National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

Systematic literature review and meta-analyses of the immunogenicity, duration of protection, effectiveness/efficacy and safety of rubella vaccination

15th September 2019

Jossy van den Boogaard, Brechje de Gier, Priscila de Oliveira Bressane Lima, Hester de Melker, Susan Hahné, Irene Veldhuijzen

Centre for Infectious Disease Control (CIb)
National Institute for Public Health and the Environment (RIVM)
Bilthoven, the Netherland

Contents

Summary

Background

This report summarises the results of a systematic review of the literature and meta-analyses of the immunogenicity, duration of protection, effectiveness/efficacy and safety of rubella-containing vaccine (RCV) in order to update the WHO rubella vaccine position paper.

Methods

We performed a systematic literature review for studies published since 2010 in which one or more doses of RCV were given at any age. We extracted data on the following outcomes: immunogenicity, duration of protection, vaccine efficacy or effectiveness and safety. Where appropriate, meta-analyses were performed. Quality of all included studies was assessed using the GRADE methodology.

Results of the search and selection

We included 36 papers (32 randomized controlled trials (RCTs) and 4 observational studies) for analysis of the immunogenicity of one or two doses of RCV (RA27/3 strain) in children and adolescent girls, and 14 papers (5 RCTs and 9 observational studies) to assess the duration of protection of RCV. One paper on vaccine effectiveness (VE) (BRDII strain) was included, and 74 studies on safety, including three on safety in pregnancy.

Results of the review of included studies

Seroconversion after a single dose of RCV (RA 27/3 strain) was 99% (95% CI: 98%-99%) in children (GRADE evidence rating, high) and 100% (100%-100%) in adolescent girls (GRADE evidence rating, moderate), independent of co-administration with other vaccines. Seropositivity after a second dose of RCV (RA 27/3 strain) was 100% (99%-100%) (GRADE evidence rating, high). For duration of protection, the studies showed a seropositivity of 88%-100% measured 1-20 years after one or two RCV doses (GRADE evidence rating, moderate). We did not find any additional studies on vaccine efficacy of RCV published since 2010. The single new study on VE of RCV reported 100% VE after one and two doses (BRDII strain) (GRADE evidence rating, low). Among 34,332 individuals participating in the RCTs, after exclusion of severe adverse events (SAE) not associated with RCV according to the authors, 140 SAE were reported as possibly related to RCV. Among the case reports on SAEs, the association with RCV was confirmed in one report, where a previously healthy man died of encephalitis. At post-mortem examination, rubella virus (vaccine strain) was detected in brain tissue. For outcomes on safety in general the GRADE evidence rating was moderate. No cases of CRS or

other SAEs were reported in studies following almost 3,000 women who were inadvertently vaccinated against rubella during pregnancy (GRADE evidence rating, low).

Conclusions

Our literature review confirms the evidence that is presented in the current WHO rubella vaccine position paper, dating from 2011. Single and two doses of RCV are highly immunogenic for a long period of time, they are effective in preventing rubella and CRS, and they are safe to be administered to immunocompetent individuals.

Abbreviations

CI	Confidence interval
CRI	Congenital Rubella Infection
CRS	Congenital Rubella Syndrome
EIA	Enzyme-linked Immunosorbent Assays
GMC	Geometric mean concentration
GMT	Geometric mean titer
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HI	Hemagglutination inhibition
HAI	Hemagglutination inhibition assay
IgG	Immunoglobulin G
LJEV	Life-attenuated Japanese Encephalitis Vaccine
MCV	Measles Containing Vaccine
MeSH	Medical Subject Headings
MR	Measles-Rubella (vaccine)
MMR	Measles-Mumps-Rubella (vaccine)
MMRV	Measles-Mumps-Rubella-Varicella (vaccine)
PAHO	Pan American Health Organization
PFU	Plaque forming unit
PRNT	Plaque reduction neutralization test
PubMed	Public MEDLINE
RCT	Randomized controlled trial
RCV	Rubella containing vaccine
RCV1	First dose of Rubella Containing Vaccine
RCV2	Second dose of Rubella Containing Vaccine
RIVM	National Institute for Public Health and the Environment (the Netherlands)
VE	Vaccine effectiveness
WHO	World Health Organization

1 Introduction

Rubella infection generally manifests as a mild viral infection with fever, malaise, lymphadenopathy and a typical rash, in the pre-vaccination era occurring mainly in children. The disease is of public health relevance due to its teratogenic potential: if rubella infection occurs around conception or in early pregnancy, there is a high risk of miscarriage, fetal death or congenital defects including ophthalmic, auditory, cardiac and craniofacial problems (congenital rubella syndrome; CRS). Rubella containing vaccines (RCV) have proven highly immunogenic with seroconversion rates of >95% and have an effectiveness of 90-100% in outbreak situations (1).

Most countries around the world (170 of 194 World Health Organization (WHO) member states; 88% as of 2017) have introduced a RCV in their routine immunization programme. This has led to a large reduction in rubella and CRS incidence worldwide. The WHO region of the Americas has eliminated CRS and rubella in 2015. Two other WHO regions (European and Western Pacific Region) are near to elimination, with current RCV coverages of >95% (1, 2).

In most national immunization programmes, rubella vaccine is provided together with measles vaccine (MR), measles and mumps vaccine (MMR), or measles, mumps and varicella vaccines (MMRV). In 2016, 95% of countries having a RCV in their immunisation programme, used a combination vaccine with measles (3). The age of administration usually follows the scheme of the measles vaccine: a first dose given at 9 or 12-15 months and a second dose at 15-18 months or 4-6 years. In measles outbreak situations or in case of individuals with high risk of measles, the first dose of measles containing vaccine (MCV) , often combined with rubella vaccine, may be given as early as 6 months of age (4). Recent evaluations show that administration of MCV at young age (<9 months) lowers the induction of a protective immune response to measles vaccine (5). Early administration of RCV might also impact the immune response to rubella vaccine.

The current WHO vaccine position paper on rubella summarizes the evidence on the immunogenicity, efficacy, effectiveness, duration of protection and safety of RCV, up to 2011 (1). The purpose of this systematic review is to update the evidence in these areas for the rubella vaccine position paper.

2 Aims and objectives

The aim of this project was to perform a systematic literature review of the available evidence published since the previous review, on the immunogenicity, duration of protection, efficacy,

effectiveness, and safety of RCV, in order to update the WHO position paper on rubella vaccine (1). Additional research questions included the safety of RCV vaccination during pregnancy and the effect of RCV administration at young age (< 9 months).

The objectives were:

- To perform a systematic search and screening of the literature to identify relevant papers published since 2010 (to cover for any papers that were published after the previous literature review that was conducted in 2010);
- To critically appraise the quality of the evidence with respect to the appropriateness of the methodology and analyses performed, according to international standards for the conduct and reporting of systematic reviews (GRADE);
- To perform quantitative and qualitative syntheses of the available evidence;
- To present the syntheses of the available evidence in such a way that the WHO vaccine position paper on rubella can be updated.

3 Methods

3.1 Review Questions

The overall question to be answered with this systematic review is: What new evidence has been published since 2010 that would have implications for rubella vaccination policies to be included in the WHO Rubella Vaccine Position Paper?

3.1.1 Primary questions

1 What is the evidence on the immunogenicity of a single (and two) dose(s) of RCV?
2 What is the evidence that RCV protects against rubella and congenital rubella syndrome (CRS); i.e. what is its efficacy and effectiveness?
3 What is the evidence for the duration of protection following a single dose and two doses of RCV?
4 Is there any new evidence on the occurrence of severe adverse events of RCV?
5 Is the effect of RCV1 -in terms of immunogenicity, efficacy or effectiveness and duration of protection- given to children younger than 9 months of age equal to or less than the effect of RCV1 administered at 9-24 months of age?
6 What is the evidence on the risk of adverse events (including CRS) when RCV is administered in pregnancy?

3.1.2 PICO's

The PICO (Population, Intervention, Comparison (where applicable), Outcome, and study designs) components that informed the review objectives, are presented in Tables 1-3.

Table 1. Structured framework underlying primary questions 1-4

Population	Intervention	Outcome	Study designs
Persons ≥ 9 months of age	Administration of a dose of any currently licensed RCV	1. Immunogenicity 2. Efficacy and effectiveness 3. Duration of protection 4. Safety	- RCTs - Observational studies including cohort and case-control studies, follow-up studies - Case series and case reports (for safety only)

Table 2. Structured framework underlying primary question 5

Population	Intervention	Comparison	Outcome	Study designs
Infants up to 24 months of age receiving a first dose of RCV	Administration of a single dose of any currently licensed RCV before the age of 9 months	Administration of a single dose of any currently licensed RCV at the age of 9-24 months	1. Immunogenicity 2. Efficacy and effectiveness 3. Duration of protection 4. Safety	- RCTs - Observational studies including outbreak investigations, cohort and case-control studies - Case studies and case reports (for safety only)

Table 3. Structured framework underlying primary question 6

Population	Intervention	Comparison	Outcome	Study designs
Pregnant women	Administration of a dose of any currently licensed RCV to pregnant women	Not applicable Or: No administration of a dose of RCV to pregnant women (for study designs including a control group)	1. Safety	- Observational studies including cohort and case-control studies - Case series and case reports (of newborns with CRS and of women who received RCV inadvertently during pregnancy)

3.1.3 Primary outcome measures

a) Immunogenicity

Humoral immunity

Serological rubella antibody responses in terms of seroconversion rates (SCRs), seropositivity, geometric mean antibody titres (GMTs) and avidity, measured by:

- Enzyme-linked immunosorbent assays (EIA)
- Haemagglutination-inhibition assays (HAI)
- Neutralization Tests (NT)
- Immunoblot/immunofluorescence assays
- Avidity tests

Seroconversion was defined by a fourfold rise in IgG titres in diagnostic samples to detect recent infection, and by a change from seronegative to seropositive (defined by cut-off values as described by the authors) in samples pre- and post-vaccination, taking into account an interval of at least 6-8 weeks between vaccination and the post-vaccination sampling.

Seropositivity was defined by cut-off values as described by the authors. We did not limit inclusion to studies that used the generally accepted threshold for protection of 10 IU/mL as the cut-off for seropositivity in EIA tests. Many studies reported results based on commercial EIA's with a cut-off value of 4 IU/mL. As evidence suggests that equivocal results obtained in EIA's (i.e. 4-10 IU/mL) can be interpreted as positives, we have included studies using a cut-off values of ≥ 4 IU/mL (6).

The principal indicator for immunogenicity that was used in this review, is seroconversion.

b) Efficacy

Vaccine efficacy against (laboratory confirmed or epidemiologically linked) rubella cases and congenital rubella syndrome as assessed from RCTs.

c) Effectiveness

Vaccine effectiveness against (laboratory confirmed or epidemiologically linked) rubella cases and congenital rubella syndrome as assessed from post-implementation field studies and outbreak reports.

d) Duration of protection

Trends in antibody levels over time since rubella vaccination, expressed both in terms of seropositivity and GMTs.

e) Safety

Severe adverse events (SAEs) as defined by the authors, including febrile convulsions, thrombocytopenic purpura and arthritis, with a focus (for this review) on rarely reported/

uncommon SAEs. For safety in pregnancy: the occurrence of CRS and any other SAE as described by the authors.

3.2 Search strategy

The search was carried out on the 17th May 2019 for any articles published in relevant databases reporting on RCV.

3.2.1 Searching literature databases

In collaboration with RIVM librarian (Rob van Spronsen), a primary search for articles that met the eligibility criteria was retrieved from the primary database for biomedicine and health sciences Embase.com (Appendix A). The database was searched using controlled vocabulary (i.e MeSH terms) with a pre-determined strategy as detailed in Appendix B. Papers in English, Dutch, German, French, Spanish and Portuguese, published from 1st January 2010 until the 17th of May 2019 (when the search was done), were included. The search results were transferred to an EndNote library. Duplicate records were removed using the EndNote "Find duplicates" function, followed by a manual check.

3.2.2 Additional reference searches

To maximize the search sensitivity, the literature searches were checked to ensure that they contained relevant papers cited in Plotkin's Vaccine (Chapter 53. Rubella Vaccines. 2018) (7).

Furthermore, a number of experts (members of the WHO Measles and Rubella working group as well as a CDC Rubella Subject Matter Expert) were consulted by email to identify additional literature or research that had not been found through the above processes.

3.3 Literature selection

Eligibility criteria were defined and references were first screened by three reviewers (JB, IV and POBL)) using a two-stage approach by reviewing the title and abstract (step 1) and the full text (step 2) as outlined below.

3.3.1 Eligibility criteria

The eligibility criteria outlined below were applied to the results of the literature search.

3.3.1.1 Types of studies

Randomized controlled trials (RCTs), outbreak investigations, cohort and case-control studies, follow-up studies, seroprevalence studies, passive surveillance studies, case series and case reports (the latter three for safety related questions) were considered for inclusion.

3.3.1.2 Types of participants

For primary questions 1-4, participants had to be individuals ≥ 9 months of age. For question 5, participants were either infants < 9 months of age who received a first dose of RCV, or infants between 9 and 24 months of age (as a comparison). For question 6, the participants were pregnant women (or a control group of non-pregnant women of reproductive age).

3.3.1.3 Types of intervention

Administration of any currently, internationally licensed RCV of strain RA 27/3, BRDII, Takahashi, Matsuura or TO-336, containing at least 1,000 Plaque Forming Units (PFU) per dose, either in monovalent variant or as a combination vaccine (measles and rubella (MR), measles, mumps and rubella (MMR), measles, mumps, rubella and varicella (MMRV) was considered relevant for this review. For immunogenicity, we focussed on studies using the RA27/3 rubella strain. We distinguished studies/study-arms where RCV was co-administered with any other vaccine.

3.3.1.4 Minimum data requirements

For inclusion in the review, the articles had to be published after the 1st of January 2010 (to cover for any publications in 2010 that had not been published at the time of review for the 2011 position paper) and report a minimum set of data as shown in Table 4.

Table 4. Minimal data requirements within articles for inclusion in review

Data requirements for all studies	
Study population	Age at vaccination
Data requirements for immunogenicity studies only	
Vaccine strain used	Vaccine strain used in RCV (and manufacturer)
Immunogenicity results	Type of laboratory test used
Time since vaccination	In months or weeks
Data requirements for safety studies only	
Safety	Severe adverse events case definition

Data requirements for studies on administration <9 months of age	
Age at vaccination	Exact age (months)
Immunogenicity results	Type of laboratory test used
Data requirements for studies on administration during pregnancy	
Study population	Pregnant or not
Safety	Severe adverse events case definition

3.3.2 Exclusion criteria

Ecological studies, non-human primate studies, meeting abstracts, editorials, newspaper articles and other forms of popular media were excluded. Studies in specific patient groups such as immunocompromised patients and patients with known hypersensitivity reactions to vaccine-components were excluded as well. For safety, epidemiological/observational studies that focussed on one or a few pre-defined and already known SAEs only, were excluded. Studies that investigated mild adverse events and reactogenicity of RCV only, were excluded as well.

Failure to meet any one of the eligibility criteria (section 3.3.1) also resulted in exclusion from the review. Data regarding the reasons for exclusion were recorded at each stage. The final decision for inclusion or exclusion was made by the researchers conducting the review.

The reasons for excluding studies (including reasons for exclusion following review of the full text) were recorded at each stage.

3.3.3 First selection step: title and abstract

The title and abstract of each article were reviewed to see if they met criteria for inclusion. To ensure inter-reviewer consistency, a random selection of ten percent of the retrieved articles was reviewed by all three reviewers. The level of agreement between reviewers was measured by the Fleiss Kappa statistic. Based on an arbitrary interpretation by Landis and Koch who characterized kappa values < 0 as indicating no agreement and 0–0.20 as slight, 0.21–0.40 as fair, 0.41–0.60 as moderate, 0.61–0.80 as substantial, and 0.81–1 as almost perfect agreement, value of at least 0.60 was considered to indicate adequate agreement (8). After the first round the kappa value was 0.58. Therefore, after discussion and consensus on the initial disagreements, another ten percent of the articles were screened by the three reviewers. The Fleiss Kappa statistic of round two was 0.71 and the remaining articles were divided for screening among the reviewers.

3.3.4 Second selection step: full article

As a next step, the three reviewers screened a random selection of ten percent of records selected for full text screening in parallel. The disagreements were discussed and a second round of screening by the three reviewers was done. By then, consistency reached nearly 100% and the remaining articles were divided among them for full text screening.

3.4 Data extraction and risk of bias assessment

The papers included after full text screening were categorized for analysis by research question. Data regarding the characteristics of included studies, such as participants, interventions (including comparators) and outcomes from relevant papers, was registered on a data extraction form, in order to facilitate extracting data from primary studies and subsequent data analysis. Different study-arms within the same study were always extracted separately. For the papers included for safety analyses, we based our assessment of the likelihood of an association between the reported SAE and RCV on the conclusions of the authors, RCV associated SAE and SAE for which the relation with RCV was not assessed by the authors were included, SAE that were not associated with RCV according to the authors were excluded. Only for the case reports we assessed the likelihood of causality ourselves as well. For this assessment, we took into account the time since vaccination at onset of symptoms (considering the incubation period of rubella), the presence of microbiological/serological evidence of rubella virus involvement, and the absence of other possible explanations for the occurrence of the SAE.

Risk of bias across studies was assessed using the approach outlined by the GRADE working group (9).

3.5 Data analyses

For immunogenicity and vaccine efficacy/effectiveness, random effects meta-analyses were performed in Stata SE 15 to generate pooled estimates of the proportion seroconverting after RCV1, the proportion seropositive after RCV2 (using metaprop command with Freeman-Tukey transformation) and the vaccine effectiveness of RCV1 (using metan command with efficacy option). For vaccine effectiveness we pooled results of studies included in the previous literature review (published <2011) and an additional study found through snowballing, because this had not been done before and no new studies on the vaccine effectiveness of the RA 27/3 strain were found.

Forest plots were stratified to explore the effect of type of RCV, age at administration and co-administration with other vaccines on seroconversion rates. Heterogeneity between studies was explored using the I^2-statistic.

