

WHO position paper on rubella vaccines

References (when available with summaries) used in the position paper and associated GRADE tables

References used in the position paper

Anderson RM, May RM. Vaccination against rubella and measles: quantitative investigations of different policies. J Hyg (Lond). 1983 Apr;90(2):259-325.

This paper uses relatively simple and deterministic mathematical models to examine the impact that different immunization policies have on the age-specific incidence of rubella and measles. Following earlier work by Knox (1980) and others, we show that immunization programmes can, under some circumstances, increase the total number of cases among older age groups; the implications for the overall incidence of measles encephalitis and of congenital rubella syndrome are examined, paying attention both to the eventual equilibrium and to the short-term effect in the first few decades after immunization is initiated. Throughout, we use data (from the U.K., and U.S.A. and other countries) both in the estimation of the epidemiological parameters in our models, and in comparison between theoretical predictions and observed facts. The conclusions defy brief summary and are set out at the end of the paper.

Beasley RP, Detels R, Kim KS, Gale JL, Lin TL, Grayston JT. Prevention of rubella during an epidemic on Taiwan. HPV-77 and RA 27-3 rubella vaccines administered subcutaneously and intranasally HPV-77 vaccine mixed with mumps and-or measles vaccines. Am J Dis Child. 1969 Aug;118(2):301-6. (No abstract available).

Best JM. Rubella. Semin Fetal Neonatal Med. 2007 Jun;12(3):182-92.

Rubella is associated with an 80% risk of congenital abnormalities if acquired in the first 12 weeks of pregnancy. Reinfection in early pregnancy presents a much smaller risk. Prenatal diagnosis may be useful to assess the risk to the fetus. Congenital rubella is a progressive disease and some abnormalities will not be present at birth. Rubella and congenital rubella are usually diagnosed by detection of rubella-specific IgM; it may be difficult to confirm a diagnosis of congenital rubella in children over 3 months of age. Rubella vaccines are usually combined with measles and mumps vaccines. Their use has enabled some industrialised countries to eliminate rubella and congenital rubella. Countries should ensure that susceptible women of child-bearing age and health care workers are offered a rubella-containing vaccine. Rubella vaccine is contraindicated during pregnancy, but if a pregnant woman is inadvertently vaccinated it is not an indication for termination or prenatal diagnosis.

Bullens D et al. Congenital rubella syndrome after maternal reinfection. *Clinical Pediatrics (Phila)*, 2000, 39:113–116. (No abstract available).

Castillo-Solórzano C, Carrasco P, Tambini G, Reef S, Brana M, de Quadros CA. New horizons in the control of rubella and prevention of congenital rubella syndrome in the Americas. *J Infect Dis*. 2003 May 15;187 Suppl 1:S146-52.

Data from the regional measles surveillance system have documented widespread rubella virus circulation in many different countries in the Americas. In response to the ongoing endemic incidence of the disease and the potential for a major rubella epidemics in the region, the Pan American Health Organization Technical Advisory Group on Vaccine Preventable Diseases recommended the implementation of a regional initiative to strengthen rubella and congenital rubella syndrome (CRS) preventive efforts in 1997. This article summarizes and highlights the progress toward accelerated rubella control and CRS prevention in the English-speaking Caribbean and in Chile, Costa Rica, and Brazil. Useful knowledge is being generated for the adaptation of similar rubella strategies elsewhere. The findings also document the feasibility of implementing the recommended strategies and their rapid impact on disease burden.

Crovati P, Gabutti G, Giammanco G, Dentico P, Moiraghi AR, Ponzio F, Soncini R. Reactogenicity and immunogenicity of a new combined measles-mumps-rubella vaccine: results of a multicentre trial. *The Cooperative Group for the Study of MMR vaccines. Vaccine*. 2000 Jun 15;18(25):2796-803.

A large single blind, multi-centre study involving 1779 children was performed in Italy. Infants, aged between 12 and 27 months were divided between two groups: group A received a single dose of a new MMR vaccine, 'Priorix'(3), while group B received a widely used MMR vaccine, Triviraten(4). Solicited local and general symptoms were recorded using diary cards and antibody levels were measured, prior to and 60 days post-vaccination, using ELISA assays. The incidence of solicited symptoms (evaluated in 1754 subjects) was comparable between groups, with the exception of fever which was significantly lower in group B. Immunogenicity was evaluated in 686 subjects. Of note, was the significantly higher anti-mumps seroconversion rate ($p < 0.001$) observed in group A (97.0%) compared to group B (35.4%). However the anti-measles and anti-rubella seroconversion rates were equivalent between groups. Significantly higher ($p < 0.001$) post-vaccination GMTs were in group A vs group B for anti-measles (2830 vs 784 IU/ml) and anti-mumps (1640 vs 469 U/ml), however the anti-rubella GMTs were significantly higher ($p < 0.001$) in group B (117.6 IU/ml) compared to group A (92.6 IU/ml). The persistence of antibodies in 35 subjects was assessed 1 year after vaccination and the results showed no appreciable decline in titres with either vaccine. The trial demonstrates 'Priorix' is well tolerated and highly immunogenic.

Cusi MG, Valensin PE, Cellesi C. Possibility of reinfection after immunisation with RA27/3 live attenuated rubella virus. *Arch Virol*. 1993;129(1-4):337-40.

A serological study was carried out on 527 girls immunized with RA 27/3 rubella vaccine. Data from all scheduled serum samples over a 5-year follow-up were available for 102 vaccinees, 10 (9.8%) of whom showed evidence of reinfection during the 5th year after immunisation, a year in which there was a rubella outbreak in the Siena area (Italy). We examined in greater detail the serological responses of these vaccinees after reinfection and the consequent implications pertinent to the duration of the protective immunity.

Cutts FT, Vynnycky E. Modelling the incidence of congenital rubella syndrome in developing countries. *Int J Epidemiol.* 1999 Dec;28(6):1176-84.

BACKGROUND: As of 1997, less than one-third of developing countries included rubella vaccine in their national immunization programme. In countries that have achieved high coverage of measles vaccine, an ideal opportunity exists to include control of rubella and congenital rubella syndrome (CRS) in enhanced measles control activities. Data on the burden of congenital rubella syndrome are important to guide rubella vaccination policies.

METHODS: We reviewed the literature to identify studies of rubella antibody prevalence in developing countries that were conducted on populations with no major selection bias, prior to wide-scale rubella vaccination in the country. We used a simple catalytic model to describe the age-specific prevalence of susceptibility to rubella virus infection in given populations. Estimates of the incidence of infection among pregnant women were calculated using expressions for the average prevalence of susceptibility to infection and the incidence of infection during gestation. To estimate the number of cases of CRS, we assumed an overall risk of 65% after infection in the first 16 weeks of pregnancy and zero risk thereafter. These estimates were derived for each country for which data were available, then for each World Health Organization region, excluding Europe.

RESULTS: The estimated mean incidence of CRS per 100,000 live births was lowest in the Eastern Mediterranean region (77.4, range 0-212) and highest in the Americas (175, range 0-598). The mean of the estimates of the total number of cases of CRS in developing countries in 1996 was approximately 110,000. The range was, however, very wide, from as few as 14,000 to as many as 308,000 cases.

CONCLUSIONS: Congenital rubella syndrome is an under-recognized public health problem in many developing countries. There is an urgent need for collection of appropriate data to estimate the cost-effectiveness of a potential global rubella control programme.

Inclusion of rubella vaccine in the national immunization program was found to be implemented in less than one-third of the developing countries in a review conducted by WHO. This paper examines the incidence of congenital rubella syndrome (CRS) cases in developing countries using published rubella infection prevalence. Documented literature of previous studies and medical data on women attending antenatal clinics were gathered and rubella antibody prevalence was identified before the wide-scale rubella vaccination. A catalytic model was used in describing age-specific prevalence of rubella virus infection in given populations, while expressions for the average prevalence of susceptibility to infection and incidence of infection during gestation was used to estimate the incidence of infection among pregnant women. Using the data gathered from each country and WHO regions, an overall risk of 65% after infection in the first 16 weeks and zero risk of defect later in pregnancy was assumed to estimate the incidence of CRS. Results revealed that the estimated

mean incidence of CRS per 100,000 live births was significantly lower in the eastern Mediterranean region (77.4, range 0-212) and higher in the Americas (175, range 0-598). On the other hand, the 1996 CRS mean estimate for developing countries was approximately 110,000, ranging from 14,000 to 308,000 cases. This study concludes with the stated need for an improved CRS program in developing countries as well as adequate data collection necessary for cost-effectiveness evaluation of potential global rubella control programs.

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.

Demicheli V, Jefferson T, Rivetti A, Price D. Vaccines for measles, mumps and rubella in children. Cochrane Database Syst Rev. 2005 Oct 19;(4):CD004407.

BACKGROUND: Public debate over the safety of the trivalent measles, mumps and rubella (MMR) vaccine, and the resultant drop in vaccination rates in several countries, persists despite its almost universal use and accepted effectiveness.

OBJECTIVES: We carried out a systematic review to assess the evidence of effectiveness and unintended effects associated with MMR.

SEARCH STRATEGY: We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue 4, 2004), MEDLINE (1966 to December 2004), EMBASE (1974 to December 2004), Biological Abstracts (from 1985 to December 2004), and Science Citation Index (from 1980 to December 2004). Results from reviews, handsearching and from the consultation of manufacturers and authors were also used.

SELECTION CRITERIA: Eligible studies were comparative prospective or retrospective trials testing the effects of MMR compared to placebo, do-nothing or a combination of measles, mumps and rubella antigens on healthy individuals up to 15 years of age. These studies were carried out or published by 2004.

DATA COLLECTION AND ANALYSIS: We identified 139 articles possibly satisfying our inclusion criteria and included 31 in the review.

MAIN RESULTS: MMR was associated with a lower incidence of upper respiratory tract infections, a higher incidence of irritability, and similar incidence of other adverse effects compared to placebo. The vaccine was likely to be associated with benign thrombocytopenic purpura, parotitis, joint and limb complaints, febrile convulsions within two weeks of vaccination and aseptic meningitis (mumps) (Urabe strain-containing MMR). Exposure to MMR was unlikely to be associated with Crohn's disease, ulcerative colitis, autism or aseptic meningitis (mumps) (Jeryl-Lynn strain-containing MMR). We could not identify studies assessing the effectiveness of MMR that fulfilled our inclusion criteria even though the impact of mass immunisation on the elimination of the diseases has been largely demonstrated. **AUTHORS' CONCLUSIONS:** The design and reporting of safety outcomes in MMR vaccine studies, both pre- and post-marketing, are largely inadequate. The evidence of adverse events following immunisation with MMR cannot be separated from its role in preventing the target diseases.

da Silva e Sá GR, Camacho LA, Siqueira MM, Stavola MS, Ferreira DA. Seroepidemiological profile of pregnant women after inadvertent rubella vaccination in the state of Rio de Janeiro, Brazil, 2001-2002. Rev Panam Salud Publica. 2006 Jun;19(6):371-8.

OBJECTIVES: To analyze postvaccination serological status in pregnant women inadvertently vaccinated against rubella in the state of Rio de Janeiro, Brazil.

METHODS: This was a cross-sectional study of pregnant women 15 to 29 years old, vaccinated against rubella and measles from November 2001 to March 2002, who were unaware of their pregnancy at the time of vaccination or who became pregnant within 30 days thereafter. They were tested for rubella-specific immunoglobulin M (IgM) and G (IgG) and classified as immune (IgM-negative, IgG-positive, tested within 30 days after vaccination), susceptible (IgM-positive after vaccination) or indeterminate (IgM-negative, IgG-positive, vaccination-serological testing interval greater than 30 days).

RESULTS: Of 2 292 women, 288 (12.6%) were susceptible, 316 (13.8%) immune, 1 576 (68.8%) indeterminate, 8 (0.3%) ineligible, and 104 (4.5%) lost to follow-up. IgM seropositivity by vaccination-serological testing interval was 16.1% (\leq 30 days), 15.4% (30-60 days), and 14.2% (61-90 days). Considering the campaign's target age, the 20-to-24-year age group had the largest proportion of individuals susceptible to rubella (14.8%) and represented 42.4% (122/288) of all susceptible women. In 75% of susceptible pregnant women, gestational age was 5 weeks or less at the time of vaccination.

CONCLUSIONS: Mass immunization of childbearing-age women was justified on the basis of epidemiological and serological data. Follow-up of vaccinated pregnant women revealed no cases of congenital rubella syndrome due to rubella vaccination. However, the observed rate of congenital infection supports the recommendation to avoid vaccinating pregnant women, and to avoid conception for up to 1 month following rubella vaccination.

DeStefano F, Thompson WW. MMR vaccine and autism: an update of the scientific evidence. Expert Rev Vaccines. 2004 Feb; 3(1):19-22.

An hypothesis published in 1998 suggested that measles-mumps-rubella vaccine may cause autism as a result of persistent measles virus infection of the gastrointestinal tract. Results of early studies were not supportive and in 2001 a review by the Institute of Medicine concluded that the evidence favors the rejection of a causal relationship at the population level between measles-mumps-rubella vaccine and autistic spectrum disorder. Studies published since the Institute of Medicine report have continued not to find an increased risk of autistic spectrum disorder associated with measles-mumps-rubella. The vaccine also has not been found to be associated with a unique syndrome of developmental regression and gastrointestinal disorders. The evidence now is convincing that the measles-mumps-rubella vaccine does not cause autism or any particular subtypes of autistic spectrum disorder.

Enders G, Nickerl-Pacher U, Miller E, Cradock-Watson JE. Outcome of confirmed periconceptual maternal rubella. Lancet. 1988 Jun 25; 1(8600):1445-7.

61 pregnant women in whom confirmed rubella occurred from 5 weeks before to 6 weeks after the last menstrual period (LMP) were followed up prospectively. In 39, the pregnancy was terminated and the fetal tissues or mixed products of conception were examined for rubella virus. In 22, the pregnancy continued to term and cord serum was tested for specific IgM antibody. No evidence of intrauterine infection was found in 38 pregnancies in which the mother's rash appeared before, or within 11 days after, the last menstrual period. The shortest interval at which fetal infection occurred was when the rash appeared 12 days after the last menstrual period. All 10 pregnancies in which the rash appeared 3-6 weeks after the last menstrual period resulted in fetal infection: 4 of these pregnancies went to term, and all 4 infants were damaged. The risk to the fetus when rubella occurs before the mother's last menstrual period is probably negligible.

Goh P, Lim FS, Han HH, Willems P. Safety and immunogenicity of early vaccination with two doses of tetravalent measles-mumps-rubella-varicella (MMRV) vaccine in healthy children from 9 months of age. Infection. 2007 Oct; 35(5):326-33.

