

WHO position paper on rubella vaccines, WER July 2011:

Grading tables for assessment of scientific evidence

Table III: What is the evidence that rubella vaccination¹ is not associated with serious adverse events including the development of congenital rubella syndrome (CRS) in pregnancy? (Table III is presented as IIIa and IIIb).

Table IIIa. What is the evidence that rubella vaccination ¹ is not associated with serious adverse reactions?				
		Rating	Adjustment to score	
Quality Assessment	No of Studies/Starting Score		5 RCTs	4
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Does-response	Not applicable	0
		Mitigated bias and confounding	Not applicable	0
	Final numerical score of quality of evidence			4 (maximum score)
Summary of Findings	Statement on quality of evidence		We are very confident that the true effect lies close to that of the estimate of effect on health outcome	
	Conclusion		Very strong evidence that current rubella vaccines are safe including for pregnant women	

¹Current rubella-containing vaccines (RCVs) are considered comparable in terms of safety, i.e. not being causally linked to serious adverse events.

In addition to the 5 RCTs that include a total of about 3400 vaccinees, numerous observational studies covering millions of vaccinees have been published on issues of safety of RCVs. Some studies focus on one specific type of adverse events, such as high fever or the vaccine’s possible association with autism, others on the whole spectre of potential adverse reactions. All these studies conclude that rubella vaccines are not causing serious adverse events. (Vaccine safety in pregnant women is presented in Table IIb).

Most data on adverse reactions caused by currently available rubella vaccines originate from trials based on the MMR combination. A Cochrane review (*Demicheli V et al 2005*) of 31 controlled trials included 26 observational studies and 5 RCTs (*see reference list*). It was concluded that within the periods of observation of these 31 studies (weeks to years) MMR was unlikely to be causally associated with Crohn's disease and ulcerative colitis. No cases of anaphylaxis were reported. Among the RCTs included in the Cochrane review is the double-blind, placebo-controlled, cross-over study of 581 twin pairs by *Peltola H et al (1986)*. This study showed that the vast majority of adverse reactions following immunization of children with MMR vaccine are only temporally, not causally related to the vaccination.

Since the Cochrane review in 2005, a number of observational safety studies have been published on rubella-containing vaccines: *Khetsuriani N et al (2008)* reviewed adverse events associated with the national immunization campaign in Georgia and 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); 37 (46.8%) cases had symptoms consistent with syncope or anxiety attack (36 of these 37 were initially misdiagnosed as anaphylactic shock/allergies/"postvaccinal reactions"); and 29 (36.7%) cases had coincidental illnesses.

Halperin SA et al (2009) analysed the safety and immunogenicity of a measles-mumps-rubella-varicella vaccine given as a second dose in children up to six years of age. 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. 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. On the other hand, a large study by *Klein NP et al (2010)* showed that immunization with the combined MMRV vaccine resulted in slightly higher risk of febrile seizures compared to MMR and varicella vaccines given separately: The excess risk was 4.3 per 10,000 doses (95% confidence interval: 2.6-5.6).

Extensive reviews of the scientific literature have not provided data in support of a causal relationship between autism and MMR (*DeStefano F et al, 2004; Hensley E et al 2010*). Based on 96 cases of autistic children, *Mrozek-Budzyn D et al (2010)*, found evidence against a potential association between autism and MMR (or single measles) vaccine.

MMR vaccination of 20 seronegative bone-marrow transplanted patients without active graft-versus-host disease or ongoing immunosuppressive treatment was not associated with early or late adverse reactions (*Ljungman P et al 1989*). As compared to non-immunized HIV-positive controls, *Stermole BM et al (2011)* found no detrimental immunologic or virologic changes among 21 HIV- positive adults who were followed through 24 months post MMR-vaccination.

Although the rubella vaccine virus is grown in human diploid cells, vaccine combinations such as MMR may include components that on rare occasions cause anaphylactic reactions in children with cow milk- and egg allergies (*Yavuz ST et al, 2011*).

Table IIIb. What is the evidence that rubella vaccination ¹ in pregnancy is not associated with the development of CRS?				
		Rating	Adjustment to score	
Quality Assessment	No of Studies/Starting Score		7 observational	2
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Mitigated bias and confounding	Not applicable	0
	Final numerical score of quality of evidence			2 (maxium score is 4)
Summary of Findings	Statement on quality of evidence		Our confidence in the estimate of the effect on the health outcome is limited	
	Conclusion		Growing evidence that current rubella vaccines are safe including for pregnant women	

¹Current rubella-containing vaccines (RCVs) are considered comparable in terms of safety, i.e. not being causally linked to serious adverse events.

No cases of CRS have so far been observed among the neonates of more than 1000 susceptible women who were unknowingly rubella vaccinated in early stages of pregnancy. The included 7 studies unanimously testify to the safety of RCVs for pregnant women.

Nevertheless, the theoretical teratogenic risk of rubella vaccination of pregnant women has been calculated at a maximum of 1.3% (*Plotkin S et al 2008*). Because of this theoretical risk, in particular of minor lesions that may be hard to detect, the vaccine should not be used for vaccination of women who are knowingly pregnant.

Reyna J et al (2011) showed that of the 174 newborns delivered by women who were susceptible to rubella and inadvertently vaccinated in early pregnancy, none showed serological or clinical features of CRS at the time of birth. *Nasiri R et al (2009)* investigating a total of 60 women who had been inadvertently rubella vaccinated 1-4 weeks before or after conception, found no signs of CRS in any of the neonates. *Badilla X et al (2007)* analysed the incidences of miscarriage, stillbirth, prematurity, low birth weight, and the presence of defects compatible with CRS in 1191 mother and child pairs, of whom 797 mothers had known prevaccination immune status. No adverse pregnancy outcome was documented among rubella susceptible women who were vaccinated and unknowingly pregnant. In a Brazilian study, none of the babies delivered by 171 mothers who had been unknowingly pregnant at

the time of vaccination, showed any sign of CRS (*Minussi L et al (2008)*). Also, during a mass-vaccination campaign against rubella in Brazil, 288 pregnant women were inadvertently vaccinated; the newborn were all healthy (*da Silva e Sá GR et al, 2006*). In Iran, five IgM-positive neonates born to women who were vaccinated early in pregnancy, showed no signs compatible with congenital rubella syndrome (*Hamkar R et al 2006*). As part of the mass campaigns in 6 countries in Latin America, susceptible women who were unknowingly pregnant when vaccinated were followed throughout their pregnancies. Of 1980 pregnancies resulting in a live birth no cases of CRS occurred (*Castillo C et al 2011, in press*).

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Evidence that rubella vaccination is not associated with serious adverse reactions

Randomized, controlled trials (RCTs)

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