**Title: Safety profile of rubella vaccine administered to pregnant women: a systematic review of pregnancy related adverse events following immunisation, including congenital rubella syndrome and congenital rubella infection in the foetus or infant**

**Authors**

Punam Mangtani1\*, Stephen JW Evans1, Berit Lange1,3,4, Doris Oberle2, Julianna Smith1, Ursula Drechsel-Baeuerle2, Brigitte Keller-Stanislawski2

\*corresponding author. Email [Punam.Mangtani@lshtm.ac.uk](mailto:Punam.Mangtani@lshtm.ac.uk)

1Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK

2Paul Ehrlich-Institut, Paul-Ehrlich-Straße 51-59, 63225 Langen, Germany

3 Infectious Diseases, Department of Medicine II, Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, Germany

4 Department of Epidemiology, Helmholtz Centre for Infection Research (HZI), Braunschweig, Germany

**Abstract**

**Background:** Data on the safety of inadvertent rubella vaccination in pregnancy is important for rubella vaccination programs aimed at preventing congenital rubella syndrome.

**Methods:** The association between monovalent rubella or combination vaccinations in or shortly before pregnancy and potential harm to the foetus was examined by conducting a systematic review and meta-analysis using fixed effect methods and simulation.

**Results:** Four cohort studies of inadvertently vaccinated and unvaccinated women were found, 15 cohorts of pregnant women who were rubella susceptible at time of inadvertent vaccination and 9 cohort studies with no information on susceptibility and case series. No case of vaccine associated congenital rubella syndrome (CRS) was identified. Cohort studies with an unvaccinated comparison group were limited in number and size, and based on these only a theoretical additional risk of 6 or more cases of CRS per 1000 vaccinated women (0% observed, upper 95% CI 0.6%) could be excluded. Based on cohorts of vaccinated rubella susceptible pregnant women a maximum theoretical risk of 1 CRS case in 1008 vaccinated women (0% observed, upper 95% CI 0.099%) was estimated. Asymptomatic rubella vaccine virus infection of the neonate was alsonoted (fixed effects estimate of risk overall 1.74%, 95% CI 1.21,2.28).

**Conclusion:** There is no evidence that CRS is caused by rubella-containing vaccines but transplacental vaccine virus infection can occur. CRS is effectively prevented by vaccination, thus the risk/benefit balance is unequivocally in favour of vaccination. The data confirm previous recommendations that inadvertent vaccination during pregnancy is not an indication for termination of pregnancy.

**Key words (max 6 words): rubella containing vaccine; adverse events following immunisation; vaccine safety; pregnancy; congenital rubella syndrome; congenital rubella infection**

**Highlights**

* **The safety of inadvertent rubella vaccination in pregnancy is assessed**
* **Evidence is limited, often with no unvaccinated comparison group in registers**
* **No vaccine associated congenital rubella syndrome cases were identified but rubella infection does occur**
* **No change to policy to avoid pregnancy for one month after vaccination is suggested**
* **Inadvertent rubella vaccination in pregnancy is not an indication for abortion**

**Background**

Information on vaccine safety in pregnancy has gained more urgency with the increasing scope for and further development of vaccine programmes to directly protect pregnant women and/or new borns. Data are limited by the exclusion of pregnant women in clinical trials of most vaccines prior to marketing authorisation. While inactivated vaccines are generally thought to be safe when used in pregnancy[[1](#_ENREF_1)], the safety of some live attenuated vaccines is less certain because transplacental vaccine virus infection of the foetus is a potential risk. Live attenuated vaccines are usually contra-indicated in pregnancy based on the precautionary principle. We examined the safety profile of rubella monovalent and combination vaccines in women inadvertently vaccinated a few weeks before conception and in the first three months of pregnancy.

Rubella vaccine is a highly effective live attenuated vaccine used to prevent foetal death or congenital rubella syndrome (CRS) which can occur when a susceptible (non-immune) pregnant woman is infected with the rubella wild virus. This risk of transmission of rubella infection to the foetus during the first 10 weeks of pregnancy is as high as 90 % and declines thereafter [[2](#_ENREF_2),[3](#_ENREF_3)]. CRS is classically defined as one or more of deafness, heart defects, or cataracts with evidence of rubella infection. Other manifestations such as hepatosplenomegaly and learning difficulties can also occur[[4](#_ENREF_4),[5](#_ENREF_5)]. Rubella vaccines were introduced in the late 1960s leading to a large decrease in the incidence of CRS that, prior to mass vaccination, ranged from 10 to 400 per 100,000 live births during epidemic periods[[6](#_ENREF_6)]. Rubella vaccination is delivered in many countries via childhood vaccination programmes with combined vaccines that contain live attenuated measles and mumps viruses; or rubella containing vaccination is offered to school-aged children who are moving into child-bearing age together with vaccination of rubella susceptible adult women[[4](#_ENREF_4)]. However, due to variations in levels of vaccine coverage or a lack of vaccine recommendations, rubella virus is still circulating in many regions of the world and cases of CRS are still being reported[[7](#_ENREF_7),[8](#_ENREF_8)] .

