the combined vaccine group at 6 weeks, but there was no statistical difference in cell-mediated immune responses. One-year geometric mean titers were not statistically different. Seroconversion rates for measles, mumps, and rubella were 100% for both vaccine at 6 weeks and 1 year. Long-term follow-up of these immune responses is planned.

Matter L, Kogelschatz K, Germann D. Serum levels of rubella virus antibodies indicating immunity: response to vaccination of subjects with low or undetectable antibody concentrations. J Infect Dis. 1997 Apr;175(4):749-55.

To define the concentration of anti-rubella virus (RV) antibodies discriminating nonimmune from immune persons and to characterize immune responses to rubella vaccination, serologic studies were performed after rubella vaccination in persons with low or undetectable antibody concentrations. Thirty-six subjects with primary immune responses had prevaccination anti-RV IgG concentrations <15 IU/mL by ELISA and negative results by radial hemolysis. Eighty-three subjects with secondary immune responses had mean IgG increases of 9 IU/mL within 2 weeks. Eight of them had initial IgG levels <15 IU/mL, and 2 were negative by radial hemolysis. Both groups attained similar antibody levels after 1-3 months. Secondary immune responses to rubella vaccination were delayed by >2 weeks and thus resembled the time course of primary immunization, but IgM responses and IgG avidity were distinct between subjects with primary or secondary immune responses. Thresholds for immunity <15 IU/mL entail the risk of withholding rubella vaccination from susceptible persons.

Peltola H, Heinonen OP. Frequency of true adverse reactions to measles-mumps-rubella vaccine. A double-blind placebo-controlled trial in twins. Lancet. 1986 Apr 26;1(8487):939-42.

The vast majority of adverse reactions following immunisation of children with live measles-mumps-rubella (MMR) vaccine were shown in a double-blind, placebo-controlled, cross-over study in 581 twin pairs to be only temporally but not causally related to the vaccination. The true frequency of side-effects caused

by MMR vaccine, estimated from the discordance rates of individual signs and symptoms between MMR vaccinees and their placebo-injected twins, was between 0.5 and 4.0%. Moreover, respiratory symptoms, nausea, and vomiting were observed more frequently in the placebo-injected group than in the MMR vaccinated group.

Howson CP, Fineberg HV. Adverse events following pertussis and rubella vaccines. Summary of a report of the Institute of Medicine. JAMA. 1992 Jan 15;267(3):392-6

In August 1991, the Institute of Medicine released a report entitled Adverse Effects of Pertussis and Rubella Vaccines, which examined 18 adverse events in relation to diphtheria-tetanus-pertussis (DTP) vaccine and four adverse events in relation to the currently used rubella vaccine strain, RA 27/3. The committee spent 20 months reviewing a wide range of information sources, including case series and individual case reports, both published and unpublished, epidemiologic studies, studies in animals, and other laboratory studies. The committee found that the evidence indicates a causal relation between DTP vaccine and anaphylaxis and between the pertussis component of DTP vaccine and extended periods of inconsolable crying or screaming. The committee also reported that the evidence indicates a causal relation between the rubella vaccine and acute arthritis in adult women. The committee found the available evidence weaker but still consistent with a causal relation between DTP vaccine and two conditions--acute encephalopathy and hypotonic, hyporesponsive episodes--and between rubella vaccine and chronic arthritis in adult women. Estimated incidence rates of these adverse events following vaccination are provided, where possible. The committee found that the evidence does not indicate a causal relation between the DTP vaccine and infantile spasms, hypsarrhythmia, Reye's syndrome, and sudden infant death syndrome. The committee found insufficient evidence to indicate either the presence or absence of a causal relation between DTP vaccine and chronic neurologic damage, aseptic meningitis, erythema multiforme or other rash, Guillain-Barre syndrome, hemolytic anemia, juvenile diabetes, learning disabilities and attention-deficit disorder, peripheral mononeuropathy, or thrombocytopenia, and between rubella vaccine and radiculoneuritis and other neuropathies or thrombocytopenic purpura. The committee's evaluative methods are briefly described and a summary of research needs is provided.

Slater PE, Ben-Zvi T, Fogel A, Ehrenfeld M, Ever-Hadani S. Absence of an association between rubella vaccination and arthritis in underimmune postpartum women. Vaccine. 1995 Nov;13(16):1529-32.

In a double-blind historical cohort study, 485 underimmune women who received rubella vaccine post-partum during 1985-1990 and 493 controls matched for age, place of residence and date of delivery were queried by phone concerning joint complaints following the pregnancy in question. Those reporting joint symptoms

were invited for a personal interview at which joint symptoms and dates of their occurrence were explored in detail. Nineteen women in the vaccinated group (3.9%) and 16 from the control group (3.2%) were judged to have had joint symptoms compatible with the study definition of arthritis. The difference was not statistically significant. Thus, we were unable to find evidence for an association between rubella vaccination of underimmune adult women vaccinated post-partum and the subsequent development of arthritis. Rubella vaccine should continue to be used to immunize susceptible adult women against rubella in order to further the goal of elimination of the congenital rubella syndrome.