BACKGROUND: This open, randomized, controlled study [208136/018] assessed the safety and immunogenicity of early vaccination with an experimental tetravalent measles-mumps-rubella-varicella (MMRV) vaccine (GlaxoSmithKline Biologicals) compared to concomitant administration of separate licensed MMR (Priorix) and varicella (Varilrix) vaccines (MMR+V). **METHODS:** Vaccines were administered as a two-dose course in healthy children at 9 and 12 months of age (N = 153 in the MMRV group and N = 146 in the MMR+V group). **RESULTS:** The incidence of fever of any intensity (axillary temperature ≥ 37.5 degrees C) during the 15 days of follow-up post-dose 1 was higher in the MMRV group than in the MMR+V group (48.3% vs 25.7%, respectively) but was low in both groups post-dose 2 (20.3% and 22.1%, respectively). The incidence of fever > 39.0 degrees C and the incidence of solicited local symptoms (pain, redness, swelling) were low ($\leq 5.3\%$ and $\leq 13.7\%$, respectively) in the two groups after each vaccine dose. Seroconversion rates were similar in the two groups for all vaccine antigens after each vaccine dose and were $\geq 99.2\%$ for each antigen post-dose 2. Anti-measles GMT was higher in the MMRV group than in the MMR+V group after the first vaccine dose. After the second dose, slight to moderate increases in measles, mumps and rubella antibody titers and a substantial increase in

varicella antibody titer were seen in both groups, leading to higher GMTs in the MMRV group compared with the MMR+V group for measles, mumps and varicella. Anti-rubella antibody GMTs were similar in the two groups post-dose 2. CONCLUSION: Early vaccination with two doses of this experimental MMRV vaccine at 9 and 12 months of age was well-tolerated and at least as immunogenic as two doses of separate licensed MMR and varicella vaccines.

Grading of scientific evidence: Table I (Ia and Ib) Protection against rubella and CRS. Available at http://www.who.int/entity/immunization/rubella_grad_protection.pdf .

Grading of scientific evidence: Table II Duration of protection. Available at http://www.who.int/entity/immunization/rubella_grad_duration.pdf.

Grading of scientific evidence: Table III (IIIa and IIIb) Safety. Available at http://www.who.int/entity/immunization/rubella_grad_safety.pdf .

Grillner L, Forsgren M, Barr B, Böttiger M, Danielsson L, De Verdier C. Outcome of rubella during pregnancy with special reference to the 17th-24th weeks of gestation. Scand J Infect Dis. 1983;15(4):321-5.

The consequences of rubella during pregnancy were studied with special reference to infections occurring during the 17th to 24th weeks of gestation. Laboratory confirmed rubella infected pregnancies were followed and the infants were examined clinically and serologically at a mean age of 20 months. In addition children born to mothers with verified rubella in earlier epidemics were examined clinically at the age of 4 or 7 yr. 491 cases of rubella in pregnant women from 1978-1980 were reported and 118 children were followed-up. Intrauterine transmission occurred in greater than 50% during the 16 first weeks of pregnancy compared to in 17% during the 21st to 24th weeks. Rubella defects appeared in a declining rate from 5/6 congenitally infected during the first 12 weeks to 1/7 at weeks 15 and 16. Three cases with deafness were found among the 65 children from earlier epidemics. Only 1 child with hearing impairment was found among children whose mothers were infected after the 16th week. Although rubella infections during the 17th to 24th weeks of pregnancy result in transmission to the fetus in about one fifth, sequelae seem to be a rare event.

Hinman AR, Irons B, Lewis M, Kandola K. Economic analyses of rubella and rubella vaccines: a global review. Bull World Health Organ. 2002;80(4):264-70.

OBJECTIVE: To investigate whether the incorporation of rubella vaccine into immunization programmes in developing countries is economically justified.

METHODS: A MEDLINE search was conducted for articles published between 1970 and 2000 that dealt with economic analyses of rubella and rubella-containing vaccines. The Eastern Mediterranean, South-East Asia, and Africa regional Index Medicus databases and the LILACS database for Latin America and the Caribbean were also searched.

FINDINGS: For developed countries, five cost-benefit analyses of rubella vaccine and five of measles-mumps-rubella vaccine as well as two cost-effectiveness analyses were found. For developing countries, five cost analyses and five cost-benefit analyses were found. All the cost-benefit analyses had a benefit:cost ratio greater than 1 and the cost-effectiveness studies indicated that rubella immunization was a cost-effective means of reducing the impact of congenital rubella syndrome. However, the methodologies were not standardized.

CONCLUSION: The data support the inclusion of rubella vaccine in the immunization programmes of both developing and developed countries and indicate economic benefits comparable to those associated with hepatitis B vaccine and Haemophilus influenzae type b vaccine. More studies should be carried out on costs for care and immunization using standardized methodologies and locally obtained information.

Irons B, Lewis MJ, Dahl-Regis M, Castillo-Solórzano C, Carrasco PA, de Quadros CA. Strategies to eradicate rubella in the English-speaking Caribbean. Am J Public Health. 2000 Oct;90(10):1545-9.

OBJECTIVE: This report presents the strategies used to eradicate rubella in the Caribbean region and the challenges faced by that effort. **METHODS:** Using the surveillance system for measles cases that was instituted in all countries in the Caribbean Community (CARICOM), 12 countries confirmed cases of rubella between 1992 and 1996. Rubella infections occurred in epidemic proportions in 6 countries during that period. **RESULTS:** On the basis of the rubella prevalence data, rubella-congenital rubella syndrome (CRS) cost-benefit analysis, and cost-effectiveness of the mass campaign, the Council for Human and Social Development of CARICOM resolved, on April 21, 1998, that every effort would be made to eradicate rubella, as well as to prevent the occurrence of new cases of CRS by the end of 2000. Using the Pan American Health Organization's template for measles eradication, CARICOM proposed and implemented the main strategies for rubella and CRS eradication, and rubella mass campaigns were conducted in 18 countries. The target population, which included males and females (aged 20-40 years), was approximately 2.2 million. **CONCLUSION:** The major challenges for rubella eradication are attaining high vaccine coverage in the adult population and maintaining an effective surveillance system able to detect rubella activity.

Jiménez G, Avila-Aguero ML, Morice A, Gutiérrez H, Soriano A, Badilla X, Reef S, Castillo-Solórzano C. Estimating the burden of congenital rubella syndrome in Costa Rica, 1996-2001. Pediatr Infect Dis J. 2007 May;26(5):382-6.

BACKGROUND: The epidemiology of rubella in Costa Rica changed during recent decades, shifting the susceptible groups to the reproductive age. This study estimates the burden of congenital rubella syndrome (CRS) from 1996 to 2001 in this country.

METHODS: Three methods to calculate CRS incidence were used. A retrospective search ("Observed cases") was conducted using hospital discharge records of children born from 1996 to 2001 with selected codes of ICD9 and ICD10 consistent with CRS and children <3 months of age with a positive serologic test for rubella IgM antibody at the National Children's Hospital (NCH). Cases were classified as either suspected, compatible or confirmed CRS and congenital rubella infection. "Expected" incidence of CRS was calculated using reported cases of rubella (women 15-45 years of age) and fertility rates, assuming CRS probability of 0.9 during the first trimester of pregnancy and 0.5 of asymptomatic rubella

cases. "Estimated" CRS cases were calculated using incidence rates reported from modeling analysis during epidemic and endemic years.

RESULTS: Of the 577 discharge charts reviewed and the 66 children reported as rubella IgM(+), 40 compatible CRS cases, 45 confirmed, and 4 with congenital rubella infection cases were identified. The range of annual incidence rate of CRS (per 1000 live births) was as follows: "Observed" = 0.00-0.33, "Expected" = 0.00-0.35 and "Estimated" = 0.5-1.5. Compared with the estimated number of CRS cases, only 27.2% of CRS cases were detected from the retrospective search and 10.1% would be expected when calculated using rubella reported cases.

CONCLUSIONS: The under-detection of CRS cases using rubella reported cases in women of reproductive age and retrospective search of CRS reinforces the importance of suspecting CRS in the presence of a single compatible manifestation. Laboratory confirmation is indispensable to implement CRS elimination strategies and should be done in every suspected case.

Klein NP, Fireman B, Yih WK, Lewis E, Kulldorff M, Ray P, Baxter R, Hambidge S, Nordin J, Naleway A, Belongia EA, Lieu T, Baggs J, Weintraub E; Vaccine Safety Datalink. Measles-mumps-rubella-varicella combination vaccine and the risk of febrile seizures. *Pediatrics*. 2010 Jul;126(1):e1-8.

OBJECTIVE: In February 2008, we alerted the Advisory Committee on Immunization Practices to preliminary evidence of a twofold increased risk of febrile seizures after the combination measles-mumps-rubella-varicella (MMRV) vaccine when compared with separate measles-mumps-rubella (MMR) and varicella vaccines. Now with data on twice as many vaccine recipients, our goal was to reexamine seizure risk after MMRV vaccine.

METHODS: Using 2000-2008 Vaccine Safety Datalink data, we assessed seizures and fever visits among children aged 12 to 23 months after MMRV and separate MMR + varicella vaccines. We compared seizure risk after MMRV vaccine to that after MMR + varicella vaccines by using Poisson regression as well as with supplementary regressions that incorporated chart-review results and self-controlled analyses.

RESULTS: MMRV vaccine recipients (83,107) were compared with recipients of MMR + varicella vaccines (376,354). Seizure and fever significantly clustered 7 to 10 days after vaccination with all measles-containing vaccines but not after varicella vaccination alone. Seizure risk during days 7 to 10 was higher after MMRV than after MMR + varicella vaccination (relative risk: 1.98 [95% confidence interval: 1.43-2.73]). Supplementary analyses yielded similar results. The excess risk for febrile seizures 7 to 10 days after MMRV compared with separate MMR + varicella vaccination was 4.3 per 10,000 doses (95% confidence interval: 2.6-5.6).

CONCLUSIONS: Among 12- to 23-month-olds who received their first dose of measles-containing vaccine, fever and seizure were elevated 7 to 10 days after vaccination. Vaccination with MMRV results in 1 additional febrile seizure for every 2300 doses given instead of separate MMR + varicella vaccines. Providers who recommend MMRV should communicate to parents that it increases the risk of fever and seizure over that already associated with measles-containing vaccines.

Kremer JR, Schneider F, Muller CP. Waning antibodies in measles and rubella vaccinees--a longitudinal study. *Vaccine*. 2006 Mar 24;24(14):2594-601

The evolution of measles- and rubella-specific serum IgG was followed in a longitudinal study in 224 young adolescent vaccinees, with or without boost vaccination before or during the 6.8-year observation period. Antibody titres were monitored by enzyme immuno assay (Enzygnost, Dade-Behring). After revaccination (second dose) rubella seropositivity rate increased from 92.1 to 100%, whereas measles seroprevalence (about 90%) did not significantly change between the paired sera. Significantly higher IgG (> three-fold) in the second serum of 5.2% (measles) and 7.8% (rubella) of participants with low antibodies (measles: < 1500 mIU; rubella < 40 IU) in first serum, suggest a secondary immune response (SIR) during the study period, only partially explained by revaccination. Excluding individuals with SIR, minimal annual antibody decay rates of -2.9% (confidence interval, CI: -0.7 to -4.8%) for rubella and -1.6% (CI: -0.1 to -3%) for measles were determined in participants with single dose vaccination. Thus, two-dose vaccination was adequate to protect women from rubella infection at least during childbearing age. Similarly only few individuals may become seronegative for measles again after successful vaccination due to minimal waning of low antibody levels (< 1500 mIU). However, as a result of a more rapid decay of high-titre (> 1500 mIU) antibodies (-2.4%/year), many vaccinees may eventually become susceptible to vaccine-modified measles (VMM) and consequently complicate measles control strategies.

Kuter BJ, Brown ML, Hartzel J, Williams WR, EvesiKaren A, Black S, Shinefield H, Reisinger KS, Marchant CD, Sullivan BJ, Thear M, Klopfer S, Xu J, Gress JO, Schödel F; Study Group for ProQuad. Safety and immunogenicity of a combination measles, mumps, rubella and varicella vaccine (ProQuad). *Hum Vaccin*. 2006 Sep-Oct;2(5):205-14.

BACKGROUND: A combination measles, mumps, rubella, and varicella vaccine (ProQuad, Merck & Co., Inc, West Point, PA) was evaluated in five clinical trials. Use of ProQuad would result in fewer injections for children and would facilitate universal immunization against all four diseases.

OBJECTIVE: To describe the combined results obtained from the studies conducted during the clinical development program for ProQuad.

METHODS: A total of 5833 healthy children, 12-23 months of age, and 399 healthy children, 4-6 years of age, received 1 or 2 doses of ProQuad in five controlled clinical trials. M-M-R II and VARIVAX were used as the control for most studies. Safety was evaluated for six weeks postvaccination and immunogenicity was assessed six weeks after each dose by a sensitive assay (ELISA or gpELISA).

RESULTS: A single dose of ProQuad in 12- to 23-month-old children was shown to be as immunogenic as a single dose of M-M-R II and VARIVAX and was generally well tolerated. ProQuad can be used concomitantly with other vaccines (hepatitis B and Haemophilus influenzae b). A higher rate of fever was reported after 1 dose of ProQuad compared to M-M-R II and VARIVAX, but fever episodes were transient without long-term sequelae. Both a 2-dose regimen of ProQuad in 12- to 23-month-olds and use of ProQuad in place of M-M-R II at 4-6 years were shown to be immunogenic and well tolerated. The incidence of adverse experiences following a second dose of ProQuad was lower than that following the initial dose.

CONCLUSIONS: A single dose of ProQuad is as immunogenic as M-M-R II and VARIVAX and is well tolerated in a 1- or 2-dose schedule. ProQuad should easily fit into the routine immunization schedule.

Lanzieri TM, Parise MS, Siqueira MM, Fortaleza BM, Segatto TC, Prevots DR. Incidence, clinical features and estimated costs of congenital rubella syndrome after a large rubella outbreak in Recife, Brazil, 1999-2000. *Pediatr Infect Dis J.* 2004 Dec;23(12):1116-22.

BACKGROUND: During 1998-2000, a large rubella outbreak was reported from Recife, the capital municipality of Pernambuco State, in northeastern Brazil. In 2002, a study was conducted to assess the burden of congenital rubella syndrome (CRS) after this outbreak.

METHODS: To describe the rubella outbreak, we analyzed data available from the National Notifiable Disease System. A retrospective record review for CRS was conducted at 6 maternity hospitals where 53% of Recife's resident live births occurred during 1999-2000 and 1 tertiary health care center. Suspected CRS cases were infants with any manifestation of CRS or maternal infection during pregnancy. Standard international definitions for compatible and confirmed CRS cases were used. Direct CRS costs were based on reimbursements by the National Health System.

RESULTS: From October 1998 to July 2000, Recife reported 681 confirmed rubella cases. The highest incidence of rubella was among children 5-11 years of age (5.4 per 1000 population). Forty-five suspected CRS cases were identified; 29 were clinically compatible and 2 were laboratory-confirmed. The average annual incidence of CRS was 0.9 per 1000 live births during 1999-2000. Overall costs for the first year follow-up were estimated at 61,824 US dollars in this cohort.

CONCLUSIONS: High rubella vaccination coverage is required to prevent the severe congenital disabilities and high economic costs of CRS. Increased clinician awareness is critical for early CRS detection. Complete reporting is essential to evaluate the impact of vaccination programs and to document progress toward the goal of CRS elimination in the Americas by the year 2010.

Lawn JE, Reef S, Baffoe-Bonnie B, Adadevoh S, Caul EO, Griffin GE. Unseen blindness, unheard deafness, and unrecorded death and disability: congenital rubella in Kumasi, Ghana. *Am J Public Health.* 2000 Oct;90(10):1555-61.

