WHO position paper on rubella vaccines, WER July 2020:

Grading tables for assessment of scientific evidence[1]

1 Immunogenicity of RCV[2]

Table 1. Seroconversion after RCV1 in children > 9 months of age

Policy question: What is the evidence on the immunogenicity of a single dose of RCV (RA27/3 strain) in children aged >9 months?				
			Rating	Adjustment of score
Quality assessment	No of studies/Starting score		25 RCTs 1 observational study	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	Applicable	+1
		Dose-response	Not applicable	0
		Mitigated bias and confounding	Not applicable	0
	Final numerical score of quality of evidence			4
Summary of findings	Statement on quality of evidence			Evidence supports a high level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome
	Conclusion			There is strong evidence that a single dose of RCV is highly immunogenic in children > 9 months of age.[1] Seroconversion after RCV1 (RA 27/3 strain) was 99% (95% CI: 98%-99%).

[1] The children included in these RCTs were between 9 and 18 months when they received RCV1.

[1] Two systematic reviews leading to these GRADE tables were conducted to reflect the evidence-base until 2011 and from 2011- 2019. The GRADE tables in this document may reflect our confidence in the quality of evidence stemming from these two systematic reviews and encompass evidence from the specific time spans.

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

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Table 2. Seroconversion after RCV1 in children < 9 months of age

Policy question: What is the evidence on the immunogenicity of a single dose of RCV in children less than 9 months of age?				
			Rating	Adjustment of score
Quality assessment	No of studies/Starting score		2 RCTs/ 1 observational	4
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious	0
		Indirectness	Serious[1]	-1
		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			3
Summary of findings	Statement on quality of evidence			Evidence supports a moderate level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome
	Conclusion			There is little evidence of moderate quality on the immunogenicity of a single dose of RCV-BRDII strain in children < 9 months of age, but there is no evidence on the RA27/3 strain. Seroconversion after RCV1 (BRDII strain) in children of 8 months of age was 93% (95% CI: 92-95%).

[1] Only two studies available, both for the BRDII strain, and only one with a comparison arm of administration at 12 months of age.

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Table 3: Seroconversion after RCV1 (RA 27/3 strain) in adolescent girls

Policy question: What is the evidence on the immunogenicity of a single dose of RCV in adolescent girls?				
			Rating	Adjustment of score
Quality assessment	No of studies/Starting score		3 observational studies	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	Applicable	+1
		Dose-response	Not applicable	0
		Mitigated bias and confounding	Not applicable	0
	Final numerical score of quality of evidence			3
Summary of findings	Statement on quality of evidence			Evidence supports a moderate level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome.
	Conclusion			We are moderately confident that the immunogenicity of a single dose of RCV is very high in adolescent girls. Seroconversion after RCV1 (RA 27/3 strain) was 100% (100%-100%) in adolescent girls.

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Table 4: Seropositivity after RCV2 (RA 27/3) in children

Policy question: What is the evidence on the immunogenicity of a second dose of RCV in children?				
			Rating	Adjustment of score
Quality assessment	No of studies/Starting score		9 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	Applicable	+1
		Dose-response	Not applicable	0
		Mitigated bias and confounding	Not applicable	0
	Final numerical score of quality of evidence			4
Summary of findings	Statement on quality of evidence			Evidence supports a high level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome.
	Conclusion			There is strong evidence that RCV2 administration in children is highly immunogenic. Seropositivity after RCV2 (RA 27/3 strain) was 100% (99%-100%).

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1 Duration of protection

Table 5. Duration of protection after one or two doses of RCV (2019 Systematic Review of evidence)

Policy question: What is the evidence for the duration of protection (in terms of seropositivity and GMT) following at least one dose of RCV compared to no vaccination or control?				
			Rating	Adjustment of score
Quality assessment	No of studies/Starting score		5 RCTs, 8 observational studies	4
	Factors decreasing confidence	Limitation in study design	Serious[1]	-1
		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			3
Summary of findings	Statement on quality of evidence			Evidence supports a moderate level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome
	Conclusion			There is low quality evidence that long-term (1-20 years after RCV1 and RCV2) seropositivity is high. Seropositivity up to 20 years after one or two RCV doses ranged from 88%-100% in most studies.