For duration of protection, data from relevant studies were summarized in a descriptive way and where appropriate, GMT ratios were calculated to describe the average decline in GMT over time.

For safety, RCTs were screened for data on solicited and passive reporting of any SAE (including febrile convulsions, arthritis and thrombocytopenic purpura). Epidemiological/observational studies and passive surveillance studies that did not focus on a particular, pre-defined adverse event but covered any SAE, were summarized for the occurrence of rare or uncommonly reported SAEs. From case reports the likelihood of a true association between RCV and the SAE reported was assessed.

For safety of RCV administration during pregnancy, results from relevant studies were summarized, taking into account whether rubella-susceptibility of (accidently) immunized pregnant women was appraised.

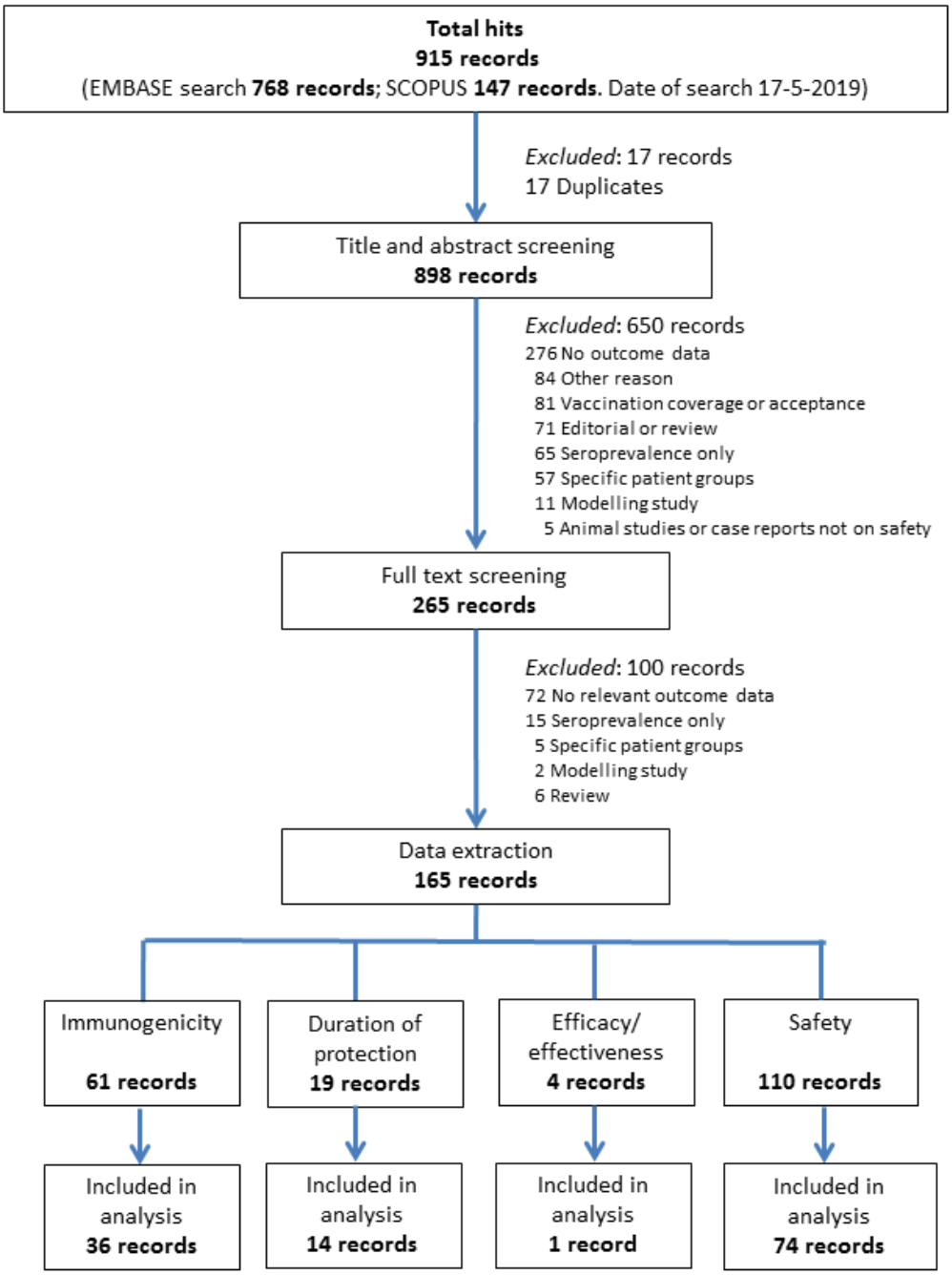
A classification of the evidence was made according to GRADE criteria and synthesised into GRADE tables.

4 Results of the literature search

The literature search carried out on 17 May 2019 yielded a total of 915 references (Figure 1). A total of 98 studies were included in the review.

4.1 PRISMA flow chart

Figure 1: Flow chart of the literature search with excluded and included articles, and number of studies according to outcome measure*



*Data were extracted from some studies for multiple outcomes

5 Results by outcomes

5.1 Immunogenicity

5.1.1 Seroconversion after RCV1

Our meta-analysis, based on 55 observations from 26 studies (10-35), showed that 99% (95% confidence interval (CI): 98-99%) of children aged between 9 and 18 months seroconvert after administration of RCV1 containing the RA 27/3 rubella strain (Figure 2). Heterogeneity between types of RCV was statistically significant, but the lowest point estimate (which was for MR vaccine; 96% seroconversion) was based on only one study. As shown in Figure 3, co-administration with other vaccines did not affect seroconversion after RCV1 in children.

Based on three observational studies, seroconversion of adolescent girls after RCV1 administration containing RA 27/3 strain is 100% (Figure 4) (36-38). No studies were found presenting seroconversion after RCV1 in adults.

5.1.2 Seropositivity after RCV2

After a second dose of RCV (RCV2), 100% seropositivity was achieved in children (95% CI: 99-100%, see Figure 5). This estimate was based on 19 observations from 9 studies with children aged between 12 months and 6 years at administration of RCV2 (21, 26, 33, 34, 39-43).

5.1.3 Seroconversion after RCV1 administered <9 months of age

Only two studies were found in which RCV1 was administered before the age of 9 months (44, 45). Both studies were conducted in China and administered BRDII vaccine strain at the age of 8 months. Li et al. (44) presented seroconversion after MR administration at the age of 8 months with and without co-administration of Japanese Encephalitis vaccine (LJEV) in China. Of 507 infants, 477 (94%) seroconverted for rubella when MR was co-administered with LJEV, and of 506 infants receiving only MR, 471 seroconverted (93%) seroconverted. He et al. (45) compared immunogenicity of MMR when administered at 8 or 12 months of age. Of 8 month-old infants, 127/139 (91%) seroconverted, compared to 128/139 (92%) of 12 month-olds. After administration of a second RCV dose 10 months post-RCV1, both groups showed 100% seropositivity. Based on these two studies, seroconversion after RCV1 (BRDII strain) in children of 8 months of age is 93% (95% CI: 92-95%) (Figure 6).

Figure 2. Random effects meta-analysis of percentage seroconverted after RCV1 containing RA 27/3 strain in children, by type of RCV

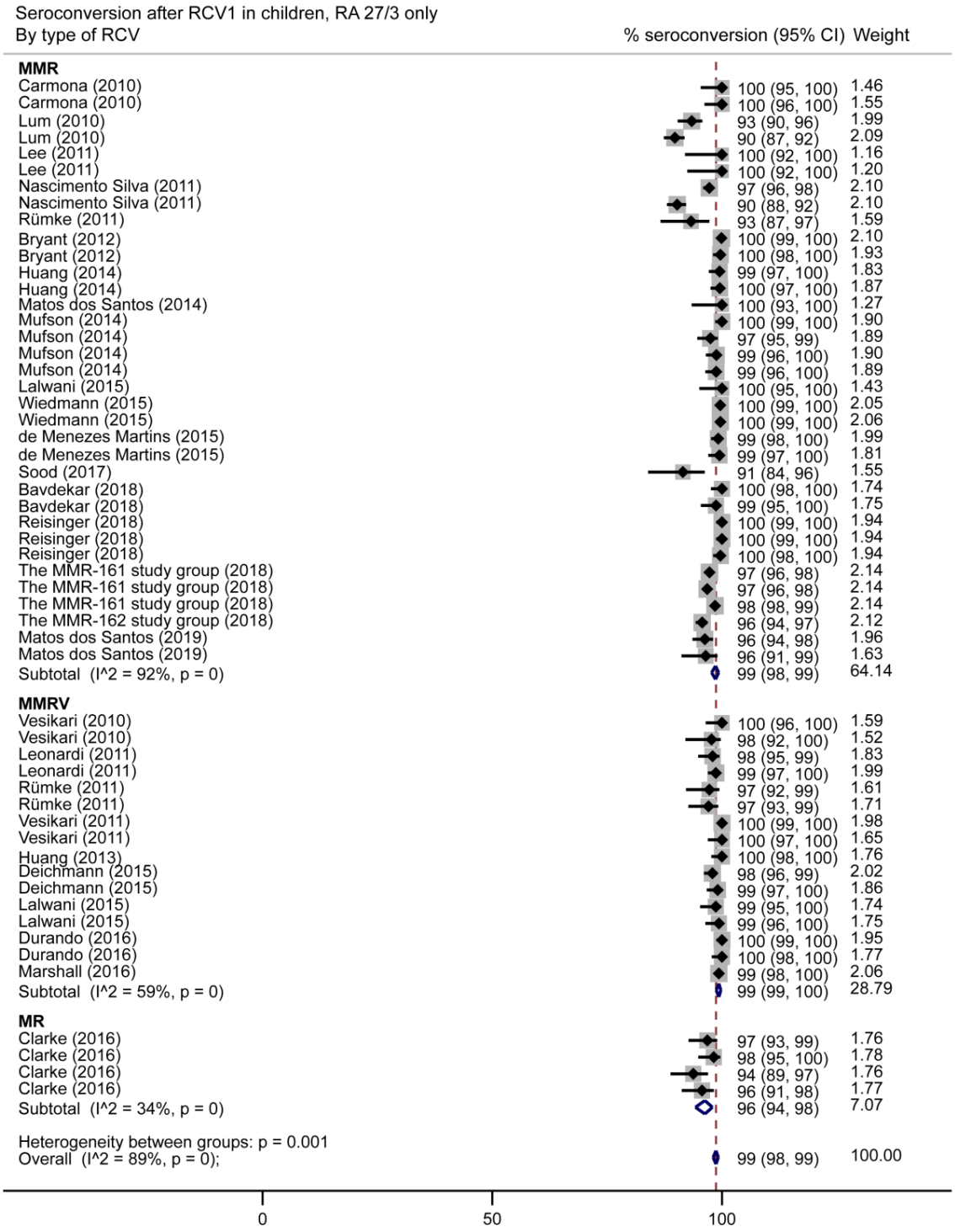


Figure 3. Random effects meta-analysis of percentage seroconverted after RCV1 containing RA 27/3 strain in children, by co-administration with another vaccine (yes/no)

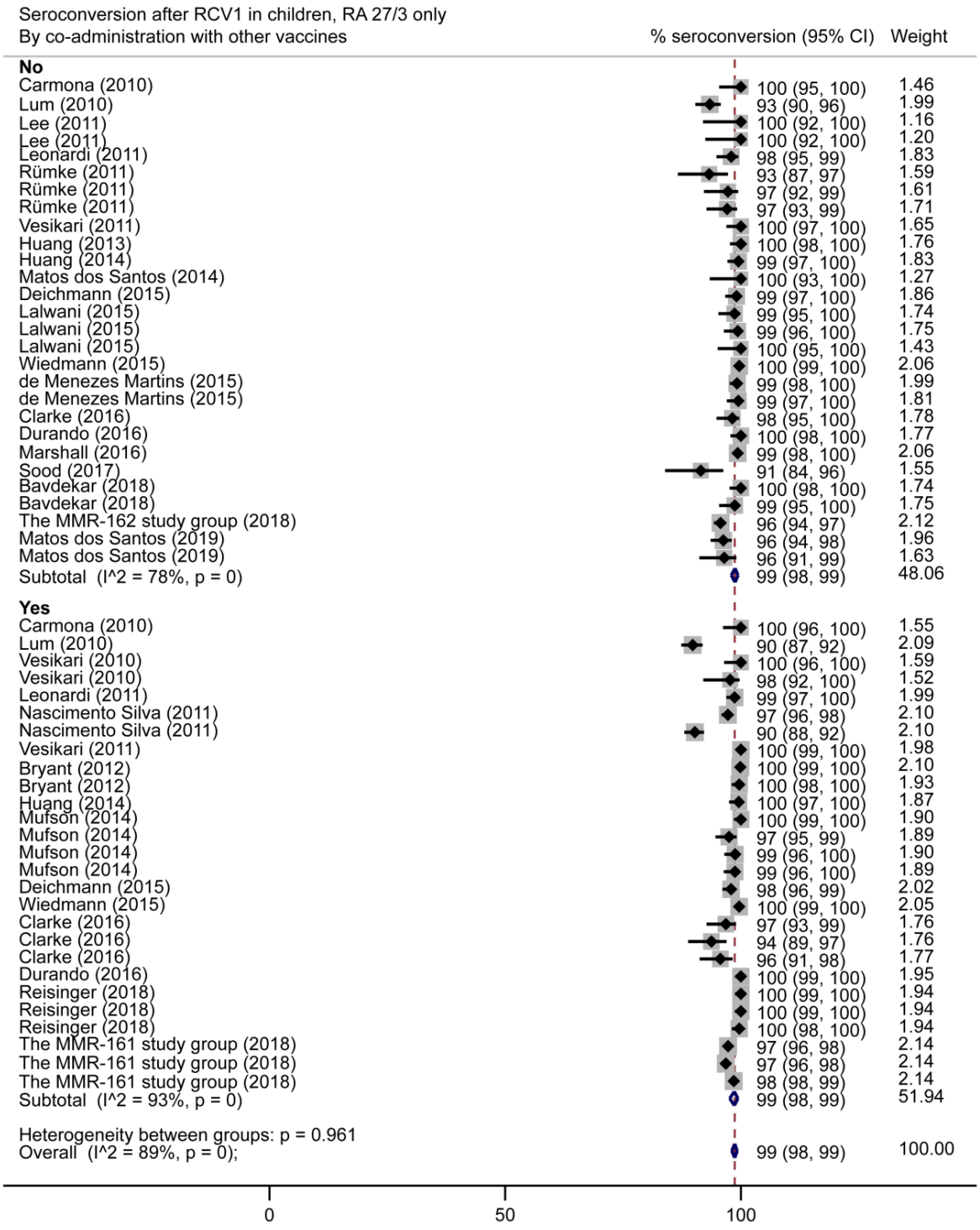


Figure 4. Random effects meta-analysis of percentage seroconverted after RCV1 containing RA 27/3 strain in adolescent girls

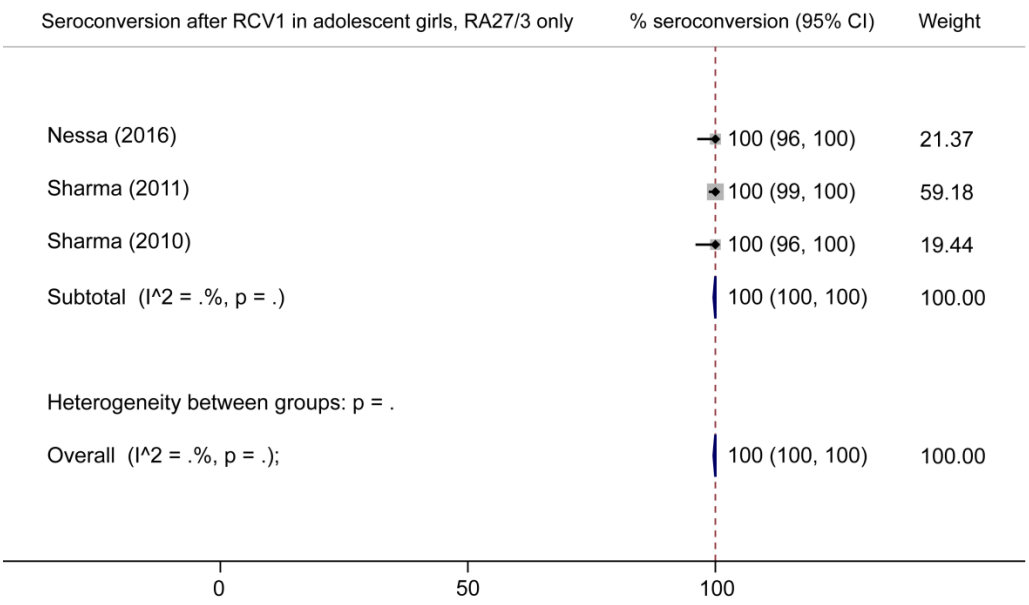


Figure 5. Random effects meta-analysis of percentage seropositive after RCV2 containing RA 27/3 strain in children