OBJECTIVES: Although rubella serosusceptibility among women of reproductive age in West Africa ranges from 10% to 30%, congenital rubella syndrome has not been reported. In Ghana, rubella immunization and serologic testing are unavailable. Our objectives were to identify congenital rubella syndrome cases, ascertain rubella antibody seroprevalence during pregnancy, and recommend strategies for congenital rubella syndrome surveillance.

METHODS: Congenital rubella syndrome cases were identified through prospective surveillance and retrospective surveys of hospital records. A rubella serosurvey of pregnant urban and rural women was performed.

RESULTS: Eighteen infants born within a 5-month period met the congenital rubella syndrome case definitions, coinciding with a 9-fold increase in presentation of infantile congenital cataract. The congenital rubella syndrome rate for this otherwise unrecorded rubella epidemic was conservatively estimated to be 0.8 per 1000 live births. A postepidemic rubella immunity rate of 92.6% was documented among 405 pregnant women; susceptibility was significantly associated with younger age ($P = .000$) and ethnicity (northern tribes, $P = .024$).

CONCLUSIONS: Congenital rubella syndrome occurs in Ghana but is not reported. Information about congenital rubella syndrome and rubella in sub-Saharan Africa is needed to evaluate inclusion of rubella vaccine in proposed measles control campaigns.

Lieberman JM, Williams WR, Miller JM, Black S, Shinefield H, Henderson F, Marchant CD, Werzberger A, Halperin S, Hartzel J, Klopfer S, Schödel F, Kuter BJ; Consistency Lot Study Group for ProQuad. The safety and immunogenicity of a quadrivalent measles, mumps, rubella and varicella vaccine in healthy children: a study of manufacturing consistency and persistence of antibody. *Pediatr Infect Dis J.* 2006 Jul;25(7):615-22.

BACKGROUND: This clinical trial was conducted to demonstrate that each of 3 consistency lots of a combined measles, mumps, rubella and varicella vaccine (MMRV) would be well tolerated, induce clinically acceptable and similar immune responses to each antigen and induce immune responses similar to measles, mumps and rubella vaccine (MMR) administered concomitantly with varicella vaccine (V). An additional objective was to evaluate the persistence of antibodies 1 year postvaccination.

METHODS: Study participants 12 to 23 months of age received a single injection of either one of 3 consistency lots of MMRV or MMR + V administered at separate injection sites.

RESULTS: A total of 3,928 healthy children were enrolled at study sites in the United States and Canada. Immune responses to measles, mumps, rubella and varicella in children immunized with each of 3 lots of MMRV were similar and the combined response to all 3 lots was comparable to that of the control group. The 1-year antibody persistence rates for measles, mumps, rubella and varicella viruses were each greater than 95% and comparable among the recipients of the 3 consistency lots of MMRV and the control group. All vaccines were generally well tolerated during the 42 days after vaccination and the overall incidence of adverse experiences was comparable between recipients of MMRV and MMR + V. Rates of fever (temperature ≥ 38.9 degrees C oral equivalent or tactile) were greater in recipients of MMRV than in recipients of MMR + V (39.1% versus 33.1%, $P = 0.001$). Fevers were transient and there was no difference in the incidence of febrile seizures.

CONCLUSIONS: MMRV was generally well tolerated and had comparable immunogenicity and overall safety profiles to MMR + V administered concomitantly. Long-term persistence of antibodies after receipt of MMRV is expected based on similar antibody titers against all 4 antigens 1 year postvaccination compared with recipients of MMR and V.

Miller E, Andrews N, Stowe J, Grant A, Waight P, Taylor B. Risks of convulsion and aseptic meningitis following measles-mumps-rubella vaccination in the United Kingdom. *Am J Epidemiol.* 2007 Mar 15;165(6):704-9.

Measles-mumps-rubella (MMR) vaccines containing the Urabe strain of mumps were withdrawn in the United Kingdom in 1992 following demonstration of an increased risk of aseptic meningitis 15-35 days after vaccination. Following introduction of a replacement MMR vaccine (Priorix; GlaxoSmithKline, London, United Kingdom) in 1998, active surveillance of aseptic meningitis and convulsion was established to evaluate the risk associated with the new vaccine. No laboratory-confirmed cases of mumps meningitis were detected among children aged 12-23 months after administration of 1.6 million doses of Priorix (upper 95% confidence limit of risk: 1:437,000) in England and Wales. The upper 95% confidence limit excluded the risk found for mumps meningitis with Urabe vaccines (1:143,000 doses). No cases of aseptic meningitis were detected among children aged 12-23 months, who had received over 99,000 doses of Priorix (upper 95% confidence limit of risk: 1:27,000), in a regional database of hospital-admitted cases. This compares with an observed risk of 1:12,400 for Urabe vaccines. An elevated relative incidence of convulsion was found in the 6- to 11-day period after receipt of Priorix (relative incidence = 6.26, 95% confidence interval: 3.85, 10.18)-consistent with the known effects of the measles component of MMR vaccine-but not in the 15- to 35-day period (relative incidence = 1.48, 95% confidence interval: 0.88, 2.50) as occurred with Urabe-containing vaccines. This study demonstrates the power of active postmarketing surveillance to identify or exclude events too rare to be detected in prelicensure trials.

Miller E, Cradock-Watson JE, Pollock TM. Consequences of confirmed maternal rubella at successive stages of pregnancy. *Lancet.* 1982 Oct 9;2(8302):781-4.

Over a thousand women with confirmed rubella infection at different stages of pregnancy were followed up prospectively. Two-thirds of the women were multiparous. Pregnancy continued in 40%, and the infants were followed up after birth both clinically and serologically. The frequency of congenital infection after maternal rubella with a rash was more than 80% during the first 12 weeks of pregnancy, 54% at 13-14 weeks, and 25% at the end of the second trimester. The infection rate then rose again to reach a high figure in the last month. Follow-up was to 2 years of age--the findings in infected children being compared with those in children who had escaped infection. Rubella defects occurred in all infants infected before the 11th week (principally congenital heart disease and deafness) and in 35% of those infected at 13-16 weeks (deafness alone). No defects attributable to rubella were found in 63 children infected after 16 weeks. Continued surveillance of cases of confirmed rubella during pregnancy is recommended as an additional way of monitoring the effect of rubella vaccination.

Nascimento Silva JR, Camacho LA, Siqueira MM, Freire MD, Castro YP, Maia MD, Yamamura AM, Martins RM, Leal MD; Collaborative Group for the Study of Yellow Fever Vaccines. Mutual interference on the immune response to yellow fever vaccine and a combined vaccine against measles, mumps and rubella. *Vaccine*, 2011 June 2 [Epub ahead of print] doi: 10.1016/j.vaccine.2011.05.019

A randomized trial was conducted to assess the immunogenicity and reactogenicity of yellow fever vaccines (YFV) given either simultaneously in separate injections, or 30 days or more after a combined measles-mumps-rubella (MMR) vaccine. Volunteers were also randomized to YFV produced from 17DD and WHO-17D-213 substrains. The study group comprised 1769 healthy 12-month-old children brought to health care centers in Brasilia for routine vaccination. The reactogenicity was of the type and frequency expected for the vaccines and no severe adverse event was associated to either vaccine. Seroconversion and seropositivity 30 days or more after vaccination against yellow fever was similar across groups defined by YFV substrain. Subjects injected YFV and MMR simultaneously had lower seroconversion rates - 90% for rubella, 70% for yellow fever and 61% for mumps - compared with those vaccinated 30 days apart - 97% for rubella, 87% for yellow fever and 71% for mumps. Seroconversion rates for measles were higher than 98% in both comparison groups. Geometric mean titers for rubella and for yellow fever were approximately three times higher among those who got the vaccines 30 days apart. For measles and mumps antibodies GMTs were similar across groups. MMR's interference in immune response of YFV and YFV's interference in immune response of rubella and mumps components of MMR had never been reported before but are consistent with previous observations from other live vaccines. These results may affect the recommendations regarding primary vaccination with yellow fever vaccine and MMR.

O'Shea S et al. Rubella vaccination: persistence of antibodies for 10–21 years. *Lancet*, 1988, 2:909. (No abstract available).

Panagiotopoulos T, Georgakopoulou T. Epidemiology of rubella and congenital rubella syndrome in Greece, 1994-2003. *Euro Surveill*. 2004 Apr;9(4):17-9.

In 1993, there was a large epidemic of rubella and congenital rubella syndrome (CRS) in Greece. The epidemiology of rubella and CRS after 1993 is described in this paper using information from surveillance data and published studies and reports. The incidence of rubella fell sharply after 1993, but a smaller outbreak occurred in 1999, mainly in young adults, and four CRS cases (4.0 per 100,000 live births) were recorded. A very high proportion of the child population in Greece are currently vaccinated for rubella, while teenagers are inadequately covered (60-80% in different studies). A substantial proportion of women of childbearing age are susceptible to rubella (10-20% in urban areas). This could lead to local or more extended outbreaks. This situation shows that a comprehensive preventive policy should be implemented.

Peltola H, Jokinen S, Paunio M, Hovi T, Davidkin I. Measles, mumps, and rubella in Finland: 25 years of a nationwide elimination programme. Lancet Infect Dis. 2008 Dec;8(12):796-803.

A nationwide programme to eliminate indigenous measles, mumps, and rubella, mainly by vaccinating children twice, was launched in Finland in 1982. Strong scientific methods to examine the immunological, clinical, and epidemiological variables have accompanied the programme. Measles was eliminated in 1996, and mumps and rubella in 1997. Now, 25 years from the start of this programme, Finland is facing new challenges. Since elimination, eight, 32, and six cases of measles, mumps, and rubella, respectively, have been reported. Of those, seven cases were failures of mumps vaccinations and one case was a rubella vaccination failure. Although outbreaks have been averted, the risks are increasing because the unvaccinated population is growing, epidemics occur in nearby countries, breakthrough cases arise, and declining antibodies suggest waning immunity. The chances for natural boosters are now at a minimum, and individuals are increasingly protected solely by vaccination. To maintain the absence of these diseases, the adopted policy should continue, but the country should also be prepared for prompt supplementary vaccinations in the case of epidemic outbreaks.

Plotkin S et al. Rubella vaccine. In: Plotkin S, Orenstein W, Offit P, eds. *Vaccines*, 5th ed. Philadelphia, Saunders, 2008:467–517. (No abstract available).

Ray P, Black S, Shinefield H, Dillon A, Schwalbe J, Holmes S, Hadler S, Chen R, Cochi S, Wassilak S. Risk of chronic arthropathy among women after rubella vaccination. Vaccine Safety Datalink Team. JAMA. 1997 Aug 20;278(7):551-6.

CONTEXT: A review by the Institute of Medicine found a possible relationship between rubella vaccination and chronic arthritis among women.

OBJECTIVE: To evaluate the risk of persistent joint and neurologic symptoms in rubella seronegative women subsequently vaccinated with RA 27/3 rubella vaccine.

DESIGN: Retrospective cohort study based on computerized laboratory data and medical record review. Records were reviewed for symptoms occurring within 2 years before and after the date of serological testing and to identify vaccinees. Possible cases were evaluated by a rheumatologist blinded to serological findings and vaccination status.

SETTING: Large health maintenance organization in northern California.

PATIENTS: Women aged 15 to 59 years serotested for rubella during 1990 with continuous health plan membership for 2 years before and after the date of their serological test. Seronegative women immunized within 1 year of serotesting (n=971) were defined as exposed. Primary comparison groups included all unvaccinated, seronegative women (n=924) and randomly selected seropositive, unvaccinated women (n=2421) matched to exposed subjects on serological test date and age (+/-3 years).

MAIN OUTCOME MEASURES: Prevalence and incidence of chronic joint and neurologic symptoms during 1-year follow-up period stratified by age and serological findings, immunization, and postpartum status.

RESULTS: No significantly increased risk was associated with receipt of rubella vaccine for any outcome except for prevalence of carpal tunnel syndrome in vaccinated women at least 30 years old compared with seropositive, unvaccinated women (2.9% vs 1.4%; P=.03). A total of 34 women had onset of conditions within the 1-year follow-up period; 9 of these were in the group of seronegative, immunized women, of whom 6 had onset of symptoms within 6 weeks of vaccination. Among these 6 women, symptoms included transient arthritis or arthralgias (<6 weeks duration) in 4 women, arthralgia of indeterminate chronicity in 1 woman, and carpal tunnel syndrome in 1 woman. Postpartum women across all groups were less likely to be seen for nontraumatic arthropathies than nonpostpartum women (4.5% vs 7.2%, P=.08 in vaccinated women; 4.8% vs 8.1%, P=.09 in seronegative controls; and 4.8% vs 10.0%, P=.01 in seropositive controls).

CONCLUSIONS: In this large retrospective cohort analysis there was no evidence of any increased risk of new onset chronic arthropathies or neurologic conditions in women receiving the RA 27/3 rubella vaccine. These data support the continued vaccination of rubella-susceptible women to reduce the risk of congenital rubella syndrome.

Reef SE, Redd SB, Abernathy E, Zimmerman L, Icenogle JP. The epidemiological profile of rubella and congenital rubella syndrome in the United States, 1998-2004: the evidence for absence of endemic transmission. Clin Infect Dis. 2006 Nov 1;43 Suppl 3:S126-32.

In 1969, the United States established its national rubella vaccination program. With the success of the program, 32 years later, reports of rubella reached record low numbers. To assess the achievement of elimination of rubella and congenital rubella syndrome (CRS) in the United States, 7 epidemiological criteria were used. Rubella cases reported to the National Notifiable Diseases Surveillance System from 1998 through 2004 and CRS cases reported to the National Congenital Rubella Syndrome Registry from 1998 through 2004 were analyzed. During 1998-2000, the median number of reported rubella cases was 272, whereas, during 2001-2004, the median number reported was 13. The incidence of rubella decreased significantly, from 0.1/100,000 population in 1998 to 0.005/100,000 population in 2004. Since 2001, 5 infants with CRS have been reported--3 were born in 2001, 1 was born in 2003, and 1 was born in 2004. The epidemiological evidence strongly supports the claim that rubella is no longer endemic in the United States. To prevent future rubella outbreaks and CRS cases, current strategies must be maintained.

Reef SE. Rubella and congenital rubella syndrome. Bulletin of the World Health Organization, 1998,76 (Suppl. 2):156-157. (No summary available).

Robertson SE, Featherstone DA, Gacic-Dobo M, Hersh BS. Robertson SE et al. Rubella and congenital rubella syndrome: global update. Revista panamericana de salud pública, 2003,14:306-315.

Worldwide, it is estimated that there are more than 100.000 infants born with congenital rubella syndrome (CRS) each year. In 1998, standard case definitions for surveillance of CRS and rubella were developed by the World Health Organization (WHO). In 2001, 123 countries/territories reported a total of 836.356 rubella cases. In the future more countries are expected to report on rubella as a global measles/rubella laboratory network is further developed under the coordination of WHO. Operational research is being conducted to improve rubella surveillance. This includes projects on initiating CRS surveillance, comparative studies on diagnostic laboratory methods, and molecular epidemiology research to expand the global understanding of patterns of rubella virus circulation. In 1996 a WHO survey found that 78 of 214 reporting countries/territories (36%) were using rubella vaccine in their routine immunization services. By the end of 2002 a total of 124 of the 214 countries/territories (58%) were using rubella vaccine. Rubella vaccine use varies by stage of economic development: 100% for industrialized countries, 71% for countries with economies in transition, and 48% for developing countries. A safe effective rubella vaccine is available, and there are proven vaccination strategies for preventing rubella and CRS. A WHO position paper provides guidance on programmatic aspects of rubella vaccine introduction. The introduction of rubella vaccine is cost-effective and cost-beneficial but requires ongoing strengthening of routine immunization services and surveillance systems.