[1] The observational studies generally had no (serological) prove that the participants actually had received a dose of RCV in the past; natural boosting between vaccination and sampling was possible in countries where rubella is still prevalent; the exact period of time between vaccination and sampling was not described in all studies.

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Table 6. Duration of protection after one dose of RCV (2011 Systematic Review of evidence)

Policy question: What is the evidence for the duration of protection (in terms of seropositivity and GMT) following a single dose of RCV compared to no vaccination or control?				
			Rating	Adjustment of score
Quality assessment	No of studies/Starting score		17 observational[3]	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[4]	Applicable	+2
		Dose-response	Not applicable	0
		Mitigated bias and confounding	Not applicable	0
	Final numerical score of quality of evidence			4
Summary of findings	Statement on quality of evidence			Evidence supports a high level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome
	Conclusion			Very strong evidence that in the majority of cases, a single dose of rubella vaccine results in long-lasting protection.

[3] 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.

[4] 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.

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2 Effectiveness of RCV

Table 7. Effectiveness (2019 Systematic Review of evidence)

Policy question: What is the evidence that rubella vaccination (RA 27/3) protects against rubella and rubella congenital syndrome; i.e. what is its effectiveness compared to no vaccination or control?				
			Rating	Adjustment of score
Quality assessment	No of studies/Starting score		4 observational studies	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[1]	0
		Dose-response	Not applicable	0
		Mitigated bias and confounding	Not applicable	0
	Final numerical score of quality of evidence			2
Summary of findings	Statement on quality of evidence			Evidence supports a limited level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome
	Conclusion			Our confidence in the evidence of the high effectiveness of RCV is low. Vaccine effectiveness of RA 27/3 strain was 97% (95% CI: 92-99%)

[1]High vaccine effectiveness, though few and generally old studies on VE of RA 27/3. Hence, studies included here are from <2010. Search for publications before 2010 was not systematic. Therefore no upgrading of evidence. Lack of laboratory confirmation

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Table 8. Efficacy/Effectiveness (2011 Systematic Review of evidence)

<table>
<tr><td colspan="5">Policy question: What is the evidence that rubella vaccination protects against rubella and rubella congenital syndrome; i.e. what is its efficacy/ effectiveness compared to no vaccination or control?</td></tr>
<tr><td colspan="3"></td><td>Rating</td><td>Adjustment of score</td></tr>
<tr><td rowspan="10">Quality assessment</td><td colspan="2">No of studies/Starting score</td><td>4 RCTs/ 17 observational studies</td><td>4</td></tr>
<tr><td rowspan="5">Factors decreasing confidence</td><td>Limitation in study design</td><td>None serious</td><td>0</td></tr>
<tr><td>Inconsistency</td><td>None serious</td><td>0</td></tr>
<tr><td>Indirectness</td><td>None serious</td><td>0</td></tr>
<tr><td>Imprecision</td><td>None serious</td><td>0</td></tr>
<tr><td>Publication bias</td><td>None serious</td><td>0</td></tr>
<tr><td rowspan="3">Factors increasing confidence</td><td>Large effect</td><td>Applicable[5]</td><td>+2</td></tr>
<tr><td>Dose-response</td><td>Applicable</td><td>+2</td></tr>
<tr><td>Mitigated bias and confounding</td><td>Not applicable</td><td>0</td></tr>
<tr><td colspan="3">Final numerical score of quality of evidence</td><td>4</td></tr>
<tr><td rowspan="2">Summary of findings</td><td colspan="3">Statement on quality of evidence</td><td>Evidence supports a high level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome.</td></tr>
<tr><td colspan="3">Conclusion</td><td>Our confidence in the evidence of the level of protection (efficacy/ effectiveness) conferred by RCV against rubella and CRS is high.</td></tr>
</table>

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[5] Very strong evidence from the RCTs and many observational studies of a very high vaccine effectiveness. All the 16 observational studies, regardless of design, conclude that rubella vaccines are highly (≥90%) efficacious.