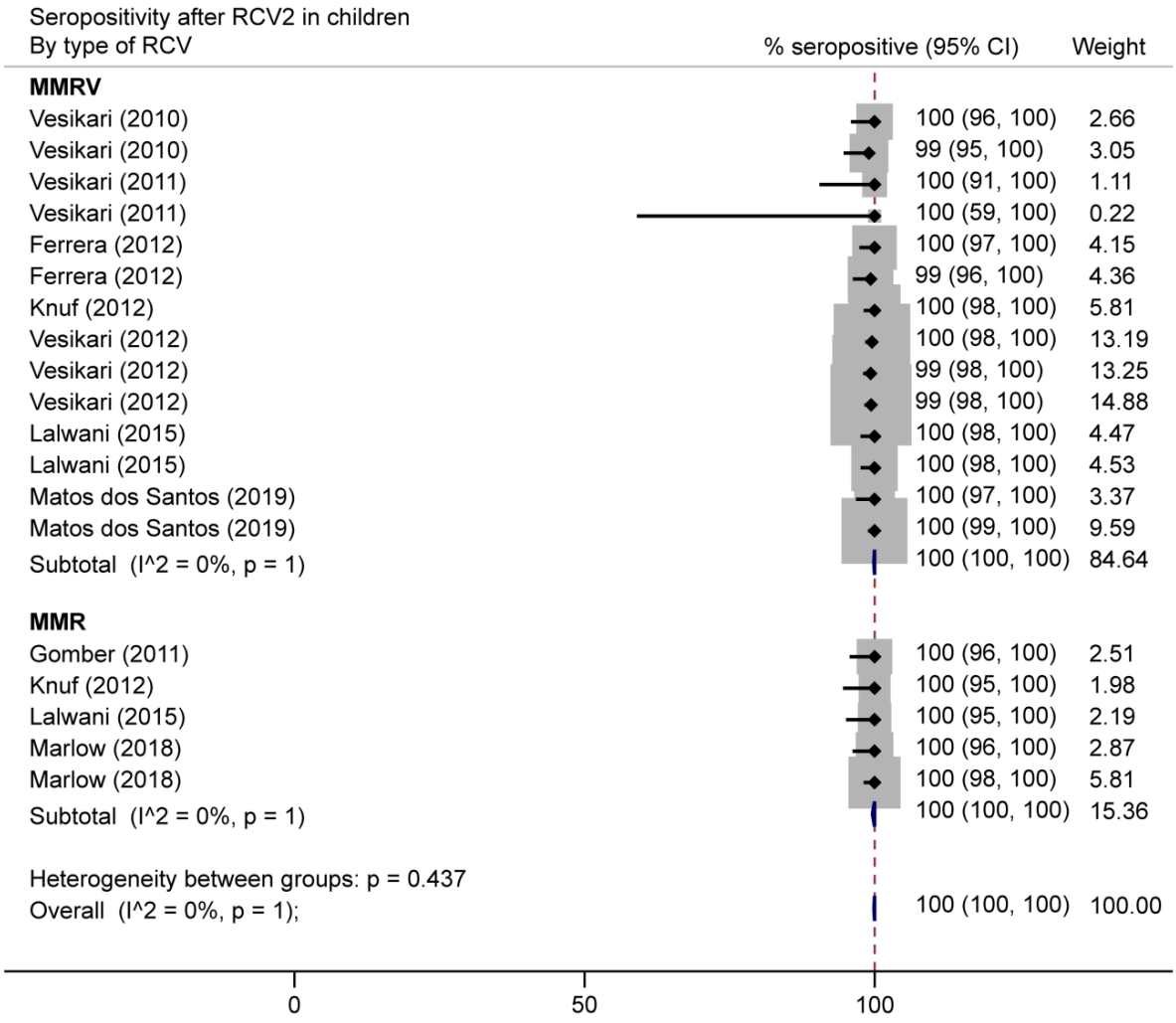
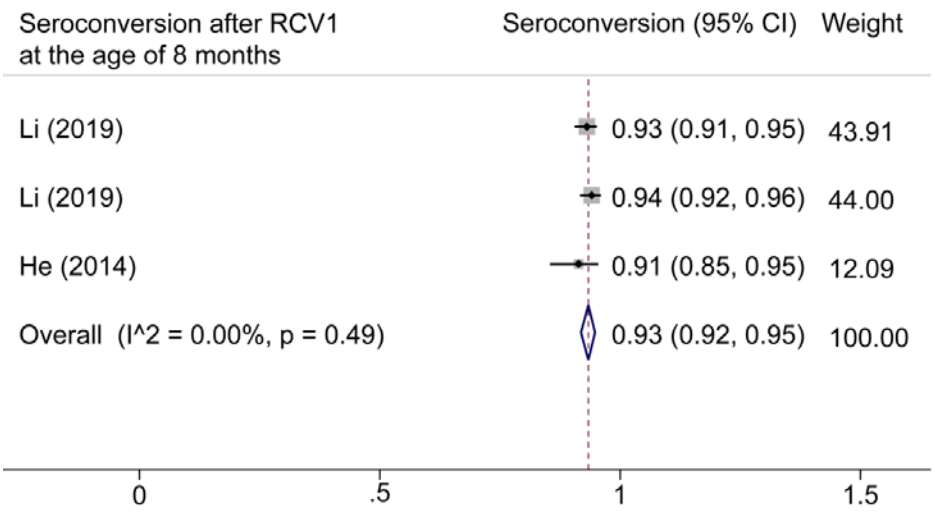


Figure 6. Random effects meta-analysis of percentage seroconverted after RCV1 administration at 8 months of age



5.1.4 Duration of protection

Seven studies (one RCT (20) and six observational studies (40, 46-50)) described seropositivity between 1 and 20 years after a single dose of RCV. Six studies described seropositivity 1-20 years after two RCV doses (three RCTs (51-53) and three observational studies (54-56)). In the observational studies (mainly seroprevalence studies), confirmation of vaccine administration was usually obtained from vaccination cards, and pre-vaccination sampling (to exclude children who were already seropositive due to natural exposure) was generally not available in these studies. A summary of these studies is presented in Table 5. From three RCTs, the decline in GMTs in the first 1-3 years after RCV2 could be calculated (41, 51, 52).

5.1.4.1 Duration of protection after a single dose of RCV

One year after a single dose of RCV administered between 12 and 60 months of age, seropositivity was between 99.5% and 100% in studies by Huang et al (2014) and Okafuji et al (2016), the latter using Takahashi rubella strain and showing 100% seropositivity up to 10 years post-RCV1 (20, 46). 100% seropositivity was also observed two years after RCV1 administered at 11-16 months of age, in a Finnish study (49). In longer term, Shoho et al (2018) found seropositivity rates between 98% and 100% 3-20 years after RCV1 administered at respectively 1 or 12-13 years of age (48). Paulke – Korinek et al (2011) observed 54% seropositivity 4.2 years after RCV1 administered at 1.8 years of age, using haemagglutination tests (47). However, the authors concluded that their cut-off value (1:32) might have been too strict and when they changed to a cut-off value of 1:16, over 90% of children reached seropositivity. In the seroprevalence study by Gomber et al (2011), seropositivity of 76% was found almost 3.5 years after RCV1 (MMR1) administered between 15 and 18 months of age (40). In this study, that was designed to assess the seroprotection after a single dose and study the immune response to a second dose of MMR, seropositivity against measles was as low as 20.4% (mumps 87.4%) after MMR1, raising questions about the potency of vaccine used. Proof of having received MMR1 was obtained from vaccination cards. The seropositivity increased to 72.6% for measles and 100% for rubella and mumps after MMR2 among the 84 children included in the study. Linder et al (2011) observed 91.6% seropositivity in children 3-4 years after MMR1 at the age of 1 year (50).

5.1.4.2 Duration of protection after 2 doses of RCV

The two RCTs by Díaz-Ortega et al. (2010 and 2017) comparing RCV administration by injection or aerosol, showed 100% seropositivity 1 year post RCV2 administered at age 6-7 years or 18-25 years, both for injection and aerosol (51, 52). In an observational study from Portugal, seropositivity 10 years after a second dose of RCV administered at 10-11 years of age was 88%, and 6 and 13 years

after RCV2 administered at 6 years of age 88% and 90% respectively (in two different study populations) (54). In a 12-year follow-up period after RCV2 administered at 4-6 years of age, 3.7% of individuals seroconverted to negative (after at least one previous positive sample post vaccination) (56). In the study by McLean et al (2018), 98.2% of individuals were seropositive after a median of 15.6 years post MMR2 (53). The study with the longest follow-up period after two doses of RCV by Kontio et al (2012), including Finnish children who received MMR1 at age 14-18 months and MMR2 at 6 years of age. They reported that 100% of children had detectable antibodies after 20 years, but 24% had antibody concentrations below 10 IU/ml (measured by ELISA). The authors also analysed the mean avidity index over time and this did not change over the 20-year period (55). There is a lack of knowledge on the relation between the evolution of the avidity index over time and the risk of (re)infection. Although high antibody avidity might indicate better protection against disease, the influence of time since vaccination on this relation is unclear (55, 57).

5.1.4.3 Duration of protection: GMT decline

From the two RCTs by Díaz-Ortega et al (2010 and 2017) the mean decline in GMT could be calculated in the first year after RCV2 administered at 6-7 years or 18-25 years of age: GMT ratios of 0.61 and 0.81 respectively in the study arms where RCV2 was administered by injection (51, 52). The average decline in GMT was 0.79 per year in the first three years after RCV2 in a RCT where MMRV administration was compared to administration of MMR+V (first dose at 12-18 months, second dose at 42-56 months) (41). Finally, Kontio et al. (2012) reported a GMT decline of 65% over a 20-year period post RCV2 (whereas the avidity index remained unchanged) (55).

Table 5. Summary of studies included in evaluation of duration of protection (seropositivity) of one or two doses of RCV

Study	Study design	Country	Number of RCV doses relevant for duration of protection [@]	Age at vaccination	Post-vaccination sample taken (to confirm sero-conversion shortly after vaccination)?	Time between vaccination and follow-up sample	Test and cut-off value used for seropositivity	Proportion seropositive (n/N)*
Huang (2014) (20)	RCT	Taiwan	1	13 months	Yes	1 year	ELISA; ≥10 IU/mL	99.5% (90/91), 100% (174/174) and 100% (203/203) in different study-arms (with and without JECV)
Okafuji (2016) (46)	Seroprevalence study	Japan	1[$]	1-5 years	No	1-10 years	HAI; 1:8	100% (276/276)
Kontio (2016) (49)	Seroprevalence study	Finland	1	Group 1: 11-13 months Group 2: 14-16 months Group 3: 17-19 months	No	2 years	ELISA; ≥7 IU/mL	Group 1: 100% (85/85) Group 2: 100% (32/32) Group 3: 100% (70/70)
Shoho (2018) (48)	Seroprevalence study	Japan	1 or 2[&]	Group 1: RCV1 at 1 year Group 2: RCV1 at 12-13 years Group 3: RCV1 at 1 year and RCV2 at 12-13 years	No	At age 15-22 years	HAI; 1:8	Group 1: 98% (82/84) Group 2: 100% (36/36) Group 3: 99% (715/719)
Paulke-Korinek (2011) (47)	Seroprevalence study	Austria	1 or 2	Group 1: RCV1 at 1.8 years Group 2: RCV1 at 1.4 years and RCV2 at 2.1 years	No	Resp. 4.2 years and 3.7 years	HAI; 1:32	Group 1: 53.7% (29/54) at HAI cut-off 1:32 Group 2: 63.8% (185/290) at HAI cut-off 1:32 At HAI cut-off of 1:16 90% of

								both groups reached seroprotection
Gomber (2011) (40)	Intervention study (immunogenicity of MMR2) with seroprevalence after MMR1	India	1	15-18 months	No	3.4 years	ELISA; ≥15 IU/mL	75.7% (78/103)
Linder (2011) (50)	Seroprevalence study	Israel	1[&]	1 year	No	3-4 years	ELISA; ≥15 IU/mL	91.6% (186/203)
Díaz-Ortega (2010) (52)	RCT	Mexico	2	18-25 years	Yes	1 year	ELISA; ≥10 IU/mL	100% (95/95) of individuals in aerosol study-arm; 100% (96/96 and 92/92) of individuals in two injection study-arms
Díaz-Ortega (2017) (51)	RCT	Mexico	2	6-7 years	Yes	1 year	ELISA; ≥10 IU/mL	100% (123/123) of individuals in injection study-arm; 100% (118/118) of individuals in aerosol study-arm
Gonçalves (2016) (54)	Seroprevalence study	Portugal	2	Group 1: 6 years Group 2: 10-11 years	No	5.8 years (group 1a), 12.9 years (group 1b), 9.6 years (group 2)	ELISA; sero-negativity defined as <8 IU/ml	Group 1a: 87.8% (36/41) Group 1b: 90% (53/59) Group 2: 87.9% (58/66)
Seagle (2018) (56)	Seroprevalence follow-up study	USA	2[&]	4-6 years	Yes	12 years	Plaque reduction neutralization test; titers of ≥10	96.3% (291/302)
McLean	RCT	USA	2[&]	4-6 years	Yes	15.6 years	Plaque reduction	98.2% (667/679)

(2018) (53)			(3rd dose given in this study)				neutralization test; titers of ≥10 U/mL	
Kontio (2012) (55)	Seroprevalence follow-up study	Finland	2	6 years	No	6 months to 20 years	ELISA; Cut-off not mentioned ("measurable antibodies")	100% (71/71 and 48/48)

* Seropositivity as defined by the authors

@ RA 27/3 strain used unless specified otherwise: & rubella strain unknown; $ Takahashi strain

5.2 Vaccine efficacy and effectiveness

5.2.1 Vaccine efficacy

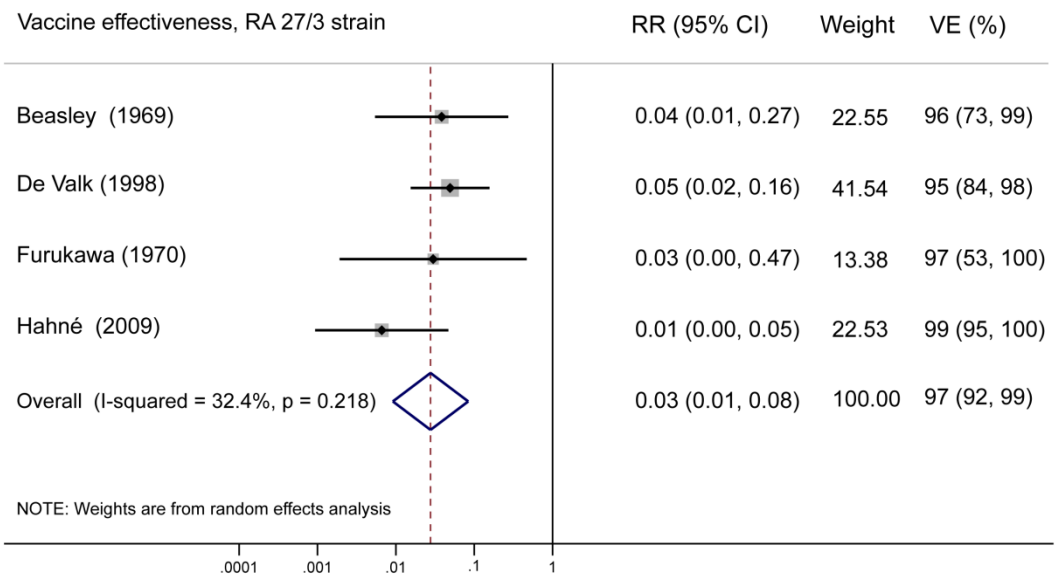
No studies assessing vaccine efficacy of RCV were identified.

5.2.2 Vaccine effectiveness

Our search retrieved only one eligible study published since 2010 to estimate the vaccine effectiveness (VE) of RCV1. This study by Xu et al (2013) found a VE of 100% after one or two RCV doses containing the BRDII rubella strain (58).

No recent studies on the VE of RA 27/3 strain were found. VE studies of RA 27/3 strain from before 2010 were identified via the 2011 WHO rubella position paper and snowballing, which yielded four studies eligible for meta-analysis (59-62). The pooled VE estimate for RA 27/3 strain (one or two doses) against rubella was 97% (95% CI: 92-99%, see Figure 7).

Figure 7. Random effects meta-analysis of vaccine effectiveness of RCV containing RA 27/3 from studies before 2010



5.3 Safety

We analysed a variety of papers that studied safety of RCV: 40 RCTs (10-26, 28-31, 33-35, 39, 42, 43, 63-75), 6 observational studies (76-81), 9 passive surveillance studies (82-90) and 16 case reports (91-106), reporting on severe adverse events (SAEs) after one or two doses of RCV; in some studies co-administered with other vaccines. In one passive surveillance study, follow-up was done on reports of unintentional administration of RCV in pregnancy (89). Two follow-up studies were also included for safety analysis of RCV in pregnancy (107, 108).

5.3.1 Severe Adverse Events

In total, 34,332 persons participated in the 40 RCTs included for safety analysis of RCV; 33,421 children and 911 adults. After exclusion of severe adverse events (SAE) not associated with RCV according to the authors, among the 911 adults, no SAEs were reported (63); among the 33,421 children, 140 SAEs were reported, including 25 febrile convulsions (0.07% of children), 4 cases of idiopathic thrombocytopenic purpura (0.01%), 1 juvenile idiopathic arthritis, 1 hospitalisation for pyrexia, 1 atypical Kawasaki disease, 1 encephalitis of viral origin, 1 inguinal adenitis, 1 autism, 1 grade 3 parotid/salivary gland swelling, 1 anorexia, 1 ataxia, 2 papular/vesicular rashes including 1 bacterial superinfection, 1 peritonsillar abscess, 1 perineal abscess and 1 pneumonia (10, 11, 18-20, 24, 25, 28, 31, 64, 65, 67, 69, 70, 73, 75). The remaining 97 SAEs were not specified (24, 65), although Lum et al. (2010) provided a summary of the most frequently reported SAEs among the 62 unspecified SAEs in their study: “gastroenteritis, convulsions, bronchospasms, pneumonia, pharyngitis and fever” (24). For most of the 140 SAEs insufficient information was available to assess the likelihood of a true association with RCV. No deaths or life-long disabilities that could possibly be related to RCV according to the authors, were reported in any of these studies. The follow-up period generally ranged from a few days post vaccination to a maximum of six months.

Among the six observational studies included for the safety analysis after one, two or three doses of RCV, there was 1 case-control study on postpartum administration of RCV (78) and five follow-up studies (76, 77, 79-81). No SAEs were observed among 13,017 children and 163 adults included in these studies where participants (or their parents) were invited to report any adverse events (partly solicited, partly unsolicited) during a follow-up period lasting from 15 minutes to four weeks post vaccination. The case-control study by Finale et al (2017) did not show an increased risk of arthralgia in 163 women who were vaccinated with RCV compared to 163 women not vaccinated (78).

Eight passive surveillance studies did not reveal any uncommon, unknown SAEs after RCV administered to children < 9 months of age (90), children > 9 months of age (82, 84-88) or adults (89).

The study of Cunha et al. (2013) reported one "other serious and/or unusual event" after RCV, but this event was not further specified and its likelihood of association with RCV not investigated (83).