Frenkel LM, Nielsen K, Garakian A, Jin R, Wolinsky JS, Cherry JD. A search for persistent rubella virus infection in persons with chronic symptoms after rubella and rubella immunization and in patients with juvenile rheumatoid arthritis. Clin Infect Dis. 1996 Feb;22(2):287-94.

Peripheral blood polymorphonuclear leukocytes, mononuclear cells, and plasma and nasopharyngeal specimens were obtained from 6 subjects with persistent symptoms following rubella immunization, 1 subject with persistent symptoms following rubella, 11 children with juvenile rheumatoid arthritis, 17 recently immunized control subjects, and 1 control subject with acute clinical rubella. Rubella virus was isolated from the blood or nasopharynx of four of the 18 control subjects. In contrast, rubella virus was not recovered from any specimens from the seven subjects with persistent symptoms following immunization or natural infection or from the 11 children with juvenile rheumatoid arthritis. A polymerase chain reaction assay detected rubella virus in the blood from three of 14 control subjects but not in the blood from two subjects with persistent symptoms following rubella immunization or in that from three children with juvenile rheumatoid arthritis. We have not been able to confirm the findings of others who have reportedly recovered rubella virus from lymphocytes of persons with persistent symptoms following rubella or rubella immunization.

Protective immunity

Christenson B, Bottiger M. Long-term follow-up study of rubella antibodies in naturally immune and vaccinated young adults. Vaccine. 1994 Jan;12(1):41-5

Selective rubella vaccination of 12-year-old schoolgirls was introduced in Sweden in 1973 and at the same time a long-term follow-up cohort study was initiated. In 1982, a two-dose programme with a combined vaccine against measles, mumps and rubella (MMR) was introduced and vaccinations were given at the ages of 18 months and 12 years to both boys and girls. The cohort initially comprised 486 girls. It was followed for between 8 and 16 years. All the girls enrolled were seronegative before vaccination and had seroconverted to a haemagglutination-inhibition (HAI) titre of at least 1:16. On the last test occasion 16 years later, 22% had titre values below 1:16, and 6% lacked detectable antibodies against rubella (<

1:8). A fourfold or greater rise in titre was seen in 36% of the girls during the first 8 years of observation, whereas during the following 8 years only 1% showed a significant increase of titre values. The geometric mean titre declined from 1:110 to 1:34 during the first 8 years and further to 1:18 during the following 8 years. From 1982 to 1990, the seroimmunity to rubella of 18-year-old girls and boys was studied yearly. The number studied was 3308 18-year-old schoolgirls and 6347 18-year-old recruits born between 1964 and 1972. The recruits were divided into two groups, 4610 unvaccinated and born in 1964-1969 and 1737 vaccinated and born in 1970-1972. Seropositive recruits in the first group were thus naturally immune only, while the second group had a mixture of natural and vaccine-induced immunity.(ABSTRACT TRUNCATED AT 250 WORDS).

Johnson CE, Kumar ML, Whitwell JK, Staehle BO, Rome LP, Dinakar C, Hurni W, Nalin DR. Antibody persistence after primary measles-mumps-rubella vaccine and response to a second dose given at four to six vs. eleven to thirteen years. *Pediatr Infect Dis J.* 1996 Aug;15(8):687-92

BACKGROUND: Since 1989 the American Academy of Pediatrics and the ACIP have recommended a second dose of measles-mumps-rubella vaccine (M-M-R-II) at either school entry or age 11 to 13 years. Unfortunately few studies are available to compare responses to vaccine at the two ages. We performed a prospective trial to determine the persistence of antibody to measles, mumps and rubella vaccination in two age groups and the response to a second dose given at either 4 to 6 or 11 to 13 years. **METHODS:** Thirty-eight children 4 to 6 years old and 57 children 11 to 13 years old were given a second dose of M-M-R-II as they presented for yearly examinations. All had received the first dose at $>$ or $=$ 15 months of age. Measles and rubella antibody were measured by enzyme-linked immunosorbent assay (ELISA) and neutralizing antibody (NT) assay, and mumps antibody was measured by an ELISA method only. An IgM-ELISA antibody assay for measles was used in selected children. Prevacination and 3- to 4-week post-vaccination sera were obtained. Measles ELISA, measles-neutralizing antibody (NT) and rubella-neutralizing antibody (NT) assays were performed in all children. Seventy-nine of the 95 children had sufficient sera for repeat measles tests, as well as mumps and rubella ELISA determinations. **RESULTS:** Before the second dose ELISA seropositivity rates for measles and mumps were not significantly different between the two groups. Rubella ELISA seropositivity was 67% in 11- to 13-year-olds, compared with 90% in 4- to 6-year-olds ($P < 0.01$), suggestive of waning immunity. Rubella NT seropositivity was also lower in 11- to 13-year-olds than in 4- to 6-year-olds (63% vs. 100%, $P < 0.01$). After revaccination, 100% of the children become seropositive for all 3 antibodies. We performed measles IgM-ELISA testing on all 17 measles-seronegative children, as well as 15 seropositive children and 19 children who were 1 month postvaccination with the first M-M-R-II at 15 months. The purpose was to determine whether the seronegative children were primary or secondary failures. Five of the 17 children with undetectable pre-second dose antibody made IgM measles antibody after revaccination, suggesting that they were primary vaccine failures. **CONCLUSIONS:** Because all children became seropositive after revaccination, the age of administration can be based on the convenience of