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3 Safety of RCV

Table 9. Safety (2019 Systematic Review of evidence)

Policy question: What is the evidence on the occurrence of severe adverse events of one or two doses RCV vs no vaccination or control?				
			Rating	Adjustment of score
Quality assessment	No of studies/Starting score		40 RCTs, 6 epidemiological studies, 9 passive surveillance studies, 16 case reports	4
	Factors decreasing confidence	Limitation in study design	Serious[1]	-1
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	No	0
		Dose-response	Not applicable	0
		Mitigated bias and confounding	Not applicable	0
	Final numerical score of quality of evidence			3
Summary of findings	Statement on quality of evidence			Evidence supports a moderate level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome
	Conclusion			We have moderate confidence in the evidence that RCV is safe.

[1] General short follow-up period, some studies reported solicited SAEs only, likelihood of a true association with RCV was not always assessed.

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Table 10. Safety (2011 Systematic Review of evidence)

Policy question: What is the evidence that rubella vaccination[6] is not associated with serious adverse reactions in healthy individuals excluding pregnant women vs no vaccination or control?				
			Rating	Adjustment of score
Quality assessment	No of studies/Starting score		5 RCTs/ 8 observational	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	No	0
		Dose-response	Not applicable	0
		Mitigated bias and confounding	Not applicable	0
	Final numerical score of quality of evidence			4
Summary of findings	Statement on quality of evidence			Evidence supports a high level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome
	Conclusion			We have high confidence in the evidence that RCV is safe in healthy individuals excluding pregnant women.

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

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Table 11. Safety of RCV in pregnancy (2019 Systematic Review of evidence)

<table>
<tr><td colspan="5">Policy question: What is the evidence on the risk of serious adverse events (including CRS) when RCV is administered in pregnancy?</td></tr>
<tr><td colspan="3"></td><td>Rating</td><td>Adjustment of score</td></tr>
<tr><td rowspan="10">Quality assessment</td><td colspan="2">No of studies/Starting score</td><td>2 follow-up studies (observational), 1 passive surveillance study</td><td>2</td></tr>
<tr><td rowspan="4">Factors decreasing confidence</td><td>Limitation in study design</td><td>None serious</td><td>0</td></tr>
<tr><td>Inconsistency</td><td>None serious</td><td>0</td></tr>
<tr><td>Indirectness</td><td>None serious</td><td>0</td></tr>
<tr><td>Imprecision</td><td>None serious</td><td>0</td></tr>
<tr><td rowspan="3">Factors increasing confidence</td><td>Publication bias</td><td>None serious</td><td>0</td></tr>
<tr><td>Large effect</td><td>Not applicable</td><td>0</td></tr>
<tr><td>Dose-response</td><td>Not applicable</td><td>0</td></tr>
<tr><td>Mitigated bias and confounding</td><td>Not applicable</td><td>0</td></tr>
<tr><td colspan="3">Final numerical score of quality of evidence</td><td>2</td></tr>
<tr><td rowspan="2">Summary of findings</td><td colspan="3">Statement on quality of evidence</td><td>Evidence supports a limited level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome</td></tr>
<tr><td colspan="3">Conclusion</td><td>We have low confidence in the evidence that RCV administered in pregnancy does not lead to CRS or other SAE.</td></tr>
</table>

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Table 12. Safety of RCV in pregnancy (2011 Systematic Review of evidence)

Policy question: What is the evidence that rubella vaccination[7] in pregnancy is not associated with the development of CRS?				
			Rating	Adjustment of score
Quality assessment	No of studies/Starting score		7 observational studies	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**
Summary of findings	Statement on quality of evidence			Evidence supports a limited level of confidence that the true effect lies close to that of the estimate of the effect on the health outcome.
	Conclusion			We have low confidence in the evidence that RCV administered in pregnancy does not lead to CRS or other SAE.

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

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