Finally, we examined 16 case reports of SAEs that could be related to RCV according to the authors (91-106). The association with the rubella component of the vaccine administered (usually MMR) was assessed as unlikely by our study team in four case studies (Table 6) (92, 94, 103, 106). From the remaining nine case reports, the association with RCV was assessed as possible (no other explanation found that could explain the symptoms and symptoms occurring within the incubation period of rubella) (91, 95, 97-100, 102, 104, 105). In three case-reports additional evidence supporting a probable association of the reported SAE with RCV (93, 96, 101). Okazaki et al. (2011) described a case of vaccine-induced thrombocytopenic purpura in a 15-months old girl 12 days after vaccination with MMRV in Japan. Platelet-binding antibodies against both measles and rubella (measles>rubella) were detected (101). Ferrini et al (2013) reported on a case of unilateral anterior uveitis and cataract in a 12-months old girl three months after MMR1 vaccination in Switzerland (93). She received MMR2 four days after the onset of symptoms. The investigators detected intraocular rubella antibodies , in higher concentrations in the affected than in the unaffected eye. Gualberto et al. (2013) describe a 31-year old, previously healthy, Brazilian man who developed fulminant encephalitis 10 days after MR vaccination. At post-mortem examination, vaccine-strain rubella virus was found in large concentrations in his brain as well as in the cerebrovascular fluid (by PCR and culture) (96).

Table 6. Severe adverse events reported in 16 case reports and the likelihood of association with RCV

Case-report	Reported SAE	Likelihood of association as assessed by reviewers	Remarks
Yu, 2018 **(106)**	Eosinophilic cellulitis	Unlikely	Onset of symptoms 10 days after tetanus, diphtheria, pertussis, polio, hepatitis A/B and MMR vaccination. Allergy testing showed triggering of this skin reaction by neomycin and aluminium hydroxide present in respectively 3 and 2 of the administered vaccines.
Sanz, 2012	Chronic inflammatory	Unlikely	Onset of symptoms four months after rubella vaccination and one month

(103)	demyelinating polyradiculo-neuropathy and systemic lupus erythematosus		after autoimmune thyroiditis, in a 28-year old woman; no hypothesis on association with RCV mentioned by authors.
Cheng, 2012 **(92)**	Recurrent 6th nerve palsy	Unlikely	First episode of temporary 6th nerve palsy after MMR vaccination, 2nd episode after varicella vaccination; hence not likely to be specifically related to the rubella component of the vaccine.
Gál, 2016 **(94)**	Pneumococcal pneumonia	Unlikely	Onset of symptoms 24 hours after MMR vaccination in a 58-year old woman. According to authors possibly due to immunosuppressive effects of measles virus
Naciri Bennan, 2011 **(100)**	Pityriasis rubra pilaris	Possibly	Onset of symptoms two weeks after MMR vaccination in a 17-month old child
Gunatheesan, 2012 **(97)**	Pityriasis lichenoides et varioliformis acuta	Possibly	Onset of symptoms 10 days after MMR1 in a 8-year old girl
Gils-Bistes, 2012 **(95)**	Chronic pityriasis lichenoids	Possibly	Onset of symptoms 10 days after MMR2 in a 5-year old boy
Kuniyoshi, 2017 **(98)**	Acute bilateral photoreceptor degeneration	Possibly	Onset of symptoms 31 days after Hib and pneumococcal vaccination and 24days after MMR vaccination in a 13-months old boy
Verna, 2017 **(105)**	Pancreatic pseudocyst	Possibly	Onset of symptoms shortly after (“ever since”) MMR vaccination, in a 15-months old boy
Binamer, 2015 **(91)**	Acute hemorrhagic edema of infancy	Possibly	Onset of symptoms two weeks after MMR, in a two-year old boy
Owatanapanich, 2014 **(102)**	Thrombocytopenic purpura	Possibly	10-months old boy who had received MMR vaccination 8 days prior to hospital admission
Manzotti, 2010 **(99)**	3rd nerve palsy	Possibly	Onset of symptoms 20 days after MMR vaccination in a 20-month old boy
Shuper, 2010 **(104)**	Encephalitis	Possibly	Two cases: 13-months old girl who developed high fever 1 day after MMRV and seizures 6 days later; a 2-year old boy who developed symptoms 5 days after MMR vaccination after which he

			developed neurological symptoms (historical case)
Ferrini, 2013 **(93)**	Unilateral anterior uveitis and cataract	Probably	Onset of symptoms in a 12-months old girl, 3 months after MMR1; rubella antibodies detected intraocular
Okazaki, 2011 **(101)**	Vaccine-induces thrombocytopenic purpura	Probably	Onset of symptoms 12 days after sequential administration of MR, varicella and mumps vaccination with intervals of 4 weeks. Platelet-binding anti-rubella and anti-measles antibodies detected
Gualberto, 2013 **(96)**	Fulminant encephalitis	Definitely	Onset of symptoms 10 days after MR vaccination in a 31-year old previously healthy man. Vaccine strain rubella found in his brain at post mortem examination by PCR and culture.

5.3.2 Safety of RCV administered in pregnancy

Castillo-Solórzano et al (2011) provide an overview of outcomes of pregnancies of 2,894 rubella-susceptible women who were accidentally vaccinated against rubella during one of the rubella mass vaccination campaigns between 2001 and 2008 in the Americas (Costa Rica, Brazil, El Salvador, Ecuador, Paraguay, Argentina): no CRS cases were observed (except for one, but this case was shown to be due to wild-type rubella virus) (107). Among 1,980 children of these women who were followed-up, 70 cases (3.5%) of congenital rubella infection (CRI) were detected, but none of them developed congenital rubella-like symptoms. In a much smaller study by Ergenoğlu et al (2012), 62 Turkish women were followed after accidental rubella vaccination during pregnancy (first trimester): no CRS cases were observed. However, rubella susceptibility before vaccination was probably limited in these women, since all women were IgG positive with high avidity after vaccination (108). The passive surveillance report by Sukumaran et al (2015), using the Vaccine Adverse Event Reporting System (VAERS) of the USA, presented 131 cases of RCV administration in pregnancy between January and July 2013, that were followed-up. One child was born with multiple congenital anomalies not typical for CRS (anorectal anomalies and hydrocephalus), one other child developed meningitis at three weeks of age (89).

6 GRADE quality of evidence found

The evidence on immunogenicity of RCV1 and RCV2 in infants and children was mainly from RCTs. Therefore, our confidence in the evidence for seroconversion after RCV1 and seropositivity after RCV2 in children for RA 27/3 strain is high. The consistency and strength of the effect lend additional confidence to the pooled estimates. The evidence on seroconversion in adolescent girls as well as on the duration of protection was mainly from observational studies and hence, of lower quality. Our confidence in the evidence on vaccine effectiveness is limited as it comes from observational studies which lacked laboratory confirmation. The outcomes on safety were considered of moderate quality since they were based on both RCTs and observational studies and the assessment (by the authors) of the likelihood of causality of a reported SAE with RCV was unclear in most studies. Detailed results of GRADE risk of bias and quality of evidence assessments can be found in Appendix C.

7 Discussion

With this systematic literature review and meta-analyses, we analysed the evidence available since 2010 on the immunogenicity, duration of protection, vaccine effectiveness and safety of one and two doses of RCV, in order to update the WHO rubella vaccine position paper. Seroconversion of a single dose of RCV (RA27/3 strain) was 99% in children and 100% in adolescent girls in our meta-analysis of the available evidence; seropositivity following two doses of RCV (RA 27/3 strain) was 100% in children. To our knowledge, no meta-analysis has been done before on immunogenicity data of RCV. The seroconversion in our meta-analysis after a single dose of RCV is comparable to the seroconversion rates reported in the current WHO rubella position paper (95-100%) (1). Moreover, our results confirm that the type of RCV (RA 27/3 strain) and/or co-administration of RCV with other vaccines does not affect seroconversion. The high seroconversion of a single RCV dose indicates a second dose is not needed. However, since RCV is generally administered in a combination with (at least) measles vaccine, the dosing scheme usually follows the requirements for MCV which is to include a second routine dose (3).

In countries with ongoing transmission of measles, the first MCV dose is recommended to be administered at 9 months of age, and in specific situations such as an outbreak, an additional dose of MCV (MCV0) should be given at the age of 6 months (4). Measles immunogenicity is known to be lower after administration at 6 months of age (4), we therefore also searched for studies that assessed the immunogenicity of RCV administered below 9 months of age. The two studies included for this purpose, showed a seroconversion of 93% when a single RCV dose (BRDII strain) was administered at 8 months of age. However, the study in which 139 children receiving RCV1 at 12 months were included as a comparison showed a comparable seroconversion (92%) in that group. There is insufficient data comparing RCV containing the same strain below 9 months of age with older age to draw conclusions on the effect of early administration on seroconversion. Studies on seroconversion after administration of RA 27/3 RCV between 6 and 12 months of age are needed. Seroconversion after BRDII strain vaccine seems lower than after RA 27/3 strain at the age of 9 months or older but this is based on only the one study mentioned above.

In most studies included in this literature review and assessed for duration of protection, 88-100% of participants were (still) seropositive 1-20 years after one or two doses of RCV. In the 2011 WHO rubella vaccine position paper persistent seropositivity ≥95% was reported 10-21 years following a single RCV (RA 27/3 strain) dose. The studies that we included varied in quality; particularly the seroprevalence studies that lacked confirmation of seroconversion after initial vaccination and were conducted in countries where rubella virus is still circulating (such as India and Japan (109)) may have

affected the actual seropositivity due to vaccination at the longer term (as natural infection could not be excluded in these studies). The studies with over 10 years follow up from regions where rubella has been eliminated showed persistent seropositivity of ≥95% (53, 56).

We did not find any new evidence on the vaccine efficacy of RCV in studies published since 2010, and only one study on vaccine effectiveness of RCV (100% effectiveness of one and two doses RCV containing the BRDII strain). Since a meta-analysis of vaccine effectiveness results from studies published before 2010 was not done before, we decided to do this based on the studies included in the current WHO rubella vaccine position paper and an additional study found through snowballing. It resulted in a pooled estimate of 97% vaccine effectiveness (of RA 27/3 strain containing RCV). This corresponds to the vaccine effectiveness estimates described in the current vaccine position paper (95-100%).

For safety of RCV, we limited our analysis to a description of severe adverse events (SAEs, including febrile convulsions, thrombocytopenic purpura, arthritis and SAEs as defined in the studies) that were at least possibly related to RCV according to the authors of these studies. Generally, the risk of SAEs following one or two doses of RCV was very small. Several studies pointed towards a higher risk of febrile convulsions after MMRV than after MMR vaccination. Since the focus of our review was not on varicella-containing vaccines, this effect should be further reviewed. We did not find any evidence supporting the hypothesis that RCV increases the risk of arthralgia and arthritis in female adults. Among the 16 case reports included in this review, the only one with a definite association between RCV and the SAE reported was a case report on a previously healthy, 31-year old man who died of fulminant encephalitis. Although we came across neurological adverse events (such as encephalitis, nerve palsies, ataxia) described in association with RCV in other studies as well, this case report is the only study we found to prove an association between encephalitis and RCV with vaccine type rubella virus being isolated from CSF and brain tissue (post mortem).

Although the administration of live-attenuated vaccines is contra-indicated in pregnancy, it sometimes is accidentally given to pregnant women. This happened in almost 3,000 rubella susceptible women who were vaccinated during the mass vaccination campaigns in Latin America between 2001 and 2008. The studies summarizing the outcomes of follow-up of these women, did not report the occurrence of any case of CRS or other SAE that could be related to vaccination. This finding was confirmed in studies from other parts of the world as well. Thus, inadvertent RCV administration in pregnancy seems safe and no indications are found that it should be a reason for pregnancy termination.

8 Conclusions

Our literature review on the immunogenicity, duration of protection, vaccine effectiveness and safety of RCV largely confirmed the evidence that is presented in the current WHO rubella vaccine position paper, dating from 2011. Single and two doses of RCV are highly immunogenic for a long period of time, they are effective in preventing rubella and CRS, and they are safe to administer.

9 Acknowledgements

We thank the WHO IVB team for the opportunity to conduct this review. We would also like to thank Rob van Spronsen (librarian at RIVM) for performing the literature search and Rob van Binnendijk and Rogier Bodewes (microbiologists at RIVM) for providing input on the interpretation of the data on microbiological and serological testing for rubella.

10 References

1. Rubella vaccines: WHO position paper. Wkly Epidemiol Rec. 2011;86(29):301-16.
2. VanderEnde K, Gacic-Dobo M, Diallo MS, Conklin LM, Wallace AS. Global Routine Vaccination Coverage - 2017. MMWR Morb Mortal Wkly Rep. 2018;67(45):1261-4.
3. Grant GB, Reef SE, Patel M, Knapp JK, Dabbagh A. Progress in Rubella and Congenital Rubella Syndrome Control and Elimination - Worldwide, 2000-2016. MMWR Morb Mortal Wkly Rep. 2017;66(45):1256-60.
4. Measles vaccines: WHO position paper - April 2017. Wkly Epidemiol Rec. 2017;92(17):205-27.
5. Nic Lochlainn LM, van der Maas NAT, de Gier B, Strebel PM, Goodman T, van Binnendijk RS, et al. Efficacy, effectiveness and safety of measles vaccination below nine months of age: a systematic review and meta-analysis 2015 [Available from: http://www.who.int/immunization/sage/meetings/2015/october/2_MCV1_below_9_months_Effect_safety_28092015.pdf?ua=1.
6. World Health Organization. Manual for the Laboratory-based Surveillance of Measles, Rubella, and Congenital Rubella Syndrome 2018 [Third edition, June 2018:[Available from: https://www.who.int/immunization/monitoring_surveillance/burden/laboratory/manual/en/.
7. Reef SE, Plotkin SA. Rubella Vaccines. 7th edition ed. Stanley A Plotkin SA, Orenstein WA, Offit PA, Edwards KM, editors. Philadephia: Elsevier; 2018.
8. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics. 1977;33(1):159-74.
9. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011;64(4):383-94.
10. The MMR-161 study group. Immunogenicity and safety of measles-mumps-rubella vaccine at two different potency levels administered to healthy children aged 12–15months: A phase III, randomized, non-inferiority trial. Vaccine. 2018;36(38):5781-8.
11. The MMR-162 study group. Safety and immunogenicity of an upper-range release titer measles-mumps-rubella vaccine in children vaccinated at 12 to 15 months of age: a phase III, randomized study. Human Vaccines and Immunotherapeutics. 2018.
12. Bavdekar A, Oswal J, Ramanan PV, Aundhkar C, Venugopal P, Kapse D, et al. Immunogenicity and safety of measles-mumps-rubella vaccine delivered by disposable-syringe jet injector in India: A randomized, parallel group, non-inferiority trial. Vaccine. 2018;36(9):1220-6.
13. Bryant KA, McVernon J, Marchant CD, Nolan T, Marshall GS, Richmond P, et al. Immunogenicity and safety of measles-mumps-rubella and varicella vaccines coadministered with a fourth dose of Haemophilus influenzae type b and Neisseria meningitidis serogroups C and Y-tetanus toxoid conjugate vaccine in toddlers: A pooled analysis of randomized trials. Human Vaccines and Immunotherapeutics. 2012;8(8):1036-41.
14. Carmona A, Miranda M, Barrio F, De Vicente A, Mares J, Muñoz E, et al. Reactogenicity and immunogenicity of combined haemophilus influenzae type B-meningococcal serogroup C conjugate vaccine booster dose coadministered with measles, mumps, and rubella vaccinehib-menc-TT booster with routine MMR vaccine. Pediatric Infectious Disease Journal. 2010;29(3):269-71.
15. Clarke E, Saidu Y, Adetifa JU, Adigweme I, Hydara MB, Bashorun AO, et al. Safety and immunogenicity of inactivated poliovirus vaccine when given with measles–rubella combined vaccine and yellow fever vaccine and when given via different administration routes: a phase 4, randomised, non-inferiority trial in The Gambia. The Lancet Global Health. 2016;4(8):e534-e47.
16. de Menezes Martins R, Curran B, Maia MDLS, Ribeiro MDGT, Camacho LAB, da Silva Freire M, et al. Immunogenicity and safety of measles-mumps-rubella vaccine delivered by disposable-syringe jet injector in healthy Brazilian infants: A randomized non-inferiority study. Contemporary Clinical Trials. 2015;41:1-8.

