

WHO position paper on rubella vaccines, WER July 2011:

Grading tables for assessment of scientific evidence

Table II. What is the evidence of long-lasting duration of protection following a single dose of rubella vaccine?				
		Rating	Adjustment to score	
Quality Assessment	No of Studies/Starting Score		17 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	Very strong evidence ¹	+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 in most cases, a single dose of rubella vaccine results in long-lasting protection	

¹ All the 17 studies conclude that RCVs induce long-lasting protective immunity against rubella in > 80% of subjects. The majority of studies have observation periods of 15 years or more.

No RCTs are available. The current assessment is based on representative observational studies on antibody persistence and/or immunological memory.

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.

Following immunization, antibody concentrations will decline over time, sometimes to very low levels. Immunological memory seems to persist, and in most cases a secondary immune response (anamnestic response) will occur upon new exposure to rubella virus (*Johnson CE et al, 1996*). Excellent B cell memory after RA 27/3 vaccination was recently demonstrated (*Latner DR et al, 2011*)

Hillary IB et al (1984) found that all but one of 11 school children in Ireland had demonstrable rubella antibodies 15 years after rubella vaccination. *O'Shea S et al (1988)* showed that of those receiving RA27/3-based vaccine, 95%-100% were seropositive 10-21 years after immunization; similar results were obtained with other currently used rubella vaccines, and in regions without possible boosting by circulating wild-strain rubella virus (*Chu SY et al. 1988; Best JM, 1991*). Of 195 successfully vaccinated women in Germany, 98% were still seropositive when tested for rubella antibodies 13-17 years later (*Enders G et al 1988*). Similar results following an observation period of 12-17 years were obtained in a study by *Plotkin SE et al (1985)*. Of 486 initially seronegative girls in Sweden only 6% lacked detectable (< 1:8) HI- antibodies when tested 8 -16 years after rubella immunization (*Christenson B et al 1994*). In Newfoundland, 86.2% of children had antibodies ≥ 10 iu/ml 4-16 years after a single dose of MMR vaccine containing the RA27/3 rubella strain (*Ratnam S et al. 1997*). In the Republic of Korea, 81% of children had rubella antibodies ≥ 10 iu/ml three years after rubella vaccination with Takahashi or Matsuura strains (*Ki et al. 2002*).

Studies carried out in the USA before rubella was eliminated showed a significant decline in rubella antibody concentrations in children 15 years after a single dose of rubella-containing vaccine (*King JC et al. 1993*). *Orenstein WA et al. (1986)* detected very low concentrations (<7iu/ml) in 8.7% children given HPV77.DE5 10-14 years earlier. However, immune memory may persist even in cases where circulating rubella-specific antibodies may have dropped to low levels. Thus, in a study by *Johnson CE et al. (1996)* 33% of children had rubella antibodies <6iu/ml by EIA, and 37% had no neutralizing antibodies 10-12 years after the first dose of MMR, although at 3-5 years post-vaccination, 90% had EIA antibodies and 100% had NT antibodies. However, all developed rubella antibodies after a second dose of MMR. (In the latter study and in that by *King et al. (1993)*, it is probable that some children had received the less efficacious HPV77.DE5 rubella vaccine and not RA27/3, which replaced HPV77.DE5 in 1979). *Asahi T et al. (1997)* found that 25 of 26 institutionalized children immunized with the Japanese Matsuba-strain vaccine 23 years earlier showed persistence of immunity. A few had HI <8, but upon revaccination, all those developed an anamnestic response.

In most countries rubella vaccines are now given as MR or MMR. Also following two doses of these fixed combinations the long-term persistence of rubella antibodies has been demonstrated: *Davidikin I et al 2008* (20 yrs: 93% ≥ 7 IU/mL); *Vandermeulen C et al 2007* (8 yrs: 99% ≥ 10 IU/mL); and *Kakoulidou M et al 2010* (22 yrs: 91% ≥ 10 IU/mL).

References

Antibody persistence and/or evidence of an immunological memory

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