WHO position paper on rubella vaccines, WER July 2011:

Grading tables for assessment of scientific evidence

Table I: What is the evidence that rubella vaccination[1] protects against rubella and congenital rubella syndrome? (Table I is presented as Ia and Ib)

Ia. What is the evidence that rubella vaccination[1] protects against rubella?				
			Rating	Adjustment to score
Quality Assessment	No of Studies/Starting Score		4 RCTs [2]	4
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision[1]	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Very large effect[3]	+2
		Dose-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 rubella vaccination protects against rubella

[1]Current rubella-containing vaccines (RCVs) are considered comparable in terms of protective efficacy.

[2] Of these 4 randomized controlled trials (RCTs), only one evaluates protection against clinical disease, the remaining 3 are based on serological surrogate markers of protection.

[3] Very strong evidence from the RCTs and many observational studies (Table Ib) of a vaccine effectiveness of ≥90%.

The only double blind-RCT on the protective efficacy of RA 27/3 rubella vaccine against clinical rubella included 198 children who were recruited from 4 primary schools in China during a rubella outbreak (*Beasley RP et al, 1969)*. The children were distributed on 11 groups and randomly given different types of RCV. Protection against rubella was achieved in >95% of those who had received rubella vaccine.

The remaining 3 RCTs showed serological evidence of protection against rubella in >90% of the >2000 infants/young children involved in these trials (*Edees S et al, 1991; Lerman SJ, 1981; Schwarz AJ et al, 1975).*

Table Ib. What is the evidence that rubella vaccination[1] protects against rubella and congenital rubella syndrome (CRS)?				
			Rating	Adjustment to score
Quality Assessment	No of Studies/Starting Score		21 observational	2
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious	0
		Indirectness	None serious[2]	0
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Very strong evidence[3]	+2
		Dose-response	Very strong evidence[4]	+2
		Mitigated bias and confounding	Not applicable	0
	Final numerical score of quality of evidence			6 (maximum score is 4)
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 rubella vaccination protects against rubella and congenital rubella syndrome

[1]Current rubella-containing vaccines (RCVs) are considered comparable in terms of protective efficacy.

[2]5 of these 21 observational studies are based on immunogenicity trials. The indirectness of immunogenicity trials is considered outweighed by the more direct evidence provided by studies on clinical efficacy and by population based studies.

[3]All the 21 studies, regardless of design, conclude that rubella vaccines are highly (≥90%) efficacious.

[4] Very strong evidence of risk reduction with increasing vaccine coverage.

No specific type and level of antibodies are invariably correlated with absolute protection. Although rubella IgG antibodies ≥10 IU/mL are considered to provide protection to the majority of people, the serological methods as well as the positive/negative cut-off used in assays vary.

Observational studies (protection against rubella and/or CRS)

The efficacy/effectiveness of rubella vaccines has been determined by observational studies in a**)** outbreak situations (10 studies) and by b) trials using immunogenicity (mainly induction of neutralizing antibodies) as endpoint (5 studies). Also, evidence of high protective efficacy of RCVs derives from c**)** population-based observations of declining rubella and CRS incidences with increasing vaccination coverage (6 studies).

Efficacy of RCVs (studied mainly in outbreak situations)

Grayston JT et al (1969) found 94% vaccine efficacy among 3259 schoolchildren in China;100% vaccine efficacy was obtained by *Chang TW et al (1970)* who vaccinated 32 children of a childcare-centre in USA; 100% vaccine efficacy was observed in a small study of 24 school children in Japan *(Furukawa T et al (1970*; 100% protection was observed among 22 vaccinees recruited from several institutions in USA *(Davis WJ et al. (1971)* whereas *Landigran PJ et al. (1974)* reported 93.5% efficacy following vaccination of 4103 American schoolchildren. *Greaves WL et al (1983)* reported 90% protection following rubella vaccination of more than 600 students during an outbreak in a high-school in USA, and a case-control study that was conducted in order to estimate the effectiveness of rubella vaccine in preventing clinical rubella in a university population in Los Angeles, USA, estimated vaccine effectiveness at 97% (95% CI: 82% -100%) *(Strassburg MA et al 1985).* In France, *de Valk H et al (1998)* reported 95% vaccine efficacy among 119 children during a rubella outbreak in a primary school. Rubella outbreaks among crew members onboard two American cruise ship were interrupted following vaccination *(CDC MMWR 1998).* In Romania, the selective vaccination of adolescent girls implemented in a few cohorts of Bucharest in 1998 and 2002 resulted in significantly lower incidence of rubella among girls than among comparable boys during a large rubella outbreak in 2002-03 *(Rafila A et al 2004).*

b. Immunogenicity trials

A number of comparative studies have documented that the immunogenicity induced by current rubella vaccines, alone or in combinations, are similarly high. Thus, *Crovari P et al (2000)* found equivalent anti-rubella seroconversion rates (100%) when comparing two different measles, mumps and rubella vaccine (MMR) formulations; similar results were obtained when comparing three MMR vaccines *(Tischer A et al 2000). Liebermann JM et al (2006)* showed that a combined measles, mumps, rubella and varicella vaccine (MMRV) induced immune responses (all >95%) similar to MMR administered concomitantly with varicella vaccine. Anti-rubella seroconversion rates are similarly high (>90%) when MMR is given concurrently with, or 6 weeks after pneumococcal conjugate vaccine (PCV7 *(Black SB et al 2006).* Also, when MMRV plus combined *Haemophilus influenzae* type b conjugate and hepatitis B vaccines (Hib/HepB) plus combined diphtheria-tetanus-acellular pertussis vaccines (DTaP) are administered concomitantly, anti-rubella seroconversion rates reached >95% *(Shinefield H et al 2006).*

c. Population-based observations

Following large-scale rubella vaccination campaigns among adults and subsequent introduction of rubella vaccine into the national childhood vaccination programs, Cuba was first to eliminate rubella and CRS *(Castillo-Solórzano C 2003).* Accelerated introduction of rubella vaccination for children and adults in the Americas resulted in 99.3% decline in the

incidence of rubella - from 135,000 reported cases in 1998 to 923 cases in 2003 *(CDC MMRW 2008).* In Mexico alone, following the administration of 77.7 million vaccine doses during the period 1997 – 2004, the number of reported cases of rubella declined from 38,042 to 698 *(Dayan GH et al 2006).*

In Japan, during the period 2000-2004, the number of CRS cases decreased remarkably to 1-3 cases per year (from 0.2-8.1 cases/100,000 live births per year in epidemic years and 0.1-0.7 in non-epidemic years) following changes in rubella immunization policy from vaccinating junior high school girls only to vaccination of infants of both sexes *(Katow S, 2004).*

With increasing coverage of the national rubella vaccination program the incidence of rubella in the US population has decreased gradually from 0.1/100,000 in 1998 to 0.005/100,000 in 2004. Since 2001, 5 infants with CRS have been reported: 3 were born in 2001, 1 was born in 2003, and 1 in 2004. Rubella is no longer considered endemic in the United States (*Reef SE et al 2006; Reef SE, 2011)*.

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Efficacy of rubella vaccines

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Immunogenicity trials

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