vaccine scheduling. However, in view of the apparent decline in rubella antibodies at 11 to 13 years, future studies of rubella vaccination should address the issue of whether earlier boosting leads to greater susceptibility at the time of reproductive age.

Matter L, Kogelschatz K, Germann D. Serum levels of rubella virus antibodies indicating immunity: response to vaccination of subjects with low or undetectable antibody concentrations. J Infect Dis. 1997 Apr;175(4):749-55.

To define the concentration of anti-rubella virus (RV) antibodies discriminating nonimmune from immune persons and to characterize immune responses to rubella vaccination, serologic studies were performed after rubella vaccination in persons with low or undetectable antibody concentrations. Thirty-six subjects with primary immune responses had prevaccination anti-RV IgG concentrations <15 IU/mL by ELISA and negative results by radial hemolysis. Eighty-three subjects with secondary immune responses had mean IgG increases of 9 IU/mL within 2 weeks. Eight of them had initial IgG levels <15 IU/mL, and 2 were negative by radial hemolysis. Both groups attained similar antibody levels after 1-3 months. Secondary immune responses to rubella vaccination were delayed by >2 weeks and thus resembled the time course of primary immunization, but IgM responses and IgG avidity were distinct between subjects with primary or secondary immune responses. Thresholds for immunity <15 IU/mL entail the risk of withholding rubella vaccination from susceptible persons.

Asahi T, Ueda K, Hidaka Y, Miyazaki C, Tanaka Y, Nishima S. Twenty-three-year follow-up study of rubella antibodies after immunization in a closed population, and serological response to revaccination. Vaccine. 1997 Nov;15(16):1791-5.

Twenty-six institutionalized children immunized with a Japanese rubella vaccine, Matsuba strain, have been observed for 23 years and the persistence of vaccine-induced rubella immunity documented. All vaccinees were shown to have seroconverted to rubella virus in a haemagglutination inhibition (HI) test, and the geometric mean titre (GMT) of rubella HI antibody rose to 2 5-8 months after vaccination (Ueda et al., *Acta Paediatrica Japonica, Overseas Edition* 1978, 20, 8-14). The GMT then declined gradually to 2 23 years after inoculation, except in four cases (15.4%) which had reverted to negative. However, three of the four maintained a rubella HI antibody titre of 1:4. Twelve of the 26 vaccinees were revaccinated 24 years after primary vaccination, and all ten cases having initial titres of < or = 1:16 demonstrated secondary responses. Rubella immunity induced by vaccination had persisted, so routine booster immunization did not seem necessary. However, a second immunization programme should be considered to achieve high antibody-positive rates and to protect against primary vaccine failure.

Unpublished WHO documents

Control of rubella and congenital rubella syndrome (CRS) in developing countries. Geneva, 2000 (unpublished document WHO/V&B/00.03; available from Vaccines and Biologicals, World Health Organization, 1211 Geneva 27, Switzerland and on the Internet at <http://www.who.int/vaccines-documents/DocsPDF/ww9656a.pdf>).

Guidelines for surveillance of congenital rubella syndrome (CRS) and rubella - Field test version, May 1999. Geneva, 1999 (unpublished document WHO/V&B/99.22; available from Vaccines and Biologicals, World Health Organization, 1211 Geneva 27, Switzerland and on the Internet at www.who.int/vaccines-documents/DocsPDF99/www9934.pdf).

An updated version of the above surveillance guidelines is found in “WHO-recommended standards for surveillance of selected vaccine preventable diseases” WHO/IVB/03.01 at www.who.int/vaccines-documents/DocsPDF06/843.pdf

Reporting on a meeting on preventing congenital rubella syndrome (CRS): immunization strategies, surveillance needs, Geneva, 12–14 January 2000. Geneva: World Health Organization; 2000 (unpublished document WHO/V&B/00.10; available from Vaccines and Biologicals, World Health Organization, 1211 Geneva 27, Switzerland and on the Internet at www.who.int/vaccines-documents/DocsPDF00/www508.pdf).