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.

Shinefield H, Black S, Thear M, Coury D, Reisinger K, Rothstein E, Xu J, Hartzel J, Evans B, Digilio L, Schödel F, Brown ML, Kuter B; 013 Study Group for ProQuad. Safety and immunogenicity of a measles, mumps, rubella and varicella vaccine given with combined *Haemophilus influenzae* type b conjugate/hepatitis B vaccines and combined diphtheria-tetanus-acellular pertussis vaccines. *Pediatr Infect Dis J.* 2006 Apr;25(4):287-92.

BACKGROUND: A study was conducted to assess administration of a combination measles, mumps, rubella and varicella vaccine (MMRV) with other childhood vaccines.

METHODS: In this open, multicenter trial, 1915 healthy children ages 12-15 months were randomized into 3 groups: group 1, MMRV, combined Haemophilus influenzae type b conjugate-hepatitis B vaccines (Hib/HepB) and combined diphtheria-tetanus-acellular pertussis vaccines (DTaP) concomitantly; group 2, MMRV followed by Hib/HepB and DTaP 42 days later; group 3, MMR and varicella vaccine followed by Hib/HepB and DTaP 42 days later.

RESULTS: Antibody responses to measles, mumps, rubella, varicella, Hib, HepB, diphtheria and tetanus were similar between groups 1 and 2 (all >95%, except varicella, 89.7% in group 1 and 90.9% in group 2). Pertussis toxin and filamentous hemagglutinin responses were significantly lower in group 1 than in group 2 (group 1, 74.1 and 67.1%; group 2, 90.4 and 86.8%, respectively). An exploratory analysis suggested that the difference in and pertussis toxin and filamentous hemagglutinin responses was likely the result of study design rather than interference among vaccine components because the groups differed in age of receipt of DTaP (group 1, approximately 12 months; group 2, approximately 13.5 months). When the groups were matched for age, sample size was sufficient for comparison only in children > or =13.5 months old. Pertussis toxin and filamentous hemagglutinin responses were similar in these children. The safety profiles for each vaccination regimen were comparable.

CONCLUSIONS: The immunogenicity data support concomitant administration of MMRV with Hib/HepB. Limited data from an exploratory analysis indicate that MMRV can be administered concomitantly with DTaP. Concomitant administration of MMRV, Hib/HepB and DTaP is well-tolerated.

Siber GR, Werner BG, Halsey NA, Reid R, Almeida-Hill J, Garrett SC, Thompson C, Santosham M. Interference of immune globulin with measles and rubella immunization. J Pediatr. 1993 Feb;122(2):204-11.

Passively acquired antibody may interfere with the active antibody response to live viral vaccines such as measles and rubella. To evaluate the duration of this inhibitory effect, we measured the measles and rubella antibody responses of Apache children immunized with measles, mumps, and rubella vaccine at varying intervals after administration of an immune globulin termed bacterial polysaccharide immune globulin (BPIG). This specific immune globulin contained measles and rubella antibody titers similar to those in standard intramuscularly and intravenously administered immune globulins. Antibody responses to measles vaccine were inhibited for up to 5 months after a BPIG dose of 80 mg IgG per kilogram of body weight, but responses to rubella vaccine were inhibited for only 2 months. Most children who had a decreased measles antibody response to primary measles, mumps, and rubella immunization given 1 1/2 to 4 months after BPIG administration responded to a booster immunization given 6 months after their last BPIG dose. We conclude that high doses of immune globulin (> 10 mg/kg) may inhibit the antibody response to measles for more than 3 months. We propose that the interval between administration of immune globulin and measles and rubella immunization be adjusted on the basis of the dose of immune globulin.

Skendzel LP. Rubella immunity. Defining the level of protective antibody. Am J Clin Pathol. 1996 Aug;106(2):170-4.

The Rubella Subcommittee of the National Committee for Clinical Laboratory Standards has proposed lowering the breakpoint to define rubella immunity from 15 to 10 IU/mL. This recommendation stems from epidemiologic studies on vaccinated persons with low levels of antibody and anecdotal reports. Additional support comes from Centers for Disease Control and Prevention studies and reports. The effectiveness of rubella vaccination is well documented and the 10 IU/mL antibody level is protective in the vast majority of persons. Sporadic reports of viremia and/or reinfection among previously immunized persons with low antibody levels have been reported but proven cases of reinfection have also occurred in persons with titers greater than or equal to the 15 IU/mL cut-off. Despite the occasional occurrence of rubella reinfection in persons with low titers, the theoretical risks are small especially as compared with significantly greater risk in persons who have not been vaccinated. Immunity in a given patient is a clinical decision and the results of antibody tests for rubella, like other laboratory tests, must be evaluated in the context of the clinical setting.

Thant KZ, Oo WM, Myint TT, Shwe TN, Han AM, Aye KM, Aye KT, Moe K, Thein S, Robertson SE. Active surveillance for congenital rubella syndrome in Yangon, Myanmar. Bull World Health Organ. 2006 Jan;84(1):12-20.

OBJECTIVE: Rubella vaccine is not included in the immunization schedule in Myanmar. Although surveillance for outbreaks of measles and rubella is conducted nationwide, there is no routine surveillance for congenital rubella syndrome (CRS). Therefore, we organized a study to assess the burden of CRS.

METHODS: From 1 December 2000 to 31 December 2002 active surveillance for CRS was conducted among children aged 0-17 months at 13 hospitals and 2 private clinics in Yangon, the capital city. Children with suspected CRS had a standard examination and a blood sample was obtained. All serum samples were tested for rubella-specific IgM; selected samples were tested for rubella-specific IgG and for rubella RNA by reverse transcriptase-polymerase chain reaction (RT-PCR).

FINDINGS: A total of 81 children aged 0-17 months were suspected of having CRS. Of these, 18 children had laboratory-confirmed CRS (7 were IgM positive; 7 were RT-PCR positive; and 10 were IgG positive at > 6 months of age). One additional child who tested positive by RT-PCR and whose mother had had rubella during pregnancy but who had a normal clinical examination was classified as having congenital rubella infection. During 2001-02 no rubella outbreaks were detected in Yangon Division. In the 31 urban townships of Yangon Division, the annual incidence was 0.1 laboratory-confirmed cases of CRS per 1000 live births.

CONCLUSION: This is the first population-based study of CRS incidence from a developing country during a rubella-endemic period; the incidence of CRS is similar to endemic rates found in industrialized countries during the pre-vaccine era. Rubella-specific IgG tests proved practical for diagnosing CRS in children aged > 6 months. This is one of the first studies to report on the use of rubella-specific RT-PCR directly on serum samples; further studies are warranted to confirm the utility of this method as an additional means of diagnosing CRS.

Tischer A, Gerike E. Immune response after primary and re-vaccination with different combined vaccines against measles, mumps, rubella. Vaccine. 2000 Jan 31;18(14):1382-92.

The humoral immune response after primary and re-vaccination confirmed the high immunogenicity of the combined vaccines used: "MMR-Vax(R)", "Pluserix(R)" and "Triviraten(R)". The investigation of paired serum samples of prevaccinal seronegative infants (n90-100% for all three components with the exception of the mumps component of "Triviraten(R)" (38%). However, by additional methods (plaque neutralisation test, immunofluorescence test) mumps antibodies could be detected in 93.4% of infants having received vaccine "Triviraten(R)". The mean values of antibody activities against the three components did not differ significantly after vaccination with "MMR-Vax(R)" and "Pluserix(R)". However, after vaccination with "Triviraten(R)" the mean antibody values were significantly lower ($P < 0.01$) against the measles strain "Edmonston-Zagreb" and especially lower (2-20 times) against the mumps virus strain "Rubini". Revaccination of prevaccinal seropositive schoolchildren and adolescents (n=676) with "MMR-Vax(R)" and "Pluserix(R)" produced no different results. The rate of vaccinees responding with a booster reaction reached 68.4% for measles and mumps, but only 8.6% for rubella. A booster reaction could be observed in 100% of those vaccinees who had antibodies at a low level, also in the case of naturally acquired immunity. The low-level range for antibodies against measles was defined as $0.15 < 0.40$ IU/ml, mumps $1:230 \leq 1:500$ and rubella 7-16 IU/ml. The rate of vaccinees with low-level antibodies against measles can become as high as 10%, for mumps 20% and for rubella 3%. The correlation between the level of antibodies and protection against the disease is discussed. The rate of individuals in a population with doubtful protection (unvaccinated, non-responder and low responder after primary vaccination) prevents to reach the herd immunity of 95% necessary for elimination. The results of our serological studies strongly recommend re-vaccination against measles, mumps and rubella.

van Tilburg CM, Sanders EA, Rovers MM, Wolfs TF, Bierings MB. Loss of antibodies and response to (re-)vaccination in children after treatment for acute lymphocytic leukemia: a systematic review. *Leukemia*. 2006 Oct;20(10):1717-22.

Intensified chemotherapy regimens resulting in improved survival of children with acute lymphocytic leukemia (ALL) lead to concerns about therapy-induced immune damage reflected by the loss of protection of previous immunizations and the efficacy of (re-)vaccination. The severity of secondary immunodeficiency, however, is not clear and knowledge is based on a limited number of studies. We performed a systematic review on literature concerning vaccination data of children with ALL published since 1980. Eight studies fulfilled the inclusion criteria. Regarding antibody titers after treatment, the number of children who had preserved the defined protection level for antibodies differed widely, ranging from 17 to 98% for diphtheria, 27 to 82% for Bordetella pertussis, 20 to 98% for tetanus, 62 to 100% for poliomyelitis, 35 to 100% for Haemophilus influenzae type B (HiB), 29 to 92% for mumps, 29 to 60% for measles and 72 to 92% for rubella. Most patients however responded to revaccination, demonstrating immunological recovery. Although the designs and results of the included studies varied widely, it can be concluded that cytostatic therapy for ALL in children results in a temporarily reduction of specific antibody levels. Memory is preserved but revaccination may be warranted. This is the first systematic review and the best possible current approximation of chemotherapy-induced immune damage in children after ALL treatment.

WHO: Standardization of the nomenclature for genetic characteristics of wild-type rubella viruses. Geneva, World Health Organization, 2004.
(http://www.who.int/entity/immunization_monitoring/Rubella_nomenclature_report.pdf, accessed June 2011).

WHO Weekly Epidemiological Record, 2010, 85: 413–424. Controlling rubella and preventing congenital rubella syndrome – global progress, 2009.

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WHO Weekly Epidemiological Record, 2008, 83:393–400. Progress towards eliminating rubella and congenital rubella syndrome in the western hemisphere, 2003–2008.

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WHO: Manual for the laboratory diagnosis of measles and rubella virus infection, 2nd ed. Geneva, World Health Organization, 2007 (WHO/IVB/07.01). (Also available from http://www.who.int/immunization_monitoring/LabManualFinal.pdf.)

WHO-UNICEF effective vaccine store management initiative: modules 1–4. Geneva: World Health Organization, 2004 (WHO/IVB/04.16–20). (Available from http://whqlibdoc.who.int/hq/2005/WHO_IVB_04.16-20.pdf.)

WHO: Requirements for measles, mumps and rubella vaccines and combined vaccine (live). Geneva, World Health Organization, 1994 (Technical Report Series No. 840): Annex 3. (Available from www.who.int/entity/biologicals/publications/trs/areas/vaccines/rubella/en/.)

WHO-recommended standards for surveillance of selected vaccine-preventable diseases. Geneva, World Health Organization, 2003 (WHO/V&B/03.01). (Also available at http://www.who.int/immunization/documents/WHO_VB_03.01/en/index.html.)

References used in Grade tables Ia and Ib:

Efficacy of rubella vaccines; randomized controlled studies

Beasley RP, Detels R, Kim KS, Gale JL, Lin TL, Grayston JT. Prevention of rubella during an epidemic on Taiwan. HPV-77 and RA 27-3 rubella vaccines administered subcutaneously and intranasally HPV-77 vaccine mixed with mumps and-or measles vaccines. Am J Dis Child. 1969 Aug;118(2):301-6. (No abstract available).

Eedes S, Pullan CR, Hull D. A randomised single blind trial of a combined mumps measles rubella vaccine to evaluate serological response and reactions in the UK population. Public Health. 1991 Mar;105(2):91-7.

Four hundred and twenty children were randomly assigned to receive either mumps measles rubella (MMR) vaccine (207) or measles vaccine (213) in a single blind study, to investigate the reactogenicity and serology of the MMR vaccine. There was no significant difference between the number of children developing symptoms after MMR vaccination to those developing symptoms after measles vaccination. Both vaccines are associated with a rash, temperature and restlessness five to thirteen days after vaccination. The serological response to measles vaccine was similar in both groups with 92-6% seroconverting with MMR, and 96-8% with measles. Seroconversion against mumps and rubella with the MMR vaccine was 88% and 96% respectively. This study confirms the safety and efficacy of the MMR vaccine in a UK population.

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.

Schwarz AJ, Jackson JE, Ehrenkranz NJ, Ventura A, Schiff GM, Walters VW. Clinical evaluation of a new measles-mumps-rubella trivalent vaccine. Am J Dis Child. 1975 Dec;129(12):1408-12.

In a series of clinical studies of a combined measles (Schwarz strain), mumps (Jeryl Lynn strain), and rubella (Cendehill strain) vaccine, 1,481 children received the vaccine or a placebo. The vaccine did not cause any significant reactions. The frequencies of mild, transient fever or rash or both in triple-susceptible vaccinees were similar to those that follow

use of Schwarz strain measles vaccine alone. Measles, mumps, and rubella seroconversion rates in triple-susceptible vaccinees ranged from 95% to 100%. Geometric mean antibody titers were as high as those that usually result from use of these same virus strains as monovalent vaccines.

Efficacy of rubella vaccines; observational studies

Rubella among crew members of commercial cruise ships--Florida, 1997. Centers for Disease Control and Prevention (CDC). MMWR Morb Mortal Wkly Rep. 1998 Jan 9;46(52-53):1247-50.

During April-July 1997, two different commercial cruise lines notified CDC of rubella outbreaks among crew members. In July 1997, CDC initiated an investigation on one cruise ship to determine the extent of and risk factors for rubella infection among crew members and to assess the potential risk for rubella transmission to passengers-particularly rubella-susceptible pregnant women at risk for giving birth to an infant with congenital rubella syndrome (CRS). This report summarizes rubella outbreaks involving two cruise ships and the results of the CDC investigation on one cruise ship, which demonstrate that crew members can serve as a susceptible population for rubella infection and should be vaccinated with measles-mumps-rubella vaccine (MMR) if they are not immune. Although the outbreaks were limited to crew members, cruise ship travel provides an environment conducive to the potential spread of rubella and other infectious diseases among crew and passengers; therefore, women of childbearing age, particularly pregnant women, should be immune to rubella before traveling on cruise ships to reduce the risks for rubella infection and CRS.