17. Deichmann KA, Ferrera G, Tran C, Thomas S, Eymin C, Baudin M. Immunogenicity and safety of a combined measles, mumps, rubella and varicella live vaccine (ProQuad®) administered concomitantly with a booster dose of a hexavalent vaccine in 12-23-month-old infants. Vaccine. 2015;33(20):2379-86.
18. Durando P, Esposito S, Bona G, Cuccia M, Desole MG, Ferrera G, et al. The immunogenicity and safety of a tetravalent measles-mumps-rubella-varicella vaccine when co-administered with conjugated meningococcal C vaccine to healthy children: A phase IIIb, randomized, multi-center study in Italy. Vaccine. 2016;34(36):4278-84.
19. Huang LM, Lee BW, Chan PC, Povey M, Henry O. Immunogenicity and safety of combined measles-mumps-rubella-varicella vaccine using new measles and rubella working seeds in healthy children in Taiwan and Singapore: A phase II, randomized, double-blind trial. Human Vaccines and Immunotherapeutics. 2013;9(6):1308-15.
20. Huang LM, Lin TY, Chiu CH, Chiu NC, Chen PY, Yeh SJ, et al. Concomitant administration of live attenuated Japanese encephalitis chimeric virus vaccine (JE-CV) and measles, mumps, rubella (MMR) vaccine: Randomized study in toddlers in Taiwan. Vaccine. 2014;32(41):5363-9.
21. Lalwani S, Chatterjee S, Balasubramanian S, Bavdekar A, Mehta S, Datta S, et al. Immunogenicity and safety of early vaccination with two doses of a combined measles-mumps-rubellavaricella vaccine in healthy Indian children from 9 months of age: A phase III, randomised, non-inferiority trial. BMJ Open. 2015;5(9).
22. Lee H, Kim HW, Cho HK, Park EA, Choi KM, Kim KH. Reappraisal of MMR vaccines currently used in Korea. Pediatrics International. 2011;53(3):374-80.
23. Leonardi M, Bromberg K, Baxter R, Gardner JL, Klopfer S, Nicholson O, et al. Immunogenicity and safety of MMRV and PCV-7 administered concomitantly in healthy children. Pediatrics. 2011;128(6):e1387-e94.
24. Lum LCS, Borja-Tabora CF, Breiman RF, Vesikari T, Sablan BP, Chay OM, et al. Influenza vaccine concurrently administered with a combination measles, mumps, and rubella vaccine to young children. Vaccine. 2010;28(6):1566-74.
25. Marshall GS, Senders SD, Shepard J, Twiggs JD, Gardner J, Hille D, et al. A double blind, randomized, active controlled study to assess the safety, tolerability and immunogenicity of measles, mumps rubella, and varicella vaccine (MMRV) manufactured using an alternative process. Human Vaccines and Immunotherapeutics. 2016;12(8):2188-96.
26. Matos dos Santos E, Noronha TG, Alves IS, Cruz RLS, Ferroco CLV, Brum RC, et al. Immunogenicity and safety of the combined vaccine for measles, mumps, and rubella isolated or combined with the varicella component administered at 3-month intervals: randomised study. Memorias do Instituto Oswaldo Cruz. 2019;114:e180517.
27. Matos dos Santos E, Silva e Sá GR, Siqueira MM, Martins RM, Camacho LA, von Doellinger VR, et al. Immune response to the mumps component of the MMR vaccine in the routine of immunisation services in the Brazilian National Immunisation Program. Memórias do Instituto Oswaldo Cruz. 2014;109(3):335-9.
28. Mufson MA, Diaz C, Leonardi M, Harrison CJ, Grogg S, Carbayo A, et al. Safety and immunogenicity of human serum albumin-free MMR vaccine in US children aged 12-15 months. Journal of the Pediatric Infectious Diseases Society. 2015;4(4):339-48.
29. Nascimento Silva JR, Camacho LAB, Siqueira MM, Freire MDS, Castro YP, Maia MDLS, et al. Mutual interference on the immune response to yellow fever vaccine and a combined vaccine against measles, mumps and rubella. Vaccine. 2011;29(37):6327-34.
30. Reisinger KS, Richardson E, Malacaman EA, Levin MJ, Gardner JL, Wang W, et al. A double-blind, randomized, controlled, multi-center safety and immunogenicity study of a refrigerator-stable formulation of VARIVAX®. Vaccine. 2018.
31. Rümke HC, Loch HP, Hoppenbrouwers K, Vandermeulen C, Malfroot A, Helm K, et al. Immunogenicity and safety of a measles-mumps-rubella-varicella vaccine following a 4-week or a 12-month interval between two doses. Vaccine. 2011;29(22):3842-9.

32. Sood A, Mitra M, Joshi HA, Nayak US, Siddaiah P, Babu TR, et al. Immunogenicity and safety of a novel MMR vaccine (live, freeze-dried) containing the Edmonston-Zagreb measles strain, the Hoshino mumps strain, and the RA 27/3 rubella strain: Results of a randomized, comparative, active controlled phase III clinical trial. Human Vaccines and Immunotherapeutics. 2017;13(7):1523-30.
33. Vesikari T, Karvonen A, Bianco V, Van der Wielen M, Miller J. Tetravalent meningococcal serogroups A, C, W-135 and Y conjugate vaccine is well tolerated and immunogenic when co-administered with measles-mumps-rubella-varicella vaccine during the second year of life: An open, randomized controlled trial. Vaccine. 2011;29(25):4274-84.
34. Vesikari T, Karvonen A, Lindblad N, Korhonen T, Lommel P, Willems P, et al. Safety and immunogenicity of a booster dose of the 10-valent pneumococcal nontypeable haemophilus influenzae protein D conjugate vaccine coadministered with measles-mumps-rubella-varicella vaccine in children aged 12 to 16 months. Pediatric Infectious Disease Journal. 2010;29(6):e47-e56.
35. Wiedmann RT, Reisinger KS, Hartzel J, Malacaman E, Senders SD, Giacoletti KED, et al. M-M-R®<inf>II</inf> manufactured using recombinant human albumin (rHA) and M-M-R®<inf>II</inf> manufactured using human serum albumin (HSA) exhibit similar safety and immunogenicity profiles when administered as a 2-dose regimen to healthy children. Vaccine. 2015;33(18):2132-40.
36. Nessa A, Tabassum S, Akther T, Sultana N, Selim S. Rubella antibody prevalence and immunogenicity of single dose rubella vaccine among 16-25 years girls from Bangladesh. Bangladesh Medical Research Council Bulletin. 2016;42(2):84-9.
37. Sharma H, Chowdhari S, Raina TR, Bhardwaj S, Namjoshi G, Parekh S. Sero-Surveillance to assess immunity to rubella and assessment of immunogenicity and safety of a single dose of rubella vaccine in school girls. Indian Journal of Community Medicine. 2010;35(1):134-7.
38. Sharma HJ, Padbidri VS, Kapre SV, Jadhav SS, Dhere RM, Parekh SS, et al. Seroprevalence of rubella and immunogenicity following rubella vaccination in adolescent girls in India. Journal of Infection in Developing Countries. 2011;5(12):874-81.
39. Ferrera G, Cuccia M, Mereu G, Icardi G, Bona G, Esposito S, et al. Booster vaccination of pre-school children with reduced-antigen-content diphtheria-tetanus-acellular pertussis-inactivated poliovirus vaccine co-administered with measles-mumps-rubella-varicella vaccine: a randomized, controlled trial in children primed according to a 2 + 1 schedule in infancy. Human vaccines & immunotherapeutics. 2012;8(3):355-62.
40. Gomber S, Arora SK, Das S, Ramachandran VG. Immune response to second dose of MMR vaccine in Indian children. Indian Journal of Medical Research. 2011;134(9):302-6.
41. Knuf M, Zepp F, Helm K, Maurer H, Prieler A, Kieninger-Baum D, et al. Antibody persistence for 3 years following two doses of tetravalent measles-mumps-rubella-varicella vaccine in healthy children. European Journal of Pediatrics. 2012;171(3):463-70.
42. Marlow R, Kuriyakose S, Mesaros N, Han HH, Tomlinson R, Faust SN, et al. A phase III, open-label, randomised multicentre study to evaluate the immunogenicity and safety of a booster dose of two different reduced antigen diphtheria-tetanus-acellular pertussis-polio vaccines, when co-administered with measles-mumps-rubella vaccine in 3 and 4-year-old healthy children in the UK. Vaccine. 2018;36(17):2300-6.
43. Vesikari T, Becker T, Gajdos V, Fiquet A, Thomas S, Richard P, et al. Immunogenicity and safety of a two-dose regimen of a combined measles, mumps, rubella and varicella live vaccine (ProQuad®) in infants from 9 months of age. Vaccine. 2012;30(20):3082-9.
44. Li Y, Chu SY, Yue C, Wannemuehler K, Xie S, Zhang F, et al. Immunogenicity and safety of measles-rubella vaccine co-administered with attenuated Japanese encephalitis SA 14–14–2 vaccine in infants aged 8 months in China: a non-inferiority randomised controlled trial. The Lancet Infectious Diseases. 2019;19(4):402-9.
45. He H, Chen E, Chen H, Wang Z, Li Q, Yan R, et al. Similar immunogenicity of measles-mumps-rubella (MMR) vaccine administrated at 8 months versus 12 months age in children. Vaccine. 2014;32(31):4001-5.

46. Okafuji T, Okafuji T, Nakayama T. Persistence of immunity acquired after a single dose of rubella vaccine in Japan. Japanese Journal of Infectious Diseases. 2016;69(3):221-3.
47. Paulke-Korinek M, Fischmeister G, Grac A, Rendi-Wagner P, Kundi M, Mohsenzadeh-Rabbani A, et al. Persistence of antibodies in 4-8 year old austrian children after vaccination with hexavalent DTaP-HBV-IPV/Hib and MMR vaccines. Vaccine. 2011;29(32):5130-6.
48. Shoho Y, Kimura T, Yanagawa Y, Saito A, Inoue T, Suto C, et al. Vaccination status and antibody titers against rubella and measles among japanese female college students majoring in childcare between 2015 and 2018. Tohoku Journal of Experimental Medicine. 2018;246(2):73-9.
49. Kontio M, Palmu AA, Syrjänen RK, Lahdenkari M, Ruokokoski E, Davidkin I, et al. Similar Antibody Levels in 3-Year-Old Children Vaccinated Against Measles, Mumps, and Rubella at the Age of 12 Months or 18 Months. Journal of Infectious Diseases. 2016;213(12):2005-13.
50. Linder N, Abudi Y, Abdalla W, Badir M, Amitai Y, Samuels J, et al. Effect of season of inoculation on immune response to rubella vaccine in children. Journal of Tropical Pediatrics. 2011;57(4):299-302.
51. Díaz Ortega JL, Castaneda D, Arellano Quintanilla DM, Martínez D, Trumbo SP, Fernández de Castro J. Antibody persistence in children aged 6–7 years one year following booster immunization with two MMR vaccines applied by aerosol or by injection. Vaccine. 2017;35(23):3116-22.
52. Díaz-Ortega JL, Bennett JV, Castañeda D, Martinez D, Fernandez de Castro J. Antibody persistence in young adults 1 year after MMR immunization by aerosol or by subcutaneous route. Vaccine. 2010;28(44):7228-32.
53. McLean HQ, Fiebelkorn AP, Ogee-Nwankwo A, Hao L, Coleman LA, Adebayo A, et al. Rubella virus neutralizing antibody response after a third dose of measles-mumps-rubella vaccine in young adults. Vaccine. 2018;36(38):5732-7.
54. Gonçalves G, Frade J, Nascimento MSJ, Mesquita JR, Nunes C. Persistence of rubella and mumps antibodies, following changes in the recommended age for the second dose of MMR vaccine in Portugal. Epidemiology and Infection. 2016;144(15):3139-47.
55. Kontio M, Jokinen S, Paunio M, Peltola H, Davidkin I. Waning antibody levels and avidity: Implications for MMR vaccine-induced protection. Journal of Infectious Diseases. 2012;206(10):1542-8.
56. Seagle EE, Bednarczyk RA, Hill T, Fiebelkorn AP, Hickman CJ, Icenogle JP, et al. Measles, mumps, and rubella antibody patterns of persistence and rate of decline following the second dose of the MMR vaccine. Vaccine. 2018;36(6):818-26.
57. Steward MW, Chargelegue D. Overview: measurement and biological significance of antibody affinity and reactivity. Weir DM, Herzenberg LA, Blackwell CC, editors. Oxford, UK: Blackwell; 1997.
58. Xu H, Gao X, Bo F, Ma J, Li Y, Fan C, et al. A rubella outbreak investigation and BRD-II strain rubella vaccine effectiveness study, Harbin city, Heilongjiang province, China, 2010-2011. Vaccine. 2013;32(1):85-9.
59. 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;118(2):301-6.
60. de Valk H., I. R. Epidémie de rubéole: Evaluation de l'efficacité vaccinale sur le terrain, Ardèche, janvier mars 1997. Réseau National de Santé Publique. 1998(Jan):1-52.
61. Furukawa T, Miyata T, Kondo K, Kuno K, Isomura S, Takekoshi T. Rubella vaccination during an epidemic. JAMA. 1970;213(6):987-90.
62. Hahne S, Macey J, van Binnendijk R, Kohl R, Dolman S, van der Veen Y, et al. Rubella outbreak in the Netherlands, 2004-2005: high burden of congenital infection and spread to Canada. Pediatr Infect Dis J. 2009;28(9):795-800.
63. Abu-Elyazeed R, Jennings W, Severance R, Noss M, Caplanusi A, Povey M, et al. Immunogenicity and safety of a second dose of a measles-mumps-rubella vaccine administered to healthy participants 7 years of age or older: A phase III, randomized study. Human Vaccines and Immunotherapeutics. 2018;14(11):2624-31.

64. Berry AA, Abu-Elyazeed R, Diaz-Perez C, Mufson MA, Harrison CJ, Leonardi M, et al. Two-year antibody persistence in children vaccinated at 12–15 months with a measles-mumps-rubella virus vaccine without human serum albumin. Human Vaccines and Immunotherapeutics. 2017;13(7):1516-22.
65. Blatter MM, Klein NP, Shepard JS, Leonardi M, Shapiro S, Schear M, et al. Immunogenicity and Safety of two tetravalent (measles, mumps, rubella, varicella) vaccines coadministered with hepatitis a and pneumococcal conjugate vaccines to children twelve to fourteen months of age. Pediatric Infectious Disease Journal. 2012;31(8):e133-e40.
66. Chiu NC, Huang LM, Willemsen A, Bhusal C, Arora AK, Reynoso Mojares Z, et al. Safety and immunogenicity of a meningococcal B recombinant vaccine when administered with routine vaccines to healthy infants in Taiwan: A phase 3, open-label, randomized study. Human Vaccines and Immunotherapeutics. 2018;14(5):1075-83.
67. Crevat D, Brion JD, Gailhardou S, Laot TM, Capeding MR. First experience of concomitant vaccination against dengue and MMR in toddlers. Pediatric Infectious Disease Journal. 2015;34(8):884-92.
68. Díaz-Ortega JL, Bennett JV, Castañeda-Desales D, Quintanilla DMA, Martínez D, Castro JFD. Booster immune response in children 6-7 years of age, randomly assigned to four groups with two MMR vaccines applied by aerosol or by injection. Vaccine. 2014;32(29):3680-6.
69. Klein NP, Lewis E, Baxter R, Weintraub E, Glanz J, Naleway A, et al. Measles-containing vaccines and febrile seizures in children age 4 to 6 years. Pediatrics. 2012;129(5):809-14.
70. Knuf M, Zepp F, Meyer CU, Habermehl P, Maurer L, Burow HM, et al. Safety, immunogenicity and immediate pain of intramuscular versus subcutaneous administration of a measles-mumps-rubella-varicella vaccine to children aged 11-21 months. European Journal of Pediatrics. 2010;169(8):925-33.
71. Pina LM, Bassily E, MacHmer A, Hou V, Reinhardt A. Safety and immunogenicity of a quadrivalent meningococcal polysaccharide diphtheria toxoid conjugate vaccine in infants and toddlers: Three multicenter phase III studies. Pediatric Infectious Disease Journal. 2012;31(11):1173-83.
72. Povey M, Henry O, Riise Bergsaker MA, Chlibek R, Esposito S, Flodmark CE, et al. Protection against varicella with two doses of combined measles-mumps-rubella-varicella vaccine or one dose of monovalent varicella vaccine: 10-year follow-up of a phase 3 multicentre, observer-blind, randomised, controlled trial. The Lancet Infectious Diseases. 2019;19(3):287-97.
73. Rinderknecht S, Michaels MG, Blatter M, Gaglani M, Andrews W, Abughali N, et al. Immunogenicity and safety of an inactivated hepatitis A vaccine when coadministered with measles-mumps-rubella and varicella vaccines in children less than 2 years of age. Pediatric Infectious Disease Journal. 2011;30(10):e179-e85.
74. Yetman RJ, Shepard JS, Duke A, Stek JE, Petrecz M, Klopfer SO, et al. Concomitant administration of hepatitis A vaccine with measles/mumps/ rubella/varicella and pneumococcal vaccines in healthy 12- to 23-month-old children. Human Vaccines and Immunotherapeutics. 2013;9(8):1691-7.
75. Yurdakök K, Bakir M, Ince T, Yalçin S, Özmert E, Soysal A, et al. Immunogenicity and safety of an inactivated hepatitis A vaccine given with measles-mumps-rubella vaccine to 12-13 month old Turkish children. Journal of Vaccines and Vaccination. 2012;3(5).
76. Abedi GR, Mutuc JD, Lawler J, Leroy ZC, Hudson JM, Blog DS, et al. Adverse events following a third dose of measles, mumps, and rubella vaccine in a mumps outbreak. Vaccine. 2012;30(49):7052-8.
77. Das PK. Study of adverse events following immunisation with universal and newer vaccines in the Serampore IMA Child Clinic over a period of 7 years. Journal of the Indian Medical Association. 2013;111(4):230-5.
78. Finale E, Leonardi G, Auletta G, Amadori R, Saglietti C, Pagani L, et al. MMR vaccine in the postpartum does not expose seronegative women to untoward effects. Annali dell'Istituto superiore di sanita. 2017;53(2):152-6.