Based on the known risk of wild-type rubella infections and congenital disease during pregnancy and reports that rubella vaccine virus can cross the placenta[[9](#_ENREF_9)] , pregnancy has been an exclusion criterion for rubella vaccination; with advice if vaccinated to avoid pregnancy for a month as a precautionary measure[[10](#_ENREF_10)] [[11](#_ENREF_11)]. However there is no evidence of foetal damage by rubella vaccine, and inadvertent administration in the month before pregnancy or in the early stages of pregnancy is not considered an indication for termination of pregnancy[[4](#_ENREF_4),[10](#_ENREF_10),[12](#_ENREF_12)].

Ongoing pregnancy registers and other safety monitoring systems have been in place for many years, with surveillance standards for CRS recently updated [[13](#_ENREF_13)]. An up-to-date summary of the data available from these systems will help inform both national advisory groups and other agencies on use of MR/ MMR vaccines in measles or rubella outbreaks as well as support current advice and information on safety if identified rubella susceptible women are inadvertently vaccinated when pregnant.

This paper reports a systematic review of the literature to assess the risk of pregnancy related adverse events following rubella vaccination shortly before or during pregnancy.

# Methods

A protocol for the review was pre-specified and registered on PROSPERO[[14](#_ENREF_14)]. The search was designed to be as sensitive as possible. Both published and unpublished reports were considered. All types of studies were eligible i.e. from randomised control trials through to case series and signal detection reports.

The participants were women who were pregnant, or conceived within 3 months of receiving the rubella vaccination, as well as their children. The WHO Strategic Advisory Group of Experts shortened its recommended period to avoid pregnancy after receipt of rubella-containing vaccine from 3 months to 28 days in 2000 [[11](#_ENREF_11)] as did the US Advisory Committee for Immunization Practices (ACIP) in 2001[[10](#_ENREF_10)] and was changed subsequently in many countries. Most studies were conducted prior to the shortening of the recommended period i.e. safety was assessed if given within 3 months before pregnancy and so were included in this review. To be included, studies also had to explicitly state that the intervention, rubella vaccine (alone, or as part of a combined vaccine containing also measles, mumps and varicella vaccine virus strains) was administered to women during the specified window of pregnancy or pre-conception. This review is primarily concerned with the following outcome measures: congenital rubella syndrome (CRS), congenital rubella infection (CRI), and where study design allowed, foetal deaths (still births and spontaneous abortions) and prematurity. CRS and CRI are measured in accordance with the CDC and WHO classification[[13](#_ENREF_13),[15](#_ENREF_15)]. Intrauterine rubella infections that have been identified when products of conception are tested are not part of the case definition for CRS and are considered separately from CRS, CRI and foetal deaths. All virological tests are noted as used in the studies.

Studies were identified using a number of information sources. Searches were made of electronic databases, public health agencies’ websites as well as consultation with experts in the field. Articles from scanning reference lists of papers and reviews were also included. No limits were applied for language and non-English papers were translated . The search was applied in MEDLINE (Ovid MEDLINE(R), Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid OLDMEDLINE(R) 1946 to Present), the Cochrane Controlled Trials Register, EMBASE (Embase Classic+Embase 1947 to 2013 Week 37), BIOSIS, LILACS (1982 to present), Africa-Wide, CINAHL plus, Web of Science, and Current Contents. The last search was conducted on all databases on August 1st 2018

The following terms were used to search all databases: Pregnant women, Maternal, Mother\*, Antenatal, Gestation\*, Gravid\*, Female adolescent\*, Prenatal care, Preconception\*, Perinatal, Maternal health, Pregnancy, Vaccin\*, Immuni\*, Inoculat\*, Trivalen\*, Combin\*, Simultan\*, Tripl\*, Trebl\*, Rubella, German measles, MMR\*, Triviraten Berna, Priorix, Trimovax, Morupar and MERUVAX. MeSH terms varied by database (see appendix 2 for an example of a full search in Medline).

# Titles and abstracts were screened independently by two people (BL and JS) to select studies from all of the references retrieved during the searches. Only references that both reviewers agreed were not relevant to the review were excluded. Full texts for the remaining references were obtained and eligibility also checked independently by two individuals according to the following criteria: the paper was a primary study and rubella vaccination was used in the study administered to pregnant women (or to women up to 3 months before pregnancy) and the risk of adverse events in these vaccinated pregnant women was examined.

The review included both the current RA 27/3 human diploid fibroblast vaccine strain as well as rubella vaccine strains used in the past, such as HPV-77 strain grown in duck embryo cells, HPV-77 strain grown in dog kidney cells and Cendehill strain grown in rabbit kidney cells which were licensed in the USA in 1969 and 1970.

Data were extracted for each of the eligible studies using standardised forms by one person and cross-checked by another. Disagreements were resolved by consensus. The following data items were summarised when available: study design and recruitment methodology; study setting; baseline population characteristics; type of vaccine administered; length and nature of follow up; nature