Chang TW, Des Rosiers S, Weinstein L. Clinical and serologic studies of an outbreak of rubella in a vaccinated population. New England Journal of Medicine, 1970, 283:246-248. (No abstract available).

Davis WJ, Larson HE, Simsarian JP, Parkman PD, Meyer HM Jr. A study of rubella immunity and resistance to infection. JAMA. 1971 Jan 25;215(4):600-8. (No abstract available).

de Valk H., Rebière I. Epidémie de rubéole: Evaluation de l'efficacité vaccinale sur le terrain, Ardèche, janvier mars 1997. réseau National de santé Publique, Saint Maurice, France. janvier 1998. pp 1-52. (No abstract available).

Furukawa T, Miyata T, Kondo K, Kuno K, Isomura S, Takekoshi T. Rubella vaccination during an epidemic. JAMA: the journal of the American Medical Association, 1970, 213:987-990. (No abstract available).

Grayston JT, Detels R, Chen KP, Gutman L, Kim KS, Gale JL, Beasley RP. Field trial of live attenuated rubella virus vaccine during an epidemic on Taiwan*. JAMA: the journal of the American Medical Association, 1969, 207:1107-1110. (No abstract available).

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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.

Landrigan PJ, Stoffels MA, Anderson E, Witte JJ. Epidemic rubella in adolescent boys. *JAMA: the journal of the American Medical Association*, 1974, 227:1283-1287. (No abstract available).

Rafila A, Marin M, Pistol A, Nicolaiciuc D, Lupulescu E, Uzicanin A, Reef S. A large rubella outbreak, Romania--2003. *Euro Surveill.* 2004 Apr;9(4):7-9.

Romania experienced a large rubella outbreak in 2002-03, with more than 115,000 reported cases nationwide, and an incidence of 531 reported cases per 100,000 population. The incidence was highest in children of school age. The cohorts of adolescent girls vaccinated in 1998 and 2002 (when a rubella-containing vaccine was available) had significantly lower incidence rates ($p < 0.001$) compared with those in boys in the same age groups who were not vaccinated. In 2003, of the 150 suspected congenital rubella syndrome (CRS) cases reported, seven (4.6%) were confirmed by positive rubella IgM antibodies. In the absence of available rubella containing vaccine for outbreak control, an outbreak response plan to improve the detection of cases and to limit rubella virus transmission was developed. The following activities were conducted: surveillance of pregnant women with suspected rubella or history of exposure to rubella virus was implemented, with follow up of pregnancy outcomes; surveillance for CRS was strengthened; existing infection control guidelines to prevent disease transmission within healthcare facilities were reinforced; and a communication plan was developed. In May 2004, Romania is introducing measles, mumps and rubella (MMR) vaccine for routine vaccination of children aged 12 to 15 months, while continuing vaccination of girls in the 8th grade of school (13-14 years of age) with rubella-only vaccine.

Strassburg MA, Greenland S, Stephenson TG, Weiss BP, Auerbach D, Habel LA, Lieb LE. Clinical effectiveness of rubella vaccine in a college population. *Vaccine.* 1985 Jun;3(2):109-12.

An outbreak of rash-like illness compatible with rubella occurred among the student population of a large university in Los Angeles between November 1, 1981 and January 31, 1982. A case-control study was conducted in order to estimate the effectiveness of rubella vaccine in preventing clinical rubella in this university population. Immunization and disease histories were obtained from parents and physicians for 39 cases and 86 controls. For those students with a clear documentation of immunization history, only one of 16 cases (6%) had evidence of prior rubella immunization, compared with 40 of 56 controls (71%). This yielded an estimated vaccine effectiveness of 97% (95% confidence limits of 82% to 100%). The level of protection observed for students immunized with rubella vaccine in our study population was high and comparable to that reported in other recent studies. This supports the notion that the current large reservoir of young adult susceptibles is primarily attributable to past failures to vaccinate school-age children, rather than vaccine failures.

Efficacy of rubella vaccines; immunogenicity trials

Black SB, Cimino CO, Hansen J, Lewis E, Ray P, Corsaro B, Graepel J, Laufer D. Immunogenicity and safety of measles-mumps-rubella, varicella and Haemophilus influenzae type b vaccines administered concurrently with a fourth dose of heptavalent pneumococcal conjugate vaccine compared with the vaccines administered without heptavalent pneumococcal conjugate vaccine. *Pediatr Infect Dis J.* 2006 Apr;25(4):306-11.

BACKGROUND: Prevnar [heptavalent pneumococcal conjugate vaccine (PCV7)] is licensed in the United States for routine administration in infants and may be coadministered with other infant vaccines. Safety and immunogenicity data on the coadministration of the fourth dose of PCV7 with measles-mumps-rubella (MMR), varicella and Haemophilus influenzae type b (Hib) vaccines are limited.

METHODS: Children 12-15 months of age received either MMR with PCV7 (group 1) or MMR without PCV7 (group 2). All subjects received Hib and varicella vaccines. Group 2 received PCV7 6-9 weeks after MMR vaccination. Sera for analysis of all non-PCV7 antibodies were collected just before administration of MMR vaccine and 6 weeks later. Optimal antigen responses were assessed with the use of predetermined antibody titers. The primary end point was >90% response rate (all antigens). Noninferiority was defined as <10% difference between groups. Local and systemic reactions and postvaccination adverse events were monitored and compared between groups.

RESULTS: A total of 694 subjects (347 per group) were enrolled. After immunization with MMR plus PCV7 concurrently, or MMR followed 6 weeks later by PCV7, the percentages of subjects seroconverting were significantly greater than 90% for all antigens. The difference between the 2 groups was significantly less than 10%.

CONCLUSION: The immune response to MMR, Hib and varicella vaccines, when administered concurrently with a 4th (booster) dose of PCV7, was noninferior to that of these vaccines when given without PCV7. These results support concomitant administration of PCV7 with MMR, varicella and Hib as part of the recommended immunization schedule for children 12-15 months of age.

Crovati P, Gabutti G, Giammanco G, Dentico P, Moiraghi AR, Ponzio F, Soncini R. Reactogenicity and immunogenicity of a new combined measles-mumps-rubella vaccine:

results of a multicentre trial. The Cooperative Group for the Study of MMR vaccines. Vaccine. 2000 Jun 15;18(25):2796-803.

A large single blind, multi-centre study involving 1779 children was performed in Italy. Infants, aged between 12 and 27 months were divided between two groups: group A received a single dose of a new MMR vaccine, 'Priorix'(3), while group B received a widely used MMR vaccine, Triviraten(4). Solicited local and general symptoms were recorded using diary cards and antibody levels were measured, prior to and 60 days post-vaccination, using ELISA assays. The incidence of solicited symptoms (evaluated in 1754 subjects) was comparable between groups, with the exception of fever which was significantly lower in group B. Immunogenicity was evaluated in 686 subjects. Of note, was the significantly higher anti-mumps seroconversion rate ($p < 0.001$) observed in group A (97.0%) compared to group B (35.4%). However the anti-measles and anti-rubella seroconversion rates were equivalent between groups. Significantly higher ($p < 0.001$) post-vaccination GMTs were in group A vs group B for anti-measles (2830 vs 784 IU/ml) and anti-mumps (1640 vs 469 U/ml), however the anti-rubella GMTs were significantly higher ($p < 0.001$) in group B (117.6 IU/ml) compared to group A (92.6 IU/ml). The persistence of antibodies in 35 subjects was assessed 1 year after vaccination and the results showed no appreciable decline in titres with either vaccine. The trial demonstrates 'Priorix' is well tolerated and highly immunogenic.

Lieberman JM, Williams WR, Miller JM, Black S, Shinefield H, Henderson F, Marchant CD, Werzberger A, Halperin S, Hartzel J, Klopfer S, Schödel F, Kuter BJ; Consistency Lot Study Group for ProQuad. The safety and immunogenicity of a quadrivalent measles, mumps, rubella and varicella vaccine in healthy children: a study of manufacturing consistency and persistence of antibody. *Pediatr Infect Dis J.* 2006 Jul;25(7):615-22.

BACKGROUND: This clinical trial was conducted to demonstrate that each of 3 consistency lots of a combined measles, mumps, rubella and varicella vaccine (MMRV) would be well tolerated, induce clinically acceptable and similar immune responses to each antigen and induce immune responses similar to measles, mumps and rubella vaccine (MMR) administered concomitantly with varicella vaccine (V). An additional objective was to evaluate the persistence of antibodies 1 year postvaccination.

METHODS: Study participants 12 to 23 months of age received a single injection of either one of 3 consistency lots of MMRV or MMR + V administered at separate injection sites.

RESULTS: A total of 3,928 healthy children were enrolled at study sites in the United States and Canada. Immune responses to measles, mumps, rubella and varicella in children immunized with each of 3 lots of MMRV were similar and the combined response to all 3 lots was comparable to that of the control group. The 1-year antibody persistence rates for measles, mumps, rubella and varicella viruses were each greater than 95% and comparable among the recipients of the 3 consistency lots of MMRV and the control group. All vaccines were generally well tolerated during the 42 days after vaccination and the overall incidence of adverse experiences was comparable between recipients of MMRV and MMR + V. Rates of fever (temperature ≥ 38.9 degrees C oral equivalent or tactile) were greater in recipients of MMRV than in recipients of MMR + V (39.1% versus 33.1%, $P = 0.001$). Fevers were transient and there was no difference in the incidence of febrile seizures.

CONCLUSIONS: MMRV was generally well tolerated and had comparable immunogenicity and overall safety profiles to MMR + V administered concomitantly. Long-term persistence of antibodies after receipt of MMRV is expected based on similar antibody titers against all 4 antigens 1 year postvaccination compared with recipients of MMR and V.

Shinefield H, Black S, Thear M, Coury D, Reisinger K, Rothstein E, Xu J, Hartzel J, Evans B, Digilio L, Schödel F, Brown ML, Kuter B; 013 Study Group for ProQuad. Safety and immunogenicity of a measles, mumps, rubella and varicella vaccine given with combined Haemophilus influenzae type b conjugate/hepatitis B vaccines and combined diphtheria-tetanus-acellular pertussis vaccines. *Pediatr Infect Dis J.* 2006 Apr;25(4):287-92.

BACKGROUND: A study was conducted to assess administration of a combination measles, mumps, rubella and varicella vaccine (MMRV) with other childhood vaccines.

METHODS: In this open, multicenter trial, 1915 healthy children ages 12-15 months were randomized into 3 groups: group 1, MMRV, combined Haemophilus influenzae type b conjugate-hepatitis B vaccines (Hib/HepB) and combined diphtheria-tetanus-acellular pertussis vaccines (DTaP) concomitantly; group 2, MMRV followed by Hib/HepB and DTaP 42 days later; group 3, MMR and varicella vaccine followed by Hib/HepB and DTaP 42 days later.

RESULTS: Antibody responses to measles, mumps, rubella, varicella, Hib, HepB, diphtheria and tetanus were similar between groups 1 and 2 (all >95%, except varicella, 89.7% in group 1 and 90.9% in group 2). Pertussis toxin and filamentous hemagglutinin responses were significantly lower in group 1 than in group 2 (group 1, 74.1 and 67.1%; group 2, 90.4 and 86.8%, respectively). An exploratory analysis suggested that the difference in and pertussis toxin and filamentous hemagglutinin responses was likely the result of study design rather than interference among vaccine components because the groups differed in age of receipt of DTaP (group 1, approximately 12 months; group 2, approximately 13.5 months). When the groups were matched for age, sample size was sufficient for comparison only in children > or =13.5 months old. Pertussis toxin and filamentous hemagglutinin responses were similar in these children. The safety profiles for each vaccination regimen were comparable.

CONCLUSIONS: The immunogenicity data support concomitant administration of MMRV with Hib/HepB. Limited data from an exploratory analysis indicate that MMRV can be administered concomitantly with DTaP. Concomitant administration of MMRV, Hib/HepB and DTaP is well-tolerated.

Tischer A, Gerike E. Immune response after primary and re-vaccination with different combined vaccines against measles, mumps, rubella. *Vaccine.* 2000 Jan 31;18(14):1382-92.

The humoral immune response after primary and re-vaccination confirmed the high immunogenicity of the combined vaccines used: "MMR-Vax(R)", "Pluserix(R)" and "Triviraten(R)". The investigation of paired serum samples of prevaccinal seronegative infants (n90-100% for all three components with the exception of the mumps component of "Triviraten(R)" (38%). However, by additional methods (plaque neutralisation test, immunofluorescence test) mumps antibodies could be detected in 93.4% of infants having received vaccine "Triviraten(R)". The mean values of antibody activities against the three

components did not differ significantly after vaccination with "MMR-Vax(R)" and "Pluserix(R)". However, after vaccination with "Triviraten(R)" the mean antibody values were significantly lower ($P < 0.01$) against the measles strain "Edmonston-Zagreb" and especially lower (2-20 times) against the mumps virus strain "Rubini". Revaccination of pre-vaccinal seropositive schoolchildren and adolescents ($n=676$) with "MMR-Vax(R)" and "Pluserix(R)" produced no different results. The rate of vaccinees responding with a booster reaction reached 68.4% for measles and mumps, but only 8.6% for rubella. A booster reaction could be observed in 100% of those vaccinees who had antibodies at a low level, also in the case of naturally acquired immunity. The low-level range for antibodies against measles was defined as $0.15 < 0.40$ IU/ml, mumps $1:230 \leq 1:500$ and rubella 7-16 IU/ml. The rate of vaccinees with low-level antibodies against measles can become as high as 10%, for mumps 20% and for rubella 3%. The correlation between the level of antibodies and protection against the disease is discussed. The rate of individuals in a population with doubtful protection (unvaccinated, non-responder and low responder after primary vaccination) prevents to reach the herd immunity of 95% necessary for elimination. The results of our serological studies strongly recommend re-vaccination against measles, mumps and rubella.

Efficacy of rubella vaccines; population-based observations

Castillo-Solórzano C, Carrasco P, Tambini G, Reef S, Brana M, de Quadros CA. New horizons in the control of rubella and prevention of congenital rubella syndrome in the Americas. J Infect Dis. 2003 May 15;187 Suppl 1:S146-52.

Data from the regional measles surveillance system have documented widespread rubella virus circulation in many different countries in the Americas. In response to the ongoing endemic incidence of the disease and the potential for a major rubella epidemics in the region, the Pan American Health Organization Technical Advisory Group on Vaccine Preventable Diseases recommended the implementation of a regional initiative to strengthen rubella and congenital rubella syndrome (CRS) preventive efforts in 1997. This article summarizes and highlights the progress toward accelerated rubella control and CRS prevention in the English-speaking Caribbean and in Chile, Costa Rica, and Brazil. Useful knowledge is being generated for the adaptation of similar rubella strategies elsewhere. The findings also document the feasibility of implementing the recommended strategies and their rapid impact on disease burden.

Centers for Disease Control and Prevention (CDC). Progress toward elimination of rubella and congenital rubella syndrome--the Americas, 2003-2008. burden. MMWR Morb Mortal Wkly Rep. 2008 Oct 31;57(43):1176-9.