79. Kemmeren JM, Van Der Maas NAT, De Melker HE. Parental reports of adverse events following simultaneously given dT-IPV and MMR vaccines in healthy 9-year-old children. European Journal of Pediatrics. 2011;170(3):339-45.
80. Rüger G, Gabutti G, Rümke H, Rombo L, Bernaola E, Diez-Domingo J, et al. Safety of a 2-dose regimen of a combined measles, mumps, rubella and varicella live vaccine manufactured with recombinant human albumin. Pediatric Infectious Disease Journal. 2012;31(11):1166-72.
81. Van Der Maas NAT, Woudenberg T, Hahń SJM, De Melker HE. Tolerability of Early Measles-Mumps-Rubella Vaccination in Infants Aged 6-14 Months during a Measles Outbreak in the Netherlands in 2013-2014. Journal of Infectious Diseases. 2016;213(9):1466-71.
82. Ankrah DNA, Darko DM, Sabblah G, Mantel-Teeuwisse A, Leufkens HMG. Reporting of adverse events following immunizations in Ghana–Using disproportionality analysis reporting ratios. Human Vaccines and Immunotherapeutics. 2018;14(1):172-8.
83. Cunha MPL, Dórea JG, Marques RC, Leão RS. Vaccine adverse events reported during the first ten years (1998-2008) after introduction in the state of Rondonia, Brazil. BioMed Research International. 2013;2013.
84. Khetsuriani N, Imnadze P, Baidoshvili L, Jabidze L, Tatishili N, Kurtsikashvili G, et al. Impact of unfounded vaccine safety concerns on the nationwide measles-rubella immunization campaign, Georgia, 2008. Vaccine. 2010;28(39):6455-62.
85. Lopes SRC, Perin JLR, Prass TS, Carvalho SMD, Lessa SC, Dórea JG. Adverse events following immunization in Brazil: Age of child and vaccine-associated risk analysis using logistic regression. International Journal of Environmental Research and Public Health. 2018;15(6).
86. Meng FY, Sun Y, Shen YG, Pan HF, Tang JH, Wang BB, et al. Safety of measles-containing vaccines in postmarketing surveillance in Anhui, China. PLoS ONE. 2017;12(2).
87. Mentzer D, Meyer H, Keller-Stanislawski B. Safety and tolerability of monovalent measles and combined measles, mumps, rubella, and varicella vaccines [In German]. Bundesgesundheitsblatt - Gesundheitsforschung - Gesundheitsschutz. 2013;56(9):1253-9.
88. Pérez-Vilar S, Gutiérrez-Gimeno MV, Rodríguez-Galán MA, Díez-Domingo J, Puig-Barberà J, Gomar-Fayos J, et al. Suspected adverse events to measles, mumps and rubella vaccine reported to the Community of Valencia Pharmacovigilance Centre [in Spanish]. Anales de Pediatria. 2013;78(5):297-302.
89. Sukumaran L, McNeil MM, Moro PL, Lewis PW, Winiecki SK, Shimabukuro TT. Adverse events following measles, mumps, and rubella vaccine in adults reported to the vaccine adverse event reporting system (VAERS), 2003-2013. Clinical Infectious Diseases. 2015;60(10):e58-e65.
90. Woo EJ, Winiecki SK, Arya D, Beeler J. Adverse events after MMR or MMRV vaccine in infants under nine months old. Pediatric Infectious Disease Journal. 2016;35(8):e253-e7.
91. Binamer Y. Acute hemorrhagic edema of infancy after MMR vaccine. Annals of Saudi Medicine. 2015;35(3):254-6.
92. Cheng DR, Crawford NW, Hayman M, Buckley C, Buttery JP. Recurrent 6th nerve palsy in a child following different live attenuated vaccines: Case report. BMC Infectious Diseases. 2012;12.
93. Ferrini W, Aubert V, Balmer A, Munier FL, Abouzeid H. Anterior uveitis and cataract after rubella vaccination: A case report of a 12-month-old girl. Pediatrics. 2013;132(4):e1035-e8.
94. Gál O, Pletz MW, Ianoși ES. Severe pneumococcal pneumonia following Measles- Mumps-Rubella vaccination. Revista Romana de Medicina de Laborator. 2016;24(3):337-42.
95. Gil-Bistes D, Kluger N, Bessis D, Guillot B, Raison-Peyron N. Pityriasis lichenoides chronic after measles-mumps-rubella vaccination. Journal of Dermatology. 2012;39(5):492-3.
96. Gualberto FAS, de Oliveira MI, Alves VAF, Kanamura CT, Rosemberg S, Sato HK, et al. Fulminant encephalitis associated with a vaccine strain of rubella virus. Journal of Clinical Virology. 2013;58(4):737-40.
97. Gunatheesan S, Ferguson J, Moosa Y. Pityriasis lichenoides et varioliformis acuta: A rare association with the measles, mumps and rubella vaccine. Australasian Journal of Dermatology. 2012;53(4):e76-e8.

98. Kuniyoshi K, Hatsukawa Y, Kimura S, Fujino T, Ohguro H, Nakai R, et al. Acute bilateral photoreceptor degeneration in an infant after vaccination against measles and rubella. JAMA Ophthalmology. 2017;135(5):478-82.
99. Manzotti F, Menozzi C, Porta MR, Orsoni JG. Partial third nerve palsy after Measles Mumps Rubella vaccination. Italian journal of pediatrics. 2010;36(1):59.
100. Naciri Bennani B, Cheikh Rouhou H, Waton J, Cuny JF, Bassegoda G, Trechot P, et al. Pityriasis rubra pilaris after vaccination [in French]. Annales de Dermatologie et de Venereologie. 2011;138(11):753-6.
101. Okazaki N, Takeguchi M, Sonoda K, Handa Y, Kakiuchi T, Miyahara H, et al. Detection of platelet-binding anti-measles and anti-rubella virus IgG antibodies in infants with vaccine-induced thrombocytopenic purpura. Vaccine. 2011;29(31):4878-80.
102. Owatanapanich S, Wanlapakorn N, Tangsiri R, Poovorawan Y. Measles-mumps-rubella vaccination induced thrombocytopenia: a case report and review of the literature. The Southeast Asian journal of tropical medicine and public health. 2014;45(5):1053-7.
103. Sanz PG, Garcia Mendez CV, Cueto AL, Silva VB, Walther JC, Diez RA, et al. Chronic inflammatory demyelinating polyradiculoneuropathy in a patient with systemic lupus erythematosus and good outcome with rituximab treatment. Rheumatology International. 2012;32(12):4061-3.
104. Shuper A. Suspected measles-mumps-rubella vaccine-related encephalitis: Two cases. Scandinavian Journal of Infectious Diseases. 2010;43(1):75-8.
105. Verma A, Rastogi R, Srivastava A. Pancreatic pseudocyst after measles, mumps, and rubella vaccination. Turkish Journal of Gastroenterology. 2017;28(2):144-6.
106. Yu AM, Ito S, Leibson T, Lavi S, Fu LW, Weinstein M, et al. Pediatric Wells syndrome (eosinophilic cellulitis) after vaccination: A case report and review of the literature. Pediatric Dermatology. 2018;35(5):e262-e4.
107. Castillo-Solórzano C, Reef SE, Morice A, Vascones N, Chevez AE, Castalia-Soares R, et al. Rubella vaccination of unknowingly pregnant women during mass campaigns for rubella and congenital rubella syndrome elimination, the Americas 2001-2008. Journal of Infectious Diseases. 2011;204(SUPPL. 2):S713-S7.
108. Ergenoğlu AM, Yeniel AÖ, Yildinm N, Kazandi M, Akercan F, Sağol S. Rubella vaccination during the preconception period or in pregnancy and perinatal and fetal outcomes. Turkish Journal of Pediatrics. 2012;54(3):230-3.
109. WHO. Measles and rubella surveillance data (2015-2019) [Available from: https://www.who.int/immunization/monitoring_surveillance/burden/vpd/surveillance_type/active/measles_monthlydata/en/.

Appendix A: Databases used for literature search

Databases
Primary: databases for biomedicine and health sciences • EMBASE • Scopus

Appendix B: Database search strategy

1 Embase.com search strategy

Date of search: 14 May 2019

Set	Search terms	# records
#1	rubella vaccine'/exp/mj OR (rcv:ti NOT ('reference change value':ti,ab OR 'reversible cerebral vasoconstriction':ti,ab OR 'rabbit calicivirus':ti,ab OR 'red cell volume':ti,ab OR 'recombinant contraceptive vaccinogen':ti,ab OR 'rat coronavirus':ti,ab)) OR (mr:ti AND rubella*:ti,ab) OR (mmr:ti NOT ('molecular medicine reports':ti,ab OR 'mismatch repair':ti,ab OR 'maternal mortality ratio':ti,ab OR 'major molecular response':ti,ab)) OR mmrv:ti OR 'chickenpox measles mumps rubella vaccine'/exp/mj	2,893
#2	'measles mumps rubella vaccine'/exp/mj	2,193
#3	'mumps rubella vaccine'/exp/mj	1
#4	'measles rubella vaccine'/exp/mj	51
#5	((rubella* NEAR/2 vaccin*):ti) OR ((rubella* NEAR/2 immunizat*):ti) OR ((rubella* NEAR/2 immunisat*):ti)	1,971
#6	#1 OR #2 OR #3 OR #4 OR #5	5,074
#7	(#1 OR #2 OR #3 OR #4 OR #5) AND [2010-2019]/py	1,191
#8	(#1 OR #2 OR #3 OR #4 OR #5) AND [2010-2019]/py AND [humans]/lim	1,055
#9	(#1 OR #2 OR #3 OR #4 OR #5) AND [2010-2019]/py AND [animals]/lim	49
#10	#7 NOT #9	1,142
#11	#8 OR #10	1,162
#12	#11 AND ('conference abstract'/it OR 'conference paper'/it OR 'editorial'/it OR 'erratum'/it OR 'note'/it OR 'short survey'/it)	262
#13	#11 NOT #12	900
#14	rubella*:ti,ab OR 'ra27/3':ti,ab OR 'takahashi*':ti,ab OR 'matsuura*':ti,ab OR 'to-336':ti,ab	16,031
#15	#13 AND #14	650

#17	'rubella vaccine'/exp OR (rcv:ti,ab NOT ('reference change value':ti,ab OR 'reversible cerebral vasoconstriction':ti,ab OR 'rabbit calicivirus':ti,ab OR 'red cell volume':ti,ab OR 'recombinant contraceptive vaccinogen':ti,ab OR 'rat coronavirus':ti,ab)) OR (mr:ti,ab AND rubella*:ti,ab) OR (mmr:ti,ab NOT ('molecular medicine reports':ti,ab OR 'mismatch repair':ti,ab OR 'maternal mortality ratio':ti,ab OR 'major molecular response':ti,ab)) OR mmrv:ti,ab OR 'chickenpox measles mumps rubella vaccine'/exp	10,151
#18	'measles mumps rubella vaccine'/exp	6,856
#19	'mumps rubella vaccine'/exp	25
#20	'measles rubella vaccine'/exp	182
#21	((rubella* NEAR/2 vaccin*):ti,ab) OR ((rubella* NEAR/2 immunizat*):ti,ab) OR ((rubella* NEAR/2 immunisat*):ti,ab)	4,202
#22	#17 OR #18 OR #19 OR #20 OR #21	15,524
#23	(#17 OR #18 OR #19 OR #20 OR #21) AND [2010-2019]/py	6,982
#24	(#17 OR #18 OR #19 OR #20 OR #21) AND [2010-2019]/py AND [humans]/lim	6,213
#25	(#17 OR #18 OR #19 OR #20 OR #21) AND [2010-2019]/py AND [animals]/lim	477
#26	#23 NOT #25	6,505
#27	#24 OR #26	6,699
#28	#27 AND ('conference abstract'/it OR 'conference paper'/it OR 'editorial'/it OR 'erratum'/it OR 'note'/it OR 'short survey'/it)	2,575
#29	#27 NOT #28	4,124
#30	rubella*:ti,ab OR 'ra27/3':ti,ab OR 'takahashi*':ti,ab OR 'matsuura*':ti,ab OR 'to-336':ti,ab	16,031
#31	#29 AND #30	1,586
#32	#31 NOT #15	936
#33	'immunogenicity'/exp/mj OR 'immunogen*':ti	25,350
#34	'vaccine immunogenicity'/exp	1,641
#35	'safety'/exp/mj OR safety*:ti OR safe:ti	239,097
#36	'drug safety'/exp/mj OR 'adverse event'/exp/mj	237,430
#37	'efficacy parameters'/exp	11,571
#38	efficac*:ti OR effectiveness*:ti	336,616
#39	'antibody'/exp/mj OR antibod*:ti	534,095
#40	'immunology'/exp/mj OR immunolog*:ti	139,753

#41	'drug surveillance program'/exp/mj OR surveill*:ti	61,681
#42	'immunological procedures'/exp/mj	165,632
#43	#33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42	1,570,701
#44	#32 AND #43	196
#45	#31 NOT (#15 OR #44)	740
#46	rubella*:ti OR 'ra27/3':ti OR 'takahashi*':ti OR 'matsuura*':ti OR 'to-336':ti	9,010
#47	'vaccine'/exp/mj OR vaccin*:ti	247,214
#48	#45 AND #46 AND #47	25
#49	#45 AND 'Review'/it	118
#50	#48 OR #49	138
#51	#15 OR #44 OR #48 OR #49	984
#52	#51 AND ([dutch]/lim OR [english]/lim OR [french]/lim OR [german]/lim OR [portuguese]/lim OR [spanish]/lim)	**919**
#53	#51 NOT #52	65

2 Scopus search strategy

Date of search: 26 April 2019

TITLE (*"rubella vaccin*"*) AND (LIMIT-TO (PUBYEAR , *2019*) OR LIMIT-TO (PUBYEAR , *2018*) OR LIMIT-TO (PUBYEAR , *2017*) OR LIMIT-TO (PUBYEAR , *2016*) OR LIMIT-TO (PUBYEAR , *2015*) OR LIMIT-TO (PUBYEAR , *2014*) OR LIMIT-TO (PUBYEAR , *2013*) OR LIMIT-TO (PUBYEAR , *2012*) OR LIMIT-TO (PUBYEAR , *2011*) OR LIMIT-TO (PUBYEAR , *2010*)) AND (LIMIT-TO (DOCTYPE , *"ar"*) OR LIMIT-TO (DOCTYPE , *"re"*)) AND (EXCLUDE (SUBJAREA , *"VETE"*)) AND (EXCLUDE (SUBJAREA , *"AGRI"*) OR EXCLUDE (SUBJAREA , *"ENVI"*) OR EXCLUDE (SUBJAREA , *"MATH"*)) AND (LIMIT-TO (LANGUAGE , *"English"*) OR LIMIT-TO (LANGUAGE , *"French"*) OR LIMIT-TO (LANGUAGE , *"German"*))

N=130

TITLE (*"rubella vaccin*"*) AND (LIMIT-TO (DOCTYPE , *"ar"*) OR LIMIT-
TO (DOCTYPE , *"re"*)) AND (EXCLUDE (SUBJAREA , *"VETE"*) OR EXCLUDE (SUBJAREA , *"AGRI"*)
OR EXCLUDE (SUBJAREA , *"ENVI"*) OR EXCLUDE (SUBJAREA , *"MATH"*)) AND (LIMIT-
TO (PUBYEAR , *2019*) OR LIMIT-TO (PUBYEAR , *2018*) OR LIMIT-
TO (PUBYEAR , *2017*) OR LIMIT-TO (PUBYEAR , *2016*) OR LIMIT-
TO (PUBYEAR , *2015*) OR LIMIT-TO (PUBYEAR , *2014*) OR LIMIT-
TO (PUBYEAR , *2013*) OR LIMIT-TO (PUBYEAR , *2012*) OR LIMIT-
TO (PUBYEAR , *2011*) OR LIMIT-
TO (PUBYEAR , *2010*)) AND (EXCLUDE (LANGUAGE , *"English"*) OR EXCLUDE (LANGUAGE , *"Fre*
nch") OR EXCLUDE (LANGUAGE , *"German"*))

N=17

Appendix C: GRADE tables

1 Immunogenicity of RCV

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.

References

1. The MMR-161 study group. Immunogenicity and safety of measles-mumps-rubella vaccine at two different potency levels administered to healthy children aged 12–15months: A phase III, randomized, non-inferiority trial. Vaccine. 2018;36(38):5781-8.
2. The MMR-162 study group. Safety and immunogenicity of an upper-range release titer measles-mumps-rubella vaccine in children vaccinated at 12 to 15 months of age: a phase III, randomized study. Human Vaccines and Immunotherapeutics. 2018.
3. Bavdekar A, Oswal J, Ramanan PV, Aundhkar C, Venugopal P, Kapse D, et al. Immunogenicity and safety of measles-mumps-rubella vaccine delivered by disposable-syringe jet injector in India: A randomized, parallel group, non-inferiority trial. Vaccine. 2018;36(9):1220-6.

4. Bryant KA, McVernon J, Marchant CD, Nolan T, Marshall GS, Richmond P, et al. Immunogenicity and safety of measles-mumps-rubella and varicella vaccines coadministered with a fourth dose of Haemophilus influenzae type b and Neisseria meningitidis serogroups C and Y-tetanus toxoid conjugate vaccine in toddlers: A pooled analysis of randomized trials. Human Vaccines and Immunotherapeutics. 2012;8(8):1036-41.
5. Carmona A, Miranda M, Barrio F, De Vicente A, Mares J, Muñoz E, et al. Reactogenicity and immunogenicity of combined haemophilus influenzae type B-meningococcal serogroup C conjugate vaccine booster dose coadministered with measles, mumps, and rubella vaccinehib-menc-TT booster with routine MMR vaccine. Pediatric Infectious Disease Journal. 2010;29(3):269-71.
6. Clarke E, Saidu Y, Adetifa JU, Adigweme I, Hydara MB, Bashorun AO, et al. Safety and immunogenicity of inactivated poliovirus vaccine when given with measles–rubella combined vaccine and yellow fever vaccine and when given via different administration routes: a phase 4, randomised, non-inferiority trial in The Gambia. The Lancet Global Health. 2016;4(8):e534-e47.
7. de Menezes Martins R, Curran B, Maia MDLS, Ribeiro MDGT, Camacho LAB, da Silva Freire M, et al. Immunogenicity and safety of measles-mumps-rubella vaccine delivered by disposable-syringe jet injector in healthy Brazilian infants: A randomized non-inferiority study. Contemporary Clinical Trials. 2015;41:1-8.
8. Deichmann KA, Ferrera G, Tran C, Thomas S, Eymin C, Baudin M. Immunogenicity and safety of a combined measles, mumps, rubella and varicella live vaccine (ProQuad®) administered concomitantly with a booster dose of a hexavalent vaccine in 12-23-month-old infants. Vaccine. 2015;33(20):2379-86.
9. Durando P, Esposito S, Bona G, Cuccia M, Desole MG, Ferrera G, et al. The immunogenicity and safety of a tetravalent measles-mumps-rubella-varicella vaccine when co-administered with conjugated meningococcal C vaccine to healthy children: A phase IIIb, randomized, multi-center study in Italy. Vaccine. 2016;34(36):4278-84.
10. Huang LM, Lee BW, Chan PC, Povey M, Henry O. Immunogenicity and safety of combined measles-mumps-rubella-varicella vaccine using new measles and rubella working seeds in healthy children in Taiwan and Singapore: A phase II, randomized, double-blind trial. Human Vaccines and Immunotherapeutics. 2013;9(6):1308-15.
11. Huang LM, Lin TY, Chiu CH, Chiu NC, Chen PY, Yeh SJ, et al. Concomitant administration of live attenuated Japanese encephalitis chimeric virus vaccine (JE-CV) and measles, mumps, rubella (MMR) vaccine: Randomized study in toddlers in Taiwan. Vaccine. 2014;32(41):5363-9.
12. Lalwani S, Chatterjee S, Balasubramanian S, Bavdekar A, Mehta S, Datta S, et al. Immunogenicity and safety of early vaccination with two doses of a combined measles-mumps-rubellavaricella vaccine in healthy Indian children from 9 months of age: A phase III, randomised, non-inferiority trial. BMJ Open. 2015;5(9).
13. Lee H, Kim HW, Cho HK, Park EA, Choi KM, Kim KH. Reappraisal of MMR vaccines currently used in Korea. Pediatrics International. 2011;53(3):374-80.
14. Leonardi M, Bromberg K, Baxter R, Gardner JL, Klopfer S, Nicholson O, et al. Immunogenicity and safety of MMRV and PCV-7 administered concomitantly in healthy children. Pediatrics. 2011;128(6):e1387-e94.
15. Lum LCS, Borja-Tabora CF, Breiman RF, Vesikari T, Sablan BP, Chay OM, et al. Influenza vaccine concurrently administered with a combination measles, mumps, and rubella vaccine to young children. Vaccine. 2010;28(6):1566-74.
16. Marshall GS, Senders SD, Shepard J, Twiggs JD, Gardner J, Hille D, et al. A double blind, randomized, active controlled study to assess the safety, tolerability and immunogenicity of measles, mumps rubella, and varicella vaccine (MMRV) manufactured using an alternative process. Human Vaccines and Immunotherapeutics. 2016;12(8):2188-96.
17. Matos dos Santos E, Noronha TG, Alves IS, Cruz RLS, Ferroco CLV, Brum RC, et al. Immunogenicity and safety of the combined vaccine for measles, mumps, and rubella isolated or