In 2003, the Pan American Health Organization (PAHO) adopted a resolution calling for rubella and congenital rubella syndrome (CRS) elimination in the Americas by the year 2010. Elimination was defined as the interruption of endemic rubella virus transmission in all countries of North America, Central America, South America, and the Caribbean for more than 12 months and no occurrence of CRS cases attributed to endemic transmission. To accomplish this goal, PAHO developed a rubella and CRS elimination strategy (3) to 1) introduce rubella-containing vaccine (RCV) into routine vaccination programs of all countries

for children aged 12 months and reach $\geq 95\%$ coverage in all municipalities, 2) conduct a one-time mass campaign among adolescents and adults and periodic follow-up campaigns among children aged < 5 years, and 3) integrate rubella surveillance with measles surveillance and initiate CRS surveillance. During 1998-2006, confirmed rubella cases decreased 98% (from 135,947 to 2,998) in the Americas. However, in 2007, rubella outbreaks with a total of 13,014 cases occurred in three countries (Argentina, Brazil, and Chile), primarily in males not included in previous vaccination campaigns. This report summarizes overall progress toward reaching the 2010 goal of eliminating rubella and CRS. With completion of campaigns in Argentina, Brazil, and Haiti, all countries will have implemented the recommended PAHO strategy by the end of 2008, with the expectation of reaching the 2010 rubella and CRS elimination goal.

Dayan GH, Castillo-Solórzano C, Nava M, Hersh BS, Andrus J, Rodriguez R, Reef SE. Efforts at rubella elimination in the United States: the impact of hemispheric rubella control. Clin Infect Dis. 2006 Nov 1;43 Suppl 3:S158-63.

We examined rubella vaccination trends, rubella surveillance, and disease patterns for the Americas, Mexico, and the United States, to evaluate the impact of hemispheric rubella control on rubella elimination in the United States during 1997-2004. In 1997, 130,375 rubella cases were reported in the Americas, with 38,042 reported in Mexico. Over the next 7 years, a rubella control initiative resulted in the administration of approximately 110 million rubella-containing vaccine doses in Latin America, with 77.7 million doses administered within Mexico. By 2004, the number of reported rubella cases had declined to 3103 in the Americas and 698 in Mexico. Concurrently, the number of rubella cases in the United States fell from 817 during 1997-1999 to < 25 cases/year from 2001 onward, with loss of seasonality and geographic clustering, despite no change in vaccination rates. Implementation of rubella control strategies in the Americas, particularly in Mexico, appears to have facilitated rubella elimination in the United States.

Katow S. Surveillance of congenital rubella syndrome in Japan, 1978-2002: effect of revision of the immunization law. Vaccine. 2004 Sep 28;22(29-30):4084-91.

Infection of rubella virus at the early stages of pregnancy in women who are not immune to rubella often induces congenital anomalies in infants, namely congenital rubella syndrome (CRS). This paper is the first comprehensive report of CRS cases in Japan, compiled from a questionnaire to major hospitals, reports to journals and academic meetings, and cases for virus/virus genome verification submitted to the National Institute of Infectious Diseases. CRS incidence in Japan was determined to be 0.2-8.1 cases/100,000 live births per year in epidemic years and 0.1-0.7 in non-epidemic years, respectively. In the last 4 years, the number of CRS cases remarkably decreased to one-three cases per year. This decrease is thought to be because the immunization law was revised in 1994 for changing the focus of rubella immunization from junior high school girls to infants of both sexes.

Reef SE, Redd SB, Abernathy E, Zimmerman L, Icenogle JP. The epidemiological profile of rubella and congenital rubella syndrome in the United States, 1998-2004: the

evidence for absence of endemic transmission. Clin Infect Dis. 2006 Nov 1;43 Suppl 3:S126-32.

In 1969, the United States established its national rubella vaccination program. With the success of the program, 32 years later, reports of rubella reached record low numbers. To assess the achievement of elimination of rubella and congenital rubella syndrome (CRS) in the United States, 7 epidemiological criteria were used. Rubella cases reported to the National Notifiable Diseases Surveillance System from 1998 through 2004 and CRS cases reported to the National Congenital Rubella Syndrome Registry from 1998 through 2004 were analyzed. During 1998-2000, the median number of reported rubella cases was 272, whereas, during 2001-2004, the median number reported was 13. The incidence of rubella decreased significantly, from 0.1/100,000 population in 1998 to 0.005/100,000 population in 2004. Since 2001, 5 infants with CRS have been reported--3 were born in 2001, 1 was born in 2003, and 1 was born in 2004. The epidemiological evidence strongly supports the claim that rubella is no longer endemic in the United States. To prevent future rubella outbreaks and CRS cases, current strategies must be maintained.

Reef SE, et al Evidence Used to Support the Achievement and Maintenance of Elimination of Rubella and Congenital Rubella Syndrome in the United States. JID supplement 2011. (Not yet published 1 July 2011).

References used in Grade table II: Duration of protection

Antibody persistence and/or evidence of an immunological memory

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.

Chu SY, Bernier RH, Stewart JA, Herrmann KL, Greenspan JR, Henderson AK, Liang AP. Rubella antibody persistence after immunization. Sixteen-year follow-up in the Hawaiian Islands. JAMA. 1988 Jun 3;259(21):3133-6.

A comparative field trial of three rubella virus vaccines (Cendehill, HPV-77 DE-5, and HPV-77 DK-12) was initiated in 1969 on the islands of Kauai and Hawaii in the state of Hawaii. In 1985, follow-up was reinitiated to assess the long-term durability of vaccine-induced immunity. Enzyme-linked immunosorbent assays of serum specimens from 1290 participants demonstrated seropositive rates of 92.4% and 96.4% at screening levels of 10 (protective level) and 7 (lowest detectable level) IU/mL, respectively. The seropositive rates were not related to reinfection or reimmunizations. These findings indicate that vaccine-induced rubella antibodies are detectable in almost all persons up to 16 years after successful vaccination.

Christenson B, Böttiger 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).

Best JM. Rubella vaccines - past, present and future. *Epidemiology and Infection*, 1991,107:17-30. (No abstract available)

Davidkin I, Jokinen S, Broman M, Leinikki M, Peltola H. Persistence of Measles, Mumps, and Rubella Antibodies in an MMR-Vaccinated Cohort: A 20-Year Follow-up. *The Journal of Infectious Diseases* 2008; 197:950–6.

Background. The persistence of antibodies against measles, mumps, and rubella induced by the measles-mump-rubella (MMR) vaccine and the kinetics of antibody decline after the second MMR vaccine dose were studied in the same cohort for 20 years.

Methods. Measles, mumps, and rubella antibodies were measured by enzyme immunoassay in 20-year follow-up serum samples (n = 183) of twice-vaccinated individuals, and measles antibodies were also measured in oral fluids (n = 177). Antibody decay was determined in a group (n = 58) with subsequent samples collected 1, 8, and 15 years after the second MMR dose.

Results. In total, 95%, 74%, and 100% of 183 vaccinees were still seropositive for measles, mumps, and rubella, respectively, and 85% of 177 vaccinees had measurable measles antibodies in their oral fluids. The antibody levels declined significantly after the second dose, but subsequently the rate of decline was slower.

Conclusions. A high rate of seropositivity was found 20 years after the first MMR dose, particularly for rubella and measles. Our results show that MMR vaccine-induced antibodies wane significantly after the second dose. According to epidemiological data, the protection induced by MMR vaccination in Finland seems to persist at least until early adulthood. However, the situation requires constant vigilance.

Enders G, Nickerl U. [Rubella vaccination: antibody persistence for 14-17 years and immune status of women without and with a history of vaccination]. *Immun Infekt.* 1988 Apr;16(2):58-64. [Article in German]

Out of 1045 women who had been successfully vaccinated with Cendehill vaccine, 195 were tested for rubella antibodies 13-17 years later and still 98% were seropositive with a geometric mean titer (GMT) of 2-5.4 (1:42). In 7.8% and 21.6% only borderline or low hemagglutination inhibition (HAL) titer were found. A reinfection rate of 12.2% was determined by significant titer rises and IgM antibody detection in 466 vaccinees with 3 or more blood samples during the observation period. Out of 312 successfully vaccinated girls aged 11-16 years with HPV77DE5 and RA 27/3, 130 could be retested 14 years later and all were found seropositive with a GMT of 2-5.8. Low HAL titers of 1:16 have been found in 6.2% (8 cases). The rubella immune status of 11,0978 postpubertal and pregnant women in South-West Germany was determined between 1981 and 1987. 9824 of these women had a history of vaccination and only 2.4% were seronegative in contrast to 8.2% of 101,154 women with no history of vaccination. There was a significantly higher prevalence of low levels (HAL 1:8, 1:16) of antibodies among women with a history of vaccination (19.4%) than among those without (10.6%, p less than 0.001). The effect of reinfection in pregnancy following previous vaccination on the newborn is discussed.

Hillary IB, Griffith AH. Persistence of rubella antibodies 15 years after subcutaneous administration of Wistar 27/3 strain live attenuated rubella virus vaccine. *Vaccine.* 1984 Dec;2(4):274-6.

The rubella-specific antibody levels of children vaccinated with RA 27/3 rubella vaccine have been determined over the 15 years since vaccination. Over the period monitored, titres have declined at a comparable rate to those observed in children who had experienced natural rubella infection. In both cohorts the mean rate of decay was similar throughout the 15 years of the study. One in eleven vaccinated children monitored for the entire period of the study reverted to a state of susceptibility to rubella as judged by routine rubella antibody tests used in practice today. The implications of the findings for rubella prophylaxis are discussed.

Johnson CE, Kumar ML, Whitwell JK, Staehle BO, Rome LP, Dinakar C, Hurni W, Nalin DR. Antibody persistence after primary measles-mumps-rubellavaccine and response to a second dose given at four to six vs. eleven to thirteen years. *The Pediatric Infectious Disease Journal*, 1996, 15: 687-692.

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 \geq 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.

Kakoulidou M, Forsgren M, Lewensohn-Fuchs I, Johansen K. Serum levels of rubella-specific antibodies in Swedish women following three decades of vaccination programmes. *Vaccine*. 2010 Jan 22;28(4):1002-7.

In Sweden, more than 30 years after the introduction of vaccination for 12-year-old girls and post-partum mothers against rubella and 22 years after the introduction of routine MMR vaccination for all children at the ages of 18 months and 12 years, we have evaluated the rubella IgG activity in antenatal sera. 95.8% (39,890/41,637) of all women had anti-rubella IgG levels ≥ 10 IU/mL. Levels < 10 IU/mL were more frequent in certain subcohorts: 8.2% (153/1870) of the Swedish women born after the introduction of the programme of childhood vaccination, 7.7% (616/8025) of women born outside the Nordic countries and 10.2% (118/1155) of recent immigrants and refugees to Sweden. In order to attain the goal of protecting the unborn, we propose alternative strategies to be evaluated: routine screening for rubella immunity prior to the first pregnancy, offering individuals with uncertain immunity a booster dose, and/or routine administration of an additional dose of MMR vaccine to all young adults before they leave the educational system.

Ki M, Kim MH, Choi BY, Shin YJ, Park T. Rubella antibody loss rates in Korean children. *Epidemiol Infect*. 2002 Dec;129(3):557-64.

We followed students in eight elementary schools for rubella antibody from 1993 to 1996 (602 pairs) and 1996-9 (588 pairs) in Gyeonggi Province, Korea. We tested rubella IgG and administered rubella vaccine to the children with the titres < 10 IU/ml. The loss rates of rubella IgG during the follow-up periods were 14.3 and 15.8%, respectively. Among vaccinated groups, the loss rate was 18.8%, which was significantly higher than 13.8% of the mixture of natural and vaccine-induced immunity groups. The group that had the lower preceding antibody titre had a higher loss rate of 24.8% compared to 7.2% for the group whose titre was 40 IU/ml or above. In a multivariate analysis, age and gender were not related to antibody loss rate. Under this higher rubella antibody loss rate, in order to prevent congenital rubella syndrome, the immunization for women at childbearing age appears necessary until rubella can be eliminated or controlled.

King JC Jr, Lichenstein R, Feigelman S, Luna C, Permutt TJ, Patel J. Measles, mumps, and rubella antibodies in vaccinated Baltimore children. *Am J Dis Child*. 1993 May;147(5):558-60.

OBJECTIVE: To determine quantitative measles, mumps, and rubella serum antibody levels as a function of time since vaccination in a sample of vaccinated Baltimore children.

DESIGN: Cross-sectional serologic survey.

SETTING: Pediatric outpatient departments at the University of Maryland Medical Center, Baltimore.

PARTICIPANTS: One hundred seventy children, ranging in age from 1.5 through 16 years, who had measles, mumps, and rubella vaccination between ages 12 and 18 months.

RESULTS: Serum antibody levels to measles and rubella declined with increasing time since vaccination. However, no such decline in antibody levels to mumps was observed. Children who were vaccinated between ages 12 and 14 months did not have lower antibody levels than children who were vaccinated at age 15 months or older.

CONCLUSIONS: In areas free from natural disease, antibody levels resultant from measles, mumps, and rubella vaccine are likely to decline with advancing age. Revaccination with measles, mumps, and rubella vaccine may boost falling antibody titers.

Latner DR, McGrew M, Williams N, Lowe L, Werman R, Warnock E, Gallagher K, Doyle P, Smole S, Lett S, Cocoros N, DeMaria A, Konomi R, Brown CJ, Rota PA, Bellini WJ, Hickman CJ. Enzyme-linked immunospot assay detection of mumps-specific antibody-secreting B cells as an alternative method of laboratory diagnosis. Clin Vaccine Immunol. 2011 Jan;18(1):35-42.

Although high measles, mumps, and rubella (MMR) vaccination coverage has been successful in dramatically reducing mumps disease in the United States, mumps (re)infections occasionally occur in individuals who have been either previously vaccinated or naturally infected. Standard diagnostics that detect virus or virus-specific antibody are dependable for confirming primary mumps infection in immunologically naïve persons, but these methods perform inconsistently for individuals with prior immune exposure. We hypothesized that detection of activated mumps-specific antibody-secreting B cells (ASCs) by enzyme-linked immunospot (ELISPOT) assay could be used as a more reliable diagnostic. To test this, a time course of virus-specific ASC responses was measured by ELISPOT assay following MMR vaccination of 16 previously vaccinated or naturally exposed adult volunteers. Mumps-specific ASCs were detectable in 68% of these individuals at some point during the first 3 weeks following revaccination. In addition, mumps-specific ASCs were detected in 7/7 previously vaccinated individuals who recently had been infected as part of a confirmed mumps outbreak. These data suggest that ELISPOT detection of mumps-specific ASCs has the potential for use as an alternative method of diagnosis when suspect cases cannot be confirmed by detection of IgM or virus. In addition, it was determined that mumps-specific memory B cells are detected at a much lower frequency than measles- or rubella-specific cells, suggesting that mumps infection may not generate robust B-cell memory.

O'Shea S, Woodward S, Best JM, Banatvala JE, Holzel H, Dudgeon JA. Rubella vaccination: persistence of antibodies for 10-21 years. Lancet. 1988 Oct 15;2(8616):909. (No abstract available).

Orenstein WA, Herrmann KL, Holmgren P, Bernier R, Bart KJ, Eddins DL, Fiumara NJ. Prevalence of rubella antibodies in Massachusetts schoolchildren. Am J Epidemiol. 1986 Aug;124(2):290-8.

In 1982, 1,871 (79%) of 2,368 eligible 6th, 10th and 12th grade students in Massachusetts participated in a statewide serosurvey for rubella antibodies. Sera were screened at the Centers for Disease Control (CDC) by a reference hemagglutination inhibition assay at 1:8,

equivalent to approximately 15 International Units (IU)/ml. Sera negative by the CDC hemagglutination inhibition assay were retested using an enzyme immunoassay, a passive hemagglutination assay, and a commercial hemagglutination inhibition test. The approximate screening levels were 10 IU/ml, 7.5 IU/ml, and 5 IU/ml, respectively. Overall seroprevalence levels varied from 76.4% screening at 15 IU to 93.1% including seropositives from any of the tests. Persons with a school record of vaccination had significantly higher seroprevalence levels than persons without records. However, only 78.3% of persons with a record had antibody greater than or equal to 15 IU compared with 60.0% without records; considering any detectable antibody, the comparison is 95.6% versus 71.4%. The low titers in vaccinees appeared to be due to a falloff of antibody with time since vaccination. Of students with a single vaccination noted in the record with exact dates, 92.3% who were vaccinated 0-4 years prior to the study had antibody at 15 IU compared with less than 78% of students with antibody who were vaccinated five or more years prior to the study. In contrast, using more sensitive assays, there was no significant decline in seroprevalence with time since vaccination. Revaccination studies and epidemiologic data suggest that almost all persons with detectable antibody whether above or below 15 IU/ml are immune to rubella. Thus, immunity levels in Massachusetts schoolchildren in the 6th, 10th, and 12th grades are probably in excess of 90%.

Plotkin SA, Buser F. History of RA27/3 rubella vaccine. *Reviews of Infectious Diseases*, 1985, 7(Suppl. 1):S77-S78. (No abstract available).

Ratnam S, West R, Gadag V, Williams B, Oates E. Rubella antibody levels in school-aged children in Newfoundland: mplications for a two-dose rubella vaccination strategy. *Canadian Journal of Infectious Diseases (Journal canadien des maladies infectieuses)*, 1997, 8:85-88.

OBJECTIVE: To determine the prevailing levels of rubella immunity among school-aged children who received a single dose of measles-mumps-rubella (MMR) vaccine at one year of age.

DESIGN: Cross-sectional study with a two stage cluster sampling of randomly picked schools across the province of Newfoundland.

STUDY POPULATION AND METHODS: A total of 1053, five to 17-year-old children were enrolled; vaccination history was verified through official records; and a sample of blood was taken. Rubella immunity was determined by enzyme immunoassay based on a serum antibody protective cut-off titre of more than 10 IU.

RESULTS: A total of 145 (13.8%) were found to be nonimmune. The rate of susceptibility ranged from 3.2% to 25.9% for different age groups. The proportion susceptible was significantly higher at 16.5% in the age group eight to 17 years old versus 3.9% for the age group five to eight years old ($c^2=24.08$; $df=1$, $P<0.001$). There was a significant regression of logarithm titre values on the age of children with an average decline in titre values of 8.1% per annum.

CONCLUSIONS: A substantial number of those who were given a single dose of MMR II vaccine may not have protective immunity against rubella as they reach prime reproductive age. There is a definite need to consider a two-dose rubella vaccination strategy in Canada, and these data suggest the second dose given after eight years of age will be most beneficial. In the move towards a routine two-dose measles vaccination strategy in Canada, the MMR II vaccine is being used for the second dose and given either at 18 months of age or at school entry. While this approach will have an overall beneficial effect, the impact of the above timing of the second dose on long term rubella immunity cannot be predicted at this time. These data also underscore the continuing need for prenatal rubella screening program.

Vandermeulen C, Mathieu R, Geert LR, Pierre VD, Karel H. Long-term persistence of antibodies after one or two doses of MMR-vaccine. *Vaccine*, 2007, 25:6672-6.

Outbreaks of measles, mumps and rubella have occurred recently despite long-standing mass immunization with MMR. Antibody titres for measles, mumps and rubella of 160 students (17-23 years) with proof of at least one MMR-vaccine were studied according to the number of MMR-vaccines received. The proportion of subjects with positive antibody titres was significantly higher in those who received two vaccines against measles (77.1% versus 58.7%, $p=0.05$), mumps (67.5% versus 55.6%, $p=0.009$) and rubella (99.2% versus 71.4%, $p=0.008$). Comparable significant trends were seen for GMTs for measles and mumps. A similar non-significant trend was noted for rubella.

References used in Grade table III:

Serious adverse reactions

Bloom JL, Schiff GM, Graubarth H, Lipp RW Jr, Jackson JE, Osborn RL, Kenny MT. Evaluation of a trivalent measles, mumps, rubella vaccine in children. *J Pediatr*. 1975 Jul;87(1):85-7. (No abstract available).

Demicheli V, Jefferson T, Rivetti A, Price D. Vaccines for measles, mumps and rubella in children. *Cochrane Database Syst Rev*. 2005 Oct 19;(4):CD004407.

BACKGROUND: Public debate over the safety of the trivalent measles, mumps and rubella (MMR) vaccine, and the resultant drop in vaccination rates in several countries, persists despite its almost universal use and accepted effectiveness.

OBJECTIVES: We carried out a systematic review to assess the evidence of effectiveness and unintended effects associated with MMR.

SEARCH STRATEGY: We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue 4, 2004), MEDLINE (1966 to December 2004), EMBASE (1974 to December 2004), Biological Abstracts (from 1985 to December 2004),

and Science Citation Index (from 1980 to December 2004). Results from reviews, handsearching and from the consultation of manufacturers and authors were also used. **SELECTION CRITERIA:** Eligible studies were comparative prospective or retrospective trials testing the effects of MMR compared to placebo, do-nothing or a combination of measles, mumps and rubella antigens on healthy individuals up to 15 years of age. These studies were carried out or published by 2004.

DATA COLLECTION AND ANALYSIS: We identified 139 articles possibly satisfying our inclusion criteria and included 31 in the review.

MAIN RESULTS: MMR was associated with a lower incidence of upper respiratory tract infections, a higher incidence of irritability, and similar incidence of other adverse effects compared to placebo. The vaccine was likely to be associated with benign thrombocytopenic purpura, parotitis, joint and limb complaints, febrile convulsions within two weeks of vaccination and aseptic meningitis (mumps) (Urabe strain-containing MMR). Exposure to MMR was unlikely to be associated with Crohn's disease, ulcerative colitis, autism or aseptic meningitis (mumps) (Jeryl-Lynn strain-containing MMR). We could not identify studies assessing the effectiveness of MMR that fulfilled our inclusion criteria even though the impact of mass immunisation on the elimination of the diseases has been largely demonstrated.

AUTHORS' CONCLUSIONS: The design and reporting of safety outcomes in MMR vaccine studies, both pre- and post-marketing, are largely inadequate. The evidence of adverse events following immunisation with MMR cannot be separated from its role in preventing the target diseases.

DeStefano F, Thompson WW. MMR vaccine and autism: an update of the scientific evidence. Expert Rev Vaccines. 2004 Feb;3(1):19-22.

An hypothesis published in 1998 suggested that measles-mumps-rubella vaccine may cause autism as a result of persistent measles virus infection of the gastrointestinal tract. Results of early studies were not supportive and in 2001 a review by the Institute of Medicine concluded that the evidence favors the rejection of a causal relationship at the population level between measles-mumps-rubella vaccine and autistic spectrum disorder. Studies published since the Institute of Medicine report have continued not to find an increased risk of autistic spectrum disorder associated with measles-mumps-rubella. The vaccine also has not been found to be associated with a unique syndrome of developmental regression and gastrointestinal disorders. The evidence now is convincing that the measles-mumps-rubella vaccine does not cause autism or any particular subtypes of autistic spectrum disorder.

Eedes S, Pullan CR, Hull D. A randomised single blind trial of a combined mumps measles rubella vaccine to evaluate serological response and reactions in the UK population. Public Health. 1991 Mar;105(2):91-7.

Four hundred and twenty children were randomly assigned to receive either mumps measles rubella (MMR) vaccine (207) or measles vaccine (213) in a single blind study, to investigate the reactogenicity and serology of the MMR vaccine. There was no significant difference between the number of children developing symptoms after MMR vaccination to those developing symptoms after measles vaccination. Both vaccines are associated with a rash, temperature and restlessness five to thirteen days after vaccination. The serological response

to measles vaccine was similar in both groups with 92-6% seroconverting with MMR, and 96-8% with measles. Seroconversion against mumps and rubella with the MMR vaccine was 88% and 96% respectively. This study confirms the safety and efficacy of the MMR vaccine in a UK population.

Halperin SA, Ferrera G, Scheifele D, Predy G, Stella G, Cuccia M, Douha M, Willems P. Safety and immunogenicity of a measles-mumps-rubella-varicella vaccine given as a second dose in children up to six years of age. *Vaccine*. 2009 May 5;27(20):2701-6.

Two doses of measles-mumps-rubella vaccine (MMR) are widely recommended and consideration is being given to a similar schedule for varicella vaccine. A combined measles-mumps-rubella-varicella vaccine (MMRV) could be considered for this second dose in children previously vaccinated separately with MMR and varicella vaccines. Healthy children (N=390) aged 15-75 months (median 54 months) previously immunized with MMR and varicella vaccines were randomly allocated to receive MMRV or separate injections of MMR and varicella vaccines. Before administration of study vaccines, seropositivity rates were 96.4% for measles, 94.3% for mumps, 99.5% for rubella, and 97.9% for varicella. Post-immunization, seropositivity rates were 99.5% for measles and mumps and 100% for rubella and varicella in the MMR+varicella group and 100% for all four antigens in the MMRV group; a 26.2- and 27.2-fold increase in varicella titer was observed in the MMR+varicella vaccine and MMRV groups, respectively. Except for more frequent pain in the MMRV group (33.3% vs. 23.7%, p=0.043), there were no differences in the incidence of local and solicited symptoms between groups. In children primed with MMR and varicella vaccine, MMRV had non-inferior immunogenicity and similar safety profiles as a second dose of licensed MMR and varicella vaccine administered concomitantly.

Hensley E, Briars L. Closer look at autism and the measles-mumps-rubella vaccine. *J Am Pharm Assoc* (2003). 2010 Nov-Dec;50(6):736-41.

OBJECTIVE: To educate pharmacists regarding the hypothesis that the measles-mumps-rubella (MMR) vaccine is linked to the development of autism.

DATA SOURCES: Articles published from 1998 to 2009 were identified through electronic searches of Medline.

STUDY SELECTION: Articles were included if they evaluated or reviewed a possible link between the MMR vaccine and autism or discussed MMR epidemiology, legal proceedings involving the MMR vaccine and autism, or health professionals' impact on immunization decisions.

DATA SYNTHESIS: A total of 27 articles were identified. Of the articles, 74% (20 of 27) were included in the review because of their relevance to the study topic.

CONCLUSION: The evidence presented does not show a causal relationship between the MMR vaccine and autism. Myths presented to potentially support any relationship between the MMR vaccine and autism have not been proven. Expert testimony refuting initial scientific theories has led to Supreme Court decisions that do not support a link between the MMR vaccine and autism. Pharmacists and all health care providers are responsible for

informing and educating parents and families regarding this information so that they can make informed decisions about immunizations.

Khetsuriani N, Imnadze P, Baidoshvili L, Jabidze L, Tatishili N, Kurtsikashvili G, Lezhava T, Laurent E, Martin R. Impact of unfounded vaccine safety concerns on the nationwide measles-rubella immunization campaign, Georgia, 2008. *Vaccine*. 2010 Sep 7;28(39):6455-62.

Vaccine safety fears following media reports of adverse events led to low (50.3%) coverage in a supplementary measles-rubella immunization campaign in Georgia in 2008. Review of adverse events associated with the campaign identified 432 reports (<0.1% of □ 493,000 vaccinees) including 338 (78.2%) cases of syncope. There were no deaths. Causality assessment was performed for 79 cases perceived by providers as severe and with clinical details available. Conditions likely caused by the vaccine were identified in 13 (16.5%) cases (allergic and local reactions, thrombocytopenia). Thirty-seven (46.8%) cases had symptoms consistent with syncope or anxiety attack; 36 (97.3%) of them were initially misdiagnosed as anaphylactic shock/allergies/"postvaccinal reactions". Twenty-nine (36.7%) cases had coincidental illnesses. Safety fears were unfounded and exaggerated by media reports and providers' difficulties in recognizing syncope/anxiety attacks. Risk communication strategies to address perceived vaccine safety concerns are urgently needed to ensure that the goal of measles and rubella elimination in the European Region of the World Health Organization is met.

Klein NP, Fireman B, Yih WK, Lewis E, Kulldorff M, Ray P, Baxter R, Hambidge S, Nordin J, Naleway A, Belongia EA, Lieu T, Baggs J, Weintraub E; Vaccine Safety Datalink. Measles-mumps-rubella-varicella combination vaccine and the risk of febrile seizures. *Pediatrics*. 2010 Jul;126(1):e1-8.

OBJECTIVE: In February 2008, we alerted the Advisory Committee on Immunization Practices to preliminary evidence of a twofold increased risk of febrile seizures after the combination measles-mumps-rubella-varicella (MMRV) vaccine when compared with separate measles-mumps-rubella (MMR) and varicella vaccines. Now with data on twice as many vaccine recipients, our goal was to reexamine seizure risk after MMRV vaccine.

METHODS: Using 2000-2008 Vaccine Safety Datalink data, we assessed seizures and fever visits among children aged 12 to 23 months after MMRV and separate MMR + varicella vaccines. We compared seizure risk after MMRV vaccine to that after MMR + varicella vaccines by using Poisson regression as well as with supplementary regressions that incorporated chart-review results and self-controlled analyses.

RESULTS: MMRV vaccine recipients (83,107) were compared with recipients of MMR + varicella vaccines (376,354). Seizure and fever significantly clustered 7 to 10 days after vaccination with all measles-containing vaccines but not after varicella vaccination alone. Seizure risk during days 7 to 10 was higher after MMRV than after MMR + varicella vaccination (relative risk: 1.98 [95% confidence interval: 1.43-2.73]). Supplementary analyses yielded similar results. The excess risk for febrile seizures 7 to 10 days after MMRV

compared with separate MMR + varicella vaccination was 4.3 per 10,000 doses (95% confidence interval: 2.6-5.6).

CONCLUSIONS: Among 12- to 23-month-olds who received their first dose of measles-containing vaccine, fever and seizure were elevated 7 to 10 days after vaccination. Vaccination with MMRV results in 1 additional febrile seizure for every 2300 doses given instead of separate MMR + varicella vaccines. Providers who recommend MMRV should communicate to parents that it increases the risk of fever and seizure over that already associated with measles-containing 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.

Ljungman P, Fridell E, Lönnqvist B, Bolme P, Böttiger M, Gahrton G, Linde A, Ringdén O, Wahren B. Efficacy and safety of vaccination of marrow transplant recipients with a live attenuated measles, mumps, and rubella vaccine. J Infect Dis. 1989 Apr;159(4):610-5.