combined with the varicella component administered at 3-month intervals: randomised study. Memorias do Instituto Oswaldo Cruz. 2019;114:e180517.
18. Matos dos Santos E, Silva e Sá GR, Siqueira MM, Martins RM, Camacho LA, von Doellinger VR, et al. Immune response to the mumps component of the MMR vaccine in the routine of immunisation services in the Brazilian National Immunisation Program. Memórias do Instituto Oswaldo Cruz. 2014;109(3):335-9.
19. Mufson MA, Diaz C, Leonardi M, Harrison CJ, Grogg S, Carbayo A, et al. Safety and immunogenicity of human serum albumin-free MMR vaccine in US children aged 12-15 months. Journal of the Pediatric Infectious Diseases Society. 2015;4(4):339-48.
20. Nascimento Silva JR, Camacho LAB, Siqueira MM, Freire MDS, Castro YP, Maia MDLS, et al. Mutual interference on the immune response to yellow fever vaccine and a combined vaccine against measles, mumps and rubella. Vaccine. 2011;29(37):6327-34.
21. Reisinger KS, Richardson E, Malacaman EA, Levin MJ, Gardner JL, Wang W, et al. A double-blind, randomized, controlled, multi-center safety and immunogenicity study of a refrigerator-stable formulation of VARIVAX®. Vaccine. 2018.
22. Rümke HC, Loch HP, Hoppenbrouwers K, Vandermeulen C, Malfroot A, Helm K, et al. Immunogenicity and safety of a measles-mumps-rubella-varicella vaccine following a 4-week or a 12-month interval between two doses. Vaccine. 2011;29(22):3842-9.
23. Sood A, Mitra M, Joshi HA, Nayak US, Siddaiah P, Babu TR, et al. Immunogenicity and safety of a novel MMR vaccine (live, freeze-dried) containing the Edmonston-Zagreb measles strain, the Hoshino mumps strain, and the RA 27/3 rubella strain: Results of a randomized, comparative, active controlled phase III clinical trial. Human Vaccines and Immunotherapeutics. 2017;13(7):1523-30.
24. Vesikari T, Karvonen A, Bianco V, Van der Wielen M, Miller J. Tetravalent meningococcal serogroups A, C, W-135 and Y conjugate vaccine is well tolerated and immunogenic when co-administered with measles-mumps-rubella-varicella vaccine during the second year of life: An open, randomized controlled trial. Vaccine. 2011;29(25):4274-84.
25. Vesikari T, Karvonen A, Lindblad N, Korhonen T, Lommel P, Willems P, et al. Safety and immunogenicity of a booster dose of the 10-valent pneumococcal nontypeable haemophilus influenzae protein D conjugate vaccine coadministered with measles-mumps-rubella-varicella vaccine in children aged 12 to 16 months. Pediatric Infectious Disease Journal. 2010;29(6):e47-e56.
26. Wiedmann RT, Reisinger KS, Hartzel J, Malacaman E, Senders SD, Giacoletti KED, et al. M-M-R®II manufactured using recombinant human albumin (rHA) and M-M-R®II manufactured using human serum albumin (HSA) exhibit similar safety and immunogenicity profiles when administered as a 2-dose regimen to healthy children. Vaccine. 2015;33(18):2132-40.

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	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	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			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.

References

1. He H, Chen E, Chen H, Wang Z, Li Q, Yan R, et al. Similar immunogenicity of measles-mumps-rubella (MMR) vaccine administrated at 8 months versus 12 months age in children. Vaccine. 2014;32(31):4001-5.
2. Li Y, Chu SY, Yue C, Wannemuehler K, Xie S, Zhang F, et al. Immunogenicity and safety of measles-rubella vaccine co-administered with attenuated Japanese encephalitis SA 14–14–2 vaccine in infants aged 8 months in China: a non-inferiority randomised controlled trial. The Lancet Infectious Diseases. 2019;19(4):402-9.

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.

References

1. Nessa A, Tabassum S, Akther T, Sultana N, Selim S. Rubella antibody prevalence and immunogenicity of single dose rubella vaccine among 16-25 years girls from Bangladesh. Bangladesh Medical Research Council Bulletin. 2016;42(2):84-9.
2. Sharma H, Chowdhari S, Raina TR, Bhardwaj S, Namjoshi G, Parekh S. Sero-Surveillance to assess immunity to rubella and assessment of immunogenicity and safety of a single dose of rubella vaccine in school girls. Indian Journal of Community Medicine. 2010;35(1):134-7.
3. Sharma HJ, Padbidri VS, Kapre SV, Jadhav SS, Dhere RM, Parekh SS, et al. Seroprevalence of rubella and immunogenicity following rubella vaccination in adolescent girls in India. Journal of Infection in Developing Countries. 2011;5(12):874-81.

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%).

References

1. Ferrera G, Cuccia M, Mereu G, Icardi G, Bona G, Esposito S, et al. Booster vaccination of pre-school children with reduced-antigen-content diphtheria-tetanus-acellular pertussis-inactivated poliovirus vaccine co-administered with measles-mumps-rubella-varicella vaccine: a randomized, controlled trial in children primed according to a 2 + 1 schedule in infancy. Human vaccines & immunotherapeutics. 2012;8(3):355-62.
2. Gomber S, Arora SK, Das S, Ramachandran VG. Immune response to second dose of MMR vaccine in Indian children. Indian Journal of Medical Research. 2011;134(9):302-6.
3. Knuf M, Zepp F, Helm K, Maurer H, Prieler A, Kieninger-Baum D, et al. Antibody persistence for 3 years following two doses of tetravalent measles-mumps-rubella-varicella vaccine in healthy children. European Journal of Pediatrics. 2012;171(3):463-70.
4. Lalwani S, Chatterjee S, Balasubramanian S, Bavdekar A, Mehta S, Datta S, et al. Immunogenicity and safety of early vaccination with two doses of a combined measles-mumps-rubellavaricella vaccine in healthy Indian children from 9 months of age: A phase III, randomised, non-inferiority trial. BMJ Open. 2015;5(9).
5. Marlow R, Kuriyakose S, Mesaros N, Han HH, Tomlinson R, Faust SN, et al. A phase III, open-label, randomised multicentre study to evaluate the immunogenicity and safety of a booster dose of two different reduced antigen diphtheria-tetanus-acellular pertussis-polio vaccines, when co-administered with measles-mumps-rubella vaccine in 3 and 4-year-old healthy children in the UK. Vaccine. 2018;36(17):2300-6.

6. Matos dos Santos E, Noronha TG, Alves IS, Cruz RLS, Ferroco CLV, Brum RC, et al. Immunogenicity and safety of the combined vaccine for measles, mumps, and rubella isolated or combined with the varicella component administered at 3-month intervals: randomised study. Memorias do Instituto Oswaldo Cruz. 2019;114:e180517.
7. Vesikari T, Becker T, Gajdos V, Fiquet A, Thomas S, Richard P, et al. Immunogenicity and safety of a two-dose regimen of a combined measles, mumps, rubella and varicella live vaccine (ProQuad®) in infants from 9 months of age. Vaccine. 2012;30(20):3082-9.
8. Vesikari T, Karvonen A, Bianco V, Van der Wielen M, Miller J. Tetravalent meningococcal serogroups A, C, W-135 and Y conjugate vaccine is well tolerated and immunogenic when co-administered with measles-mumps-rubella-varicella vaccine during the second year of life: An open, randomized controlled trial. Vaccine. 2011;29(25):4274-84.
9. Vesikari T, Karvonen A, Lindblad N, Korhonen T, Lommel P, Willems P, et al. Safety and immunogenicity of a booster dose of the 10-valent pneumococcal nontypeable haemophilus influenzae protein D conjugate vaccine coadministered with measles-mumps-rubella-varicella vaccine in children aged 12 to 16 months. Pediatric Infectious Disease Journal. 2010;29(6):e47-e56.

2 Duration of protection

Table 5. Duration of protection after one or two doses of RCV

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	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			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.

References

1. Díaz Ortega JL, Castaneda D, Arellano Quintanilla DM, Martínez D, Trumbo SP, Fernández de Castro J. Antibody persistence in children aged 6–7 years one year following booster immunization with two MMR vaccines applied by aerosol or by injection. Vaccine. 2017;35(23):3116-22.
2. Díaz-Ortega JL, Bennett JV, Castañeda D, Martinez D, Fernandez de Castro J. Antibody persistence in young adults 1 year after MMR immunization by aerosol or by subcutaneous route. Vaccine. 2010;28(44):7228-32.

3. Gomber S, Arora SK, Das S, Ramachandran VG. Immune response to second dose of MMR vaccine in Indian children. Indian Journal of Medical Research. 2011;134(9):302-6.
4. Gonçalves G, Frade J, Nascimento MSJ, Mesquita JR, Nunes C. Persistence of rubella and mumps antibodies, following changes in the recommended age for the second dose of MMR vaccine in Portugal. Epidemiology and Infection. 2016;144(15):3139-47.
5. Huang LM, Lin TY, Chiu CH, Chiu NC, Chen PY, Yeh SJ, et al. Concomitant administration of live attenuated Japanese encephalitis chimeric virus vaccine (JE-CV) and measles, mumps, rubella (MMR) vaccine: Randomized study in toddlers in Taiwan. Vaccine. 2014;32(41):5363-9.
6. Kontio M, Jokinen S, Paunio M, Peltola H, Davidkin I. Waning antibody levels and avidity: Implications for MMR vaccine-induced protection. Journal of Infectious Diseases. 2012;206(10):1542-8.
7. Kontio M, Palmu AA, Syrjänen RK, Lahdenkari M, Ruokokoski E, Davidkin I, et al. Similar Antibody Levels in 3-Year-Old Children Vaccinated Against Measles, Mumps, and Rubella at the Age of 12 Months or 18 Months. Journal of Infectious Diseases. 2016;213(12):2005-13.
8. Linder N, Abudi Y, Abdalla W, Badir M, Amitai Y, Samuels J, et al. Effect of season of inoculation on immune response to rubella vaccine in children. Journal of Tropical Pediatrics. 2011;57(4):299-302.
9. McLean HQ, Fiebelkorn AP, Ogee-Nwankwo A, Hao L, Coleman LA, Adebayo A, et al. Rubella virus neutralizing antibody response after a third dose of measles-mumps-rubella vaccine in young adults. Vaccine. 2018;36(38):5732-7.
10. Okafuji T, Okafuji T, Nakayama T. Persistence of immunity acquired after a single dose of rubella vaccine in Japan. Japanese Journal of Infectious Diseases. 2016;69(3):221-3.
11. Paulke-Korinek M, Fischmeister G, Grac A, Rendi-Wagner P, Kundi M, Mohsenzadeh-Rabbani A, et al. Persistence of antibodies in 4-8 year old austrian children after vaccination with hexavalent DTaP-HBV-IPV/Hib and MMR vaccines. Vaccine. 2011;29(32):5130-6.
12. Seagle EE, Bednarczyk RA, Hill T, Fiebelkorn AP, Hickman CJ, Icenogle JP, et al. Measles, mumps, and rubella antibody patterns of persistence and rate of decline following the second dose of the MMR vaccine. Vaccine. 2018;36(6):818-26.
13. Shoho Y, Kimura T, Yanagawa Y, Saito A, Inoue T, Suto C, et al. Vaccination status and antibody titers against rubella and measles among japanese female college students majoring in childcare between 2015 and 2018. Tohoku Journal of Experimental Medicine. 2018;246(2):73-9.

3 Effectiveness of RCV in outbreak settings

Table 6. Effectiveness

Policy question: What is the evidence that rubella vaccination 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[1]	2
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious	0
		Indirectness	Serious[2]	-1
		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			**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]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

[2]Lack of laboratory confirmation

References

1. 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;118(2):301-6.
2. de Valk H., I. R. Epidémie de rubéole: Evaluation de l'efficacité vaccinale sur le terrain, Ardèche, janvier mars 1997. Réseau National de Santé Publique. 1998(Jan):1-52.
3. Furukawa T, Miyata T, Kondo K, Kuno K, Isomura S, Takekoshi T. Rubella vaccination during an epidemic. JAMA. 1970;213(6):987-90.
4. Hahne S, Macey J, van Binnendijk R, Kohl R, Dolman S, van der Veen Y, et al. Rubella outbreak in the Netherlands, 2004-2005: high burden of congenital infection and spread to Canada. Pediatr Infect Dis J. 2009;28(9):795-800.

4 Safety of RCV

Table 7. Safety

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.

References

1. The MMR-161 study group. Immunogenicity and safety of measles-mumps-rubella vaccine at two different potency levels administered to healthy children aged 12–15months: A phase III, randomized, non-inferiority trial. Vaccine. 2018;36(38):5781-8.

2. The MMR-162 study group. Safety and immunogenicity of an upper-range release titer measles-mumps-rubella vaccine in children vaccinated at 12 to 15 months of age: a phase III, randomized study. Human Vaccines and Immunotherapeutics. 2018.
3. Abedi GR, Mutuc JD, Lawler J, Leroy ZC, Hudson JM, Blog DS, et al. Adverse events following a third dose of measles, mumps, and rubella vaccine in a mumps outbreak. Vaccine. 2012;30(49):7052-8.
4. Abu-Elyazeed R, Jennings W, Severance R, Noss M, Caplanusi A, Povey M, et al. Immunogenicity and safety of a second dose of a measles-mumps-rubella vaccine administered to healthy participants 7 years of age or older: A phase III, randomized study. Human Vaccines and Immunotherapeutics. 2018;14(11):2624-31.
5. Ankrah DNA, Darko DM, Sabblah G, Mantel-Teeuwisse A, Leufkens HMG. Reporting of adverse events following immunizations in Ghana–Using disproportionality analysis reporting ratios. Human Vaccines and Immunotherapeutics. 2018;14(1):172-8.
6. Bavdekar A, Oswal J, Ramanan PV, Aundhkar C, Venugopal P, Kapse D, et al. Immunogenicity and safety of measles-mumps-rubella vaccine delivered by disposable-syringe jet injector in India: A randomized, parallel group, non-inferiority trial. Vaccine. 2018;36(9):1220-6.
7. Berry AA, Abu-Elyazeed R, Diaz-Perez C, Mufson MA, Harrison CJ, Leonardi M, et al. Two-year antibody persistence in children vaccinated at 12–15 months with a measles-mumps-rubella virus vaccine without human serum albumin. Human Vaccines and Immunotherapeutics. 2017;13(7):1516-22.
8. Binamer Y. Acute hemorrhagic edema of infancy after MMR vaccine. Annals of Saudi Medicine. 2015;35(3):254-6.
9. Blatter MM, Klein NP, Shepard JS, Leonardi M, Shapiro S, Schear M, et al. Immunogenicity and Safety of two tetravalent (measles, mumps, rubella, varicella) vaccines coadministered with hepatitis a and pneumococcal conjugate vaccines to children twelve to fourteen months of age. Pediatric Infectious Disease Journal. 2012;31(8):e133-e40.
10. Bryant KA, McVernon J, Marchant CD, Nolan T, Marshall GS, Richmond P, et al. Immunogenicity and safety of measles-mumps-rubella and varicella vaccines coadministered with a fourth dose of Haemophilus influenzae type b and Neisseria meningitidis serogroups C and Y-tetanus toxoid conjugate vaccine in toddlers: A pooled analysis of randomized trials. Human Vaccines and Immunotherapeutics. 2012;8(8):1036-41.
11. Carmona A, Miranda M, Barrio F, De Vicente A, Mares J, Muñoz E, et al. Reactogenicity and immunogenicity of combined haemophilus influenzae type B-meningococcal serogroup C conjugate vaccine booster dose coadministered with measles, mumps, and rubella vaccinehib-menc-TT booster with routine MMR vaccine. Pediatric Infectious Disease Journal. 2010;29(3):269-71.
12. Cheng DR, Crawford NW, Hayman M, Buckley C, Buttery JP. Recurrent 6th nerve palsy in a child following different live attenuated vaccines: Case report. BMC Infectious Diseases. 2012;12.
13. Chiu NC, Huang LM, Willemsen A, Bhusal C, Arora AK, Reynoso Mojares Z, et al. Safety and immunogenicity of a meningococcal B recombinant vaccine when administered with routine vaccines to healthy infants in Taiwan: A phase 3, open-label, randomized study. Human Vaccines and Immunotherapeutics. 2018;14(5):1075-83.
14. Clarke E, Saidu Y, Adetifa JU, Adigweme I, Hydara MB, Bashorun AO, et al. Safety and immunogenicity of inactivated poliovirus vaccine when given with measles–rubella combined vaccine and yellow fever vaccine and when given via different administration routes: a phase 4, randomised, non-inferiority trial in The Gambia. The Lancet Global Health. 2016;4(8):e534-e47.
15. Crevat D, Brion JD, Gailhardou S, Laot TM, Capeding MR. First experience of concomitant vaccination against dengue and MMR in toddlers. Pediatric Infectious Disease Journal. 2015;34(8):884-92.
16. Cunha MPL, Dórea JG, Marques RC, Leão RS. Vaccine adverse events reported during the first ten years (1998-2008) after introduction in the state of Rondonia, Brazil. BioMed Research International. 2013;2013.