Long-term immunity to measles, mumps, and rubella viruses was studied in 57 patients after allogeneic bone marrow transplantation. Among patients who were seropositive at the time of transplant, 51% had retained antibodies to measles, 42% had retained antibodies to mumps, and 76% had retained antibodies to rubella 2 y later. There was no difference in the ability to retain antibodies to these viruses between patients with and those without chronic graft-versus-host disease (GVHD). Twenty seronegative patients without active chronic GVHD or ongoing immunosuppressive treatment were vaccinated with a live attenuated trivalent vaccine against measles, mumps, and rubella. No early or late side effects were detected after the vaccinations. The percentages of patients who seroconverted after vaccination were 77%, 64%, and 75% for measles, mumps, and rubella, respectively. Vaccination of transplant recipients with a live attenuated vaccine against measles, mumps, and rubella is safe and usually effective 2 y after transplant if the patients do not have active chronic GVHD or ongoing immunosuppressive treatment at the time of vaccination.

Mrozek-Budzyn D, Kieltyka A, Majewska R. Lack of association between measles-mumps-rubella vaccination and autism in children: a case-control study. Pediatr Infect Dis J. 2010 May;29(5):397-400.

OBJECTIVE: The first objective of the study was to determine whether there is a relationship between the measles-mumps-rubella (MMR) vaccination and autism in children.

The second objective was to examine whether the risk of autism differs between use of MMR and the single measles vaccine.

DESIGN: Case-control study.

STUDY POPULATION: The 96 cases with childhood or atypical autism, aged 2 to 15, were included into the study group. Controls consisted of 192 children individually matched to cases by year of birth, sex, and general practitioners.

METHODS: Data on autism diagnosis and vaccination history were from physicians. Data on the other probable autism risk factors were collected from mothers. Logistic conditional regression was used to assess the risk of autism resulting from vaccination. Assessment was made for children vaccinated (1) Before diagnosis of autism, and (2) Before first symptoms of autism onset. Odds ratios were adjusted to mother's age, medication during pregnancy, gestation time, perinatal injury and Apgar score.

RESULTS: For children vaccinated before diagnosis, autism risk was lower in children vaccinated with MMR than in the nonvaccinated (OR: 0.17, 95% CI: 0.06-0.52) as well as to vaccinated with single measles vaccine (OR: 0.44, 95% CI: 0.22-0.91). The risk for vaccinated versus nonvaccinated (independent of vaccine type) was 0.28 (95% CI: 0.10-0.76). The risk connected with being vaccinated before onset of first symptoms was significantly lower only for MMR versus single vaccine (OR: 0.47, 95% CI: 0.22-0.99).

CONCLUSIONS: The study provides evidence against the association of autism with either MMR or a single measles vaccine.

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.

Schwarz AJ, Jackson JE, Ehrenkranz NJ, Ventura A, Schiff GM, Walters VW. Clinical evaluation of a new measles-mumps-rubella trivalent vaccine. Am J Dis Child. 1975 Dec;129(12):1408-12.

In a series of clinical studies of a combined measles (Schwarz strain), mumps (Jeryl Lynn strain), and rubella (Cendehill strain) vaccine, 1,481 children received the vaccine or a placebo. The vaccine did not cause any significant reactions. The frequencies of mild, transient fever or rash or both in triple-susceptible vaccinees were similar to those that follow use of Schwarz strain measles vaccine alone. Measles, mumps, and rubella seroconversion rates in triple-susceptible vaccinees ranged from 95% to 100%. Geometric mean antibody

titers were as high as those that usually result from use of these same virus strains as monovalent vaccines.

Stermole BM, Grandits GA, Roediger MP, Clark BM, Ganesan A, Weintrob AC, Crum-Cianflone NF, Ferguson TM, Macalino GE, Landrum ML. Long-term safety and serologic response to measles, mumps, and rubella vaccination in HIV-1 infected adults. *Vaccine*. 2011 Apr 5;29(16):2874-80.

We analyzed HIV viral load (VL) and CD4 count changes, and antibody responses following MMR vaccination of individuals in the U.S. Military HIV Natural History Study cohort. Cases receiving at least one dose of MMR vaccine after HIV diagnosis were matched 1:2 to HIV-positive controls not receiving the vaccine. Baseline was defined as time of vaccination for cases and indexed and matched to the time post-HIV diagnosis for controls. Changes in CD4 count and VL at 6, 12, 18 and 24 months were compared between cases and controls using a general linear model. Available sera from cases were tested for MMR seropositivity at baseline and post-vaccination at 6, 12, 18, and 24 months. Overall mean CD4 count change from baseline through 24 months was 20 (\pm 23) cells/ μ L greater for cases than controls ($p=0.39$). Similar non-significant changes in CD4 cell count were seen in the subset of those not on HAART at baseline. VL changes were small and similar between groups (mean differential change -0.04 (± 0.18) log(10) copies/mL; $p=0.84$). Of 21 vaccinated participants with baseline serologic testing, 14 (67%) were reactive to measles, 19 (91%) to mumps, and 20 (95%) to rubella. Three (43%) of 7 participants nonreactive to measles developed measles IgG; for mumps, 1 (50%) of 2 developed mumps IgG; for rubella, 1 (100%) developed rubella IgG. MMR vaccination did not result in detrimental immunologic or virologic changes through 24 months post-vaccination

Yavuz ST, Sahiner UM, Sekerel BE, Tuncer A, Kalayci O, Sackesen C. Anaphylactic reactions to measles-mumps-rubella vaccine in three children with allergies to hen's egg and cow's milk. *Acta Paediatr*. 2011 Jan 18. doi: 10.1111/j.1651-2227.2011.02165.x.

Allergies to hen's egg and cow's milk are the most frequent food allergies in infancy and childhood. Current guidelines recommend safe administration of measles-mumps-rubella (MMR) vaccine in egg allergic patients. We present three cases of anaphylaxis that we encountered after MMR vaccination in children sensitized to hen's egg and cow's milk. Even though MMR vaccine is generally known to be safe in children with egg allergy, there may still be isolated cases of anaphylaxis. Therefore, we recommend that all children not only those who were sensitized to foods should receive the MMR vaccination in a setting that is equipped to deal with anaphylactic reactions. As stated by WHO in immunization safety surveillance, 'Each vaccinator must have an emergency kit with adrenaline, and be familiar with its dosage and administration'.

Evidence that rubella vaccination is safe in pregnancy

Badilla X, Morice A, Avila-Aguero ML, Saenz E, Cerda I, Reef S, Castillo-Solórzano C. Fetal risk associated with rubella vaccination during pregnancy. *Pediatr Infect Dis J.* 2007 Sep;26(9):830-5.

BACKGROUND: Costa Rica implemented a nationwide measles-rubella vaccination campaign among men and women (15-39 years old) in May 2001. A protocol was developed to follow-up the vaccinated women who were unknowingly pregnant, to determine the risk of congenital rubella syndrome (CRS) or congenital rubella infection only associated with the administration of the rubella vaccine RA27/3 during pregnancy.

METHODS: To classify the prevaccination maternal immune status, a serum sample was taken at the initial evaluation to detect IgM and IgG rubella antibodies (enzyme-linked immunosorbent assay). All pregnancies were followed up and all newborns were evaluated. A cord serum sample of their children was taken at birth. We calculated odds ratio, OR (95% confidence interval, 95% CI) associated with miscarriage, stillbirth, prematurity, low birth weight, and the presence of defects compatible with CRS.

RESULTS: The prevaccination immune status was established in 797 women and 1191 mother and child pairs were analyzed. Adjusted OR for miscarriage (OR = 0.60, 95% CI = 0.26-1.39), stillbirth (OR = 1.32, 95% CI = 0.10-16.81), prematurity (OR = 0.25, 95% CI = 0.03-2.39), low birth weight (OR = 0.25, 95% CI = 0.03-2.23) and defects compatible with CRS (OR = 1.09, 95% CI = 0.34-3.54) showed no association between immune and susceptible maternal status. There were no cases of CRS and no children were IgM positive.

CONCLUSIONS: No adverse pregnancy outcome such as miscarriages or CRS was documented in women who were vaccinated and unknowingly pregnant. These results support RA27/3 rubella vaccine safety.

Castillio C et al. Rubella Vaccination of Unknowingly Pregnant Women During Mass Campaigns for Rubella and Congenital Rubella Syndrome Elimination, The Americas 2001 – 2008. *JID supplement*, 2011 (1 July 2011: Not yet published).

da Silva e Sá GR, Camacho LA, Siqueira MM, Stavola MS, Ferreira DA. Seroepidemiological profile of pregnant women after inadvertent rubella vaccination in the state of Rio de Janeiro, Brazil, 2001-2002. *Rev Panam Salud Publica.* 2006 Jun;19(6):371-8.

OBJECTIVES: To analyze postvaccination serological status in pregnant women inadvertently vaccinated against rubella in the state of Rio de Janeiro, Brazil.

METHODS: This was a cross-sectional study of pregnant women 15 to 29 years old, vaccinated against rubella and measles from November 2001 to March 2002, who were unaware of their pregnancy at the time of vaccination or who became pregnant within 30 days thereafter. They were tested for rubella-specific immunoglobulin M (IgM) and G (IgG) and classified as immune (IgM-negative, IgG-positive, tested within 30 days after vaccination), susceptible (IgM-positive after vaccination) or indeterminate (IgM-negative, IgG-positive, vaccination-serological testing interval greater than 30 days).

RESULTS: Of 2 292 women, 288 (12.6%) were susceptible, 316 (13.8%) immune, 1 576 (68.8%) indeterminate, 8 (0.3%) ineligible, and 104 (4.5%) lost to follow-up. IgM

seropositivity by vaccination-serological testing interval was 16.1% (≤ 30 days), 15.4% (30-60 days), and 14.2% (61-90 days). Considering the campaign's target age, the 20-to-24-year age group had the largest proportion of individuals susceptible to rubella (14.8%) and represented 42.4% (122/288) of all susceptible women. In 75% of susceptible pregnant women, gestational age was 5 weeks or less at the time of vaccination.

CONCLUSIONS: Mass immunization of childbearing-age women was justified on the basis of epidemiological and serological data. Follow-up of vaccinated pregnant women revealed no cases of congenital rubella syndrome due to rubella vaccination. However, the observed rate of congenital infection supports the recommendation to avoid vaccinating pregnant women, and to avoid conception for up to 1 month following rubella vaccination.

Hamkar R, Jalilvand S, Abdolbaghi MH, Esteghamati AR, Hagh-Goo A, Jelyani KN, Mohktari-Azad T, Zahraei M, Nategh R. Inadvertent rubella vaccination of pregnant women: evaluation of possible transplacental infection with rubella vaccine. Vaccine. 2006 Apr 24;24(17):3558-63.

During mass campaign for measles/rubella vaccination on December 2003 in Iran, many pregnant women have vaccinated mistakenly. These women were grouped to susceptible and immune against rubella before vaccination by the status of IgG avidity response to rubella vaccine, then susceptible women were followed up to delivery time and their neonates were followed up to one year. In five neonates that were born from susceptible women, rubella-specific IgM has detected in cord blood sera, but they have not shown signs compatible to congenital rubella syndrome.

Minussi L, Mohrdieck R, Bercini M, Ranieri T, Sanseverino MT, Momino W, Callegari-Jacques SM, Schuler-Faccini L. Prospective evaluation of pregnant women vaccinated against rubella in southern Brazil. Reprod Toxicol. 2008 Jan;25(1):120-3.

The rubella virus is a potent human teratogen. The highest risk of this infection occurs during pregnancy, as the virus may cause fetal damage known as congenital rubella syndrome (CRS). Since the rubella vaccine is made with attenuated live virus, there is a high level of anxiety concerning exposure during pregnancy. Although no case of CRS has been proved in children of immunized susceptible pregnant women, a risk below 1.6% cannot be ruled out. Our main purpose was to evaluate the occurrence of CRS in women who were vaccinated against rubella and did not know that they were pregnant, or became pregnant within 30 days after vaccination. We collected, prospectively, data on 171 pregnant women who were susceptible at the time of vaccination and compared them with data on the total population of pregnant women in the state of Rio Grande do Sul (RS), Brazil. A serologic sample was collected in none of 5 children born to mothers who had rubella in early pregnancy. Our study allows the safety of rubella vaccination to be extended to pregnant women.

Nasiri R, Yoseffi J, Khajedaloe M, Sarafraz Yazdi M, Delgoshai F. Congenital rubella syndrome after rubella vaccination in 1-4 weeks periconceptional period. Indian J Pediatr. 2009 Mar;76(3):279-82.

OBJECTIVE: To examine whether exposure to rubella vaccine during 1-4 wk periconceptional period can cause congenital rubella syndrome (CRS).

METHODS: This prospective study was performed in 60 pregnant women who received rubella vaccine inadvertently 1-4 wk pre or post conception. Time of conception was determined by last menstrual period (LMP) and first trimester sonography. In addition to gathering mother's obstetric and demographic information, all neonates were evaluated for CRS signs by systemic physical examination and anti rubella IgG and IgM antibody titers in cord blood samples.

RESULTS: A total of 60 pregnant women with the median gestational age of 38 weeks were studied. The mean maternal age was 22 years and 58.3% of pregnancies were unintended. In 90% of mothers there were no post vaccination side effects (fever, lymphadenopathy, arthritis, arthralgia). None of the mothers had a history of drug abuse, smoking or teratogenic exposures. Mean neonatal weight was 3100grs and 6.7% of them were premature. No signs of CRS were found in the neonates based on systemic physical exam at birth and one month later. Mean value of cord blood anti rubella IgG titer was 148/28+/-67/26 lu/ml. cord blood anti rubella IgM was negative in all of the neonates.

CONCLUSION: In this study inadvertent rubella vaccination 1-4 wk before and after conception did not cause CRS in neonates and according to all researches pregnancy termination is not indicated in these cases.

Plotkin SA, Reef SE. Rubella vaccine. In: Plotkin SA, Orenstein WO, Offit P, eds. Vaccines, 5th ed. Philadelphia, Saunders, 2008:735-771. (No abstract available).

Reyna J, Herbas I, Gómez M, Vidal P, Cruz E, Puente A, Richardson V. Perinatal Outcome of Inadvertent Immunization with the Measles-Rubella Vaccine in Pregnant Mexican Women during the Campaign for the Eradication of Congenital Rubella in 2008. World Journal of Vaccines, 2011, 1, 1-4.

ABSTRACT Objective: To investigate maternal and neonatal complications resulting from inadvertent immunization against rubella-measles during the first trimester of pregnancy. *Methods:* A prospective and descriptive study was carried out, including a total of 1,924 pregnant women, 175 (9.1%) of which were classified as non responding to infection by the rubella virus. They underwent clinical and ultrasonographic follow-up to dismiss maternal or fetal complications and complications at the time of delivery. The infant was checked to determine demographic, anthropometric, serological and clinical features at the time of birth. *Results:* No women had complications during the pregnancy, including exanthematic symptoms. 174/175 newborns were studied; one pregnancy was interrupted based on non-medical arguments. The findings in terms of the analyzed patients suggest a benign evolution after inadvertently immunizing the pregnant women, which support studies with similar results. No complications during the course of the pregnancy or phenotypic alterations of the infant at the time of birth are suggested.