17. Das PK. Study of adverse events following immunisation with universal and newer vaccines in the Serampore IMA Child Clinic over a period of 7 years. Journal of the Indian Medical Association. 2013;111(4):230-5.
18. de Menezes Martins R, Curran B, Maia MDLS, Ribeiro MDGT, Camacho LAB, da Silva Freire M, et al. Immunogenicity and safety of measles-mumps-rubella vaccine delivered by disposable-syringe jet injector in healthy Brazilian infants: A randomized non-inferiority study. Contemporary Clinical Trials. 2015;41:1-8.
19. Deichmann KA, Ferrera G, Tran C, Thomas S, Eymin C, Baudin M. Immunogenicity and safety of a combined measles, mumps, rubella and varicella live vaccine (ProQuad®) administered concomitantly with a booster dose of a hexavalent vaccine in 12-23-month-old infants. Vaccine. 2015;33(20):2379-86.
20. Díaz-Ortega JL, Bennett JV, Castañeda-Desales D, Quintanilla DMA, Martínez D, Castro JFD. Booster immune response in children 6-7 years of age, randomly assigned to four groups with two MMR vaccines applied by aerosol or by injection. Vaccine. 2014;32(29):3680-6.
21. Durando P, Esposito S, Bona G, Cuccia M, Desole MG, Ferrera G, et al. The immunogenicity and safety of a tetravalent measles-mumps-rubella-varicella vaccine when co-administered with conjugated meningococcal C vaccine to healthy children: A phase IIIb, randomized, multi-center study in Italy. Vaccine. 2016;34(36):4278-84.
22. Ferrera G, Cuccia M, Mereu G, Icardi G, Bona G, Esposito S, et al. Booster vaccination of pre-school children with reduced-antigen-content diphtheria-tetanus-acellular pertussis-inactivated poliovirus vaccine co-administered with measles-mumps-rubella-varicella vaccine: a randomized, controlled trial in children primed according to a 2 + 1 schedule in infancy. Human vaccines & immunotherapeutics. 2012;8(3):355-62.
23. Ferrini W, Aubert V, Balmer A, Munier FL, Abouzeid H. Anterior uveitis and cataract after rubella vaccination: A case report of a 12-month-old girl. Pediatrics. 2013;132(4):e1035-e8.
24. Finale E, Leonardi G, Auletta G, Amadori R, Saglietti C, Pagani L, et al. MMR vaccine in the postpartum does not expose seronegative women to untoward effects. Annali dell'Istituto superiore di sanita. 2017;53(2):152-6.
25. Gál O, Pletz MW, Ianoși ES. Severe pneumococcal pneumonia following Measles- Mumps-Rubella vaccination. Revista Romana de Medicina de Laborator. 2016;24(3):337-42.
26. Gil-Bistes D, Kluger N, Bessis D, Guillot B, Raison-Peyron N. Pityriasis lichenoides chronic after measles-mumps-rubella vaccination. Journal of Dermatology. 2012;39(5):492-3.
27. Gualberto FAS, de Oliveira MI, Alves VAF, Kanamura CT, Rosemberg S, Sato HK, et al. Fulminant encephalitis associated with a vaccine strain of rubella virus. Journal of Clinical Virology. 2013;58(4):737-40.
28. Gunatheesan S, Ferguson J, Moosa Y. Pityriasis lichenoides et varioliformis acuta: A rare association with the measles, mumps and rubella vaccine. Australasian Journal of Dermatology. 2012;53(4):e76-e8.
29. Huang LM, Lee BW, Chan PC, Povey M, Henry O. Immunogenicity and safety of combined measles-mumps-rubella-varicella vaccine using new measles and rubella working seeds in healthy children in Taiwan and Singapore: A phase II, randomized, double-blind trial. Human Vaccines and Immunotherapeutics. 2013;9(6):1308-15.
30. Huang LM, Lin TY, Chiu CH, Chiu NC, Chen PY, Yeh SJ, et al. Concomitant administration of live attenuated Japanese encephalitis chimeric virus vaccine (JE-CV) and measles, mumps, rubella (MMR) vaccine: Randomized study in toddlers in Taiwan. Vaccine. 2014;32(41):5363-9.
31. Kemmeren JM, Van Der Maas NAT, De Melker HE. Parental reports of adverse events following simultaneously given dT-IPV and MMR vaccines in healthy 9-year-old children. European Journal of Pediatrics. 2011;170(3):339-45.
32. Khetsuriani N, Imnadze P, Baidoshvili L, Jabidze L, Tatishili N, Kurtsikashvili G, et al. Impact of unfounded vaccine safety concerns on the nationwide measles-rubella immunization campaign, Georgia, 2008. Vaccine. 2010;28(39):6455-62.

33. Klein NP, Lewis E, Baxter R, Weintraub E, Glanz J, Naleway A, et al. Measles-containing vaccines and febrile seizures in children age 4 to 6 years. Pediatrics. 2012;129(5):809-14.
34. Knuf M, Zepp F, Meyer CU, Habermehl P, Maurer L, Burow HM, et al. Safety, immunogenicity and immediate pain of intramuscular versus subcutaneous administration of a measles-mumps-rubella-varicella vaccine to children aged 11-21 months. European Journal of Pediatrics. 2010;169(8):925-33.
35. Kuniyoshi K, Hatsukawa Y, Kimura S, Fujino T, Ohguro H, Nakai R, et al. Acute bilateral photoreceptor degeneration in an infant after vaccination against measles and rubella. JAMA Ophthalmology. 2017;135(5):478-82.
36. Lalwani S, Chatterjee S, Balasubramanian S, Bavdekar A, Mehta S, Datta S, et al. Immunogenicity and safety of early vaccination with two doses of a combined measles-mumps-rubellavaricella vaccine in healthy Indian children from 9 months of age: A phase III, randomised, non-inferiority trial. BMJ Open. 2015;5(9).
37. Lee H, Kim HW, Cho HK, Park EA, Choi KM, Kim KH. Reappraisal of MMR vaccines currently used in Korea. Pediatrics International. 2011;53(3):374-80.
38. Leonardi M, Bromberg K, Baxter R, Gardner JL, Klopfer S, Nicholson O, et al. Immunogenicity and safety of MMRV and PCV-7 administered concomitantly in healthy children. Pediatrics. 2011;128(6):e1387-e94.
39. Lopes SRC, Perin JLR, Prass TS, Carvalho SMD, Lessa SC, Dórea JG. Adverse events following immunization in Brazil: Age of child and vaccine-associated risk analysis using logistic regression. International Journal of Environmental Research and Public Health. 2018;15(6).
40. Lum LCS, Borja-Tabora CF, Breiman RF, Vesikari T, Sablan BP, Chay OM, et al. Influenza vaccine concurrently administered with a combination measles, mumps, and rubella vaccine to young children. Vaccine. 2010;28(6):1566-74.
41. Manzotti F, Menozzi C, Porta MR, Orsoni JG. Partial third nerve palsy after Measles Mumps Rubella vaccination. Italian journal of pediatrics. 2010;36(1):59.
42. Marlow R, Kuriyakose S, Mesaros N, Han HH, Tomlinson R, Faust SN, et al. A phase III, open-label, randomised multicentre study to evaluate the immunogenicity and safety of a booster dose of two different reduced antigen diphtheria-tetanus-acellular pertussis-polio vaccines, when co-administered with measles-mumps-rubella vaccine in 3 and 4-year-old healthy children in the UK. Vaccine. 2018;36(17):2300-6.
43. Marshall GS, Senders SD, Shepard J, Twiggs JD, Gardner J, Hille D, et al. A double blind, randomized, active controlled study to assess the safety, tolerability and immunogenicity of measles, mumps rubella, and varicella vaccine (MMRV) manufactured using an alternative process. Human Vaccines and Immunotherapeutics. 2016;12(8):2188-96.
44. Matos dos Santos E, Noronha TG, Alves IS, Cruz RLS, Ferroco CLV, Brum RC, et al. Immunogenicity and safety of the combined vaccine for measles, mumps, and rubella isolated or combined with the varicella component administered at 3-month intervals: randomised study. Memorias do Instituto Oswaldo Cruz. 2019;114:e180517.
45. Meng FY, Sun Y, Shen YG, Pan HF, Tang JH, Wang BB, et al. Safety of measles-containing vaccines in postmarketing surveillance in Anhui, China. PLoS ONE. 2017;12(2).
46. Mentzer D, Meyer H, Keller-Stanislawski B. Safety and tolerability of monovalent measles and combined measles, mumps, rubella, and varicella vaccines Sicherheit und Verträglichkeit von monovalenten Masern- und kombinierten Masern-, Mumps-, Röteln- und Varizellenimpfstoffen. Bundesgesundheitsblatt - Gesundheitsforschung - Gesundheitsschutz. 2013;56(9):1253-9.
47. Mufson MA, Diaz C, Leonardi M, Harrison CJ, Grogg S, Carbayo A, et al. Safety and immunogenicity of human serum albumin-free MMR vaccine in US children aged 12-15 months. Journal of the Pediatric Infectious Diseases Society. 2015;4(4):339-48.
48. Naciri Bennani B, Cheikh Rouhou H, Waton J, Cuny JF, Bassegoda G, Trechot P, et al. Pityriasis rubra pilaris after vaccination Pityriasis rubra pilaire après vaccination. Annales de Dermatologie et de Venereologie. 2011;138(11):753-6.

49. Nascimento Silva JR, Camacho LAB, Siqueira MM, Freire MDS, Castro YP, Maia MDLS, et al. Mutual interference on the immune response to yellow fever vaccine and a combined vaccine against measles, mumps and rubella. Vaccine. 2011;29(37):6327-34.
50. Okazaki N, Takeguchi M, Sonoda K, Handa Y, Kakiuchi T, Miyahara H, et al. Detection of platelet-binding anti-measles and anti-rubella virus IgG antibodies in infants with vaccine-induced thrombocytopenic purpura. Vaccine. 2011;29(31):4878-80.
51. Owatanapanich S, Wanlapakorn N, Tangsiri R, Poovorawan Y. Measles-mumps-rubella vaccination induced thrombocytopenia: a case report and review of the literature. The Southeast Asian journal of tropical medicine and public health. 2014;45(5):1053-7.
52. Pérez-Vilar S, Gutiérrez-Gimeno MV, Rodríguez-Galán MA, Díez-Domingo J, Puig-Barberà J, Gomar-Fayos J, et al. Suspected adverse events to measles, mumps and rubella vaccine reported to the Community of Valencia Pharmacovigilance Centre Sospecha de reacciones adversas a la vacuna triple vírica notificadas al Centro de Farmacovigilancia de la Comunidad Valenciana. Anales de Pediatria. 2013;78(5):297-302.
53. Pina LM, Bassily E, MacHmer A, Hou V, Reinhardt A. Safety and immunogenicity of a quadrivalent meningococcal polysaccharide diphtheria toxoid conjugate vaccine in infants and toddlers: Three multicenter phase III studies. Pediatric Infectious Disease Journal. 2012;31(11):1173-83.
54. Povey M, Henry O, Riise Bergsaker MA, Chlibek R, Esposito S, Flodmark CE, et al. Protection against varicella with two doses of combined measles-mumps-rubella-varicella vaccine or one dose of monovalent varicella vaccine: 10-year follow-up of a phase 3 multicentre, observer-blind, randomised, controlled trial. The Lancet Infectious Diseases. 2019;19(3):287-97.
55. Reisinger KS, Richardson E, Malacaman EA, Levin MJ, Gardner JL, Wang W, et al. A double-blind, randomized, controlled, multi-center safety and immunogenicity study of a refrigerator-stable formulation of VARIVAX®. Vaccine. 2018.
56. Rinderknecht S, Michaels MG, Blatter M, Gaglani M, Andrews W, Abughali N, et al. Immunogenicity and safety of an inactivated hepatitis A vaccine when coadministered with measles-mumps-rubella and varicella vaccines in children less than 2 years of age. Pediatric Infectious Disease Journal. 2011;30(10):e179-e85.
57. Rüger G, Gabutti G, Rümke H, Rombo L, Bernaola E, Diez-Domingo J, et al. Safety of a 2-dose regimen of a combined measles, mumps, rubella and varicella live vaccine manufactured with recombinant human albumin. Pediatric Infectious Disease Journal. 2012;31(11):1166-72.
58. Rümke HC, Loch HP, Hoppenbrouwers K, Vandermeulen C, Malfroot A, Helm K, et al. Immunogenicity and safety of a measles-mumps-rubella-varicella vaccine following a 4-week or a 12-month interval between two doses. Vaccine. 2011;29(22):3842-9.
59. Sanz PG, Garcia Mendez CV, Cueto AL, Silva VB, Walther JC, Diez RA, et al. Chronic inflammatory demyelinating polyradiculoneuropathy in a patient with systemic lupus erythematosus and good outcome with rituximab treatment. Rheumatology International. 2012;32(12):4061-3.
60. Shuper A. Suspected measles-mumps-rubella vaccine-related encephalitis: Two cases. Scandinavian Journal of Infectious Diseases. 2010;43(1):75-8.
61. Sukumaran L, McNeil MM, Moro PL, Lewis PW, Winiecki SK, Shimabukuro TT. Adverse events following measles, mumps, and rubella vaccine in adults reported to the vaccine adverse event reporting system (VAERS), 2003-2013. Clinical Infectious Diseases. 2015;60(10):e58-e65.
62. Van Der Maas NAT, Woudenberg T, Hahń SJM, De Melker HE. Tolerability of Early Measles-Mumps-Rubella Vaccination in Infants Aged 6-14 Months during a Measles Outbreak in the Netherlands in 2013-2014. Journal of Infectious Diseases. 2016;213(9):1466-71.
63. Verma A, Rastogi R, Srivastava A. Pancreatic pseudocyst after measles, mumps, and rubella vaccination. Turkish Journal of Gastroenterology. 2017;28(2):144-6.
64. Vesikari T, Becker T, Gajdos V, Fiquet A, Thomas S, Richard P, et al. Immunogenicity and safety of a two-dose regimen of a combined measles, mumps, rubella and varicella live vaccine (ProQuad®) in infants from 9 months of age. Vaccine. 2012;30(20):3082-9.

65. Vesikari T, Karvonen A, Bianco V, Van der Wielen M, Miller J. Tetravalent meningococcal serogroups A, C, W-135 and Y conjugate vaccine is well tolerated and immunogenic when co-administered with measles-mumps-rubella-varicella vaccine during the second year of life: An open, randomized controlled trial. Vaccine. 2011;29(25):4274-84.
66. Vesikari T, Karvonen A, Lindblad N, Korhonen T, Lommel P, Willems P, et al. Safety and immunogenicity of a booster dose of the 10-valent pneumococcal nontypeable haemophilus influenzae protein D conjugate vaccine coadministered with measles-mumps-rubella-varicella vaccine in children aged 12 to 16 months. Pediatric Infectious Disease Journal. 2010;29(6):e47-e56.
67. Wiedmann RT, Reisinger KS, Hartzel J, Malacaman E, Senders SD, Giacoletti KED, et al. M-M-R®II manufactured using recombinant human albumin (rHA) and M-M-R®II manufactured using human serum albumin (HSA) exhibit similar safety and immunogenicity profiles when administered as a 2-dose regimen to healthy children. Vaccine. 2015;33(18):2132-40.
68. Woo EJ, Winiecki SK, Arya D, Beeler J. Adverse events after MMR or MMRV vaccine in infants under nine months old. Pediatric Infectious Disease Journal. 2016;35(8):e253-e7.
69. Yetman RJ, Shepard JS, Duke A, Stek JE, Petrecz M, Klopfer SO, et al. Concomitant administration of hepatitis A vaccine with measles/mumps/ rubella/varicella and pneumococcal vaccines in healthy 12- to 23-month-old children. Human Vaccines and Immunotherapeutics. 2013;9(8):1691-7.
70. Yu AM, Ito S, Leibson T, Lavi S, Fu LW, Weinstein M, et al. Pediatric Wells syndrome (eosinophilic cellulitis) after vaccination: A case report and review of the literature. Pediatric Dermatology. 2018;35(5):e262-e4.
71. Yurdakök K, Bakir M, Ince T, Yalçin S, Özmert E, Soysal A, et al. Immunogenicity and safety of an inactivated hepatitis A vaccine given with measles-mumps-rubella vaccine to 12-13 month old Turkish children. Journal of Vaccines and Vaccination. 2012;3(5).

Table 8. Safety of RCV in pregnancy

Policy question: What is the evidence on the risk of serious adverse events (including CRS) when RCV is administered in pregnancy?				
			Rating	Adjustment of score
Quality assessment	No of studies/Starting score		2 follow-up studies (observational), 1 passive surveillance study	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	No	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.

References

1. Castillo-Solórzano C, Reef SE, Morice A, Vascones N, Chevez AE, Castalia-Soares R, et al. Rubella vaccination of unknowingly pregnant women during mass campaigns for rubella and congenital rubella syndrome elimination, the Americas 2001-2008. Journal of Infectious Diseases. 2011;204(SUPPL. 2):S713-S7.
2. Ergenoğlu AM, Yeniel AÖ, Yildinm N, Kazandi M, Akercan F, Sağol S. Rubella vaccination during the preconception period or in pregnancy and perinatal and fetal outcomes. Turkish Journal of Pediatrics. 2012;54(3):230-3.
3. Sukumaran L, McNeil MM, Moro PL, Lewis PW, Winiecki SK, Shimabukuro TT. Adverse events following measles, mumps, and rubella vaccine in adults reported to the vaccine adverse event reporting system (VAERS), 2003-2013. Clinical Infectious Diseases. 2015;60(10):e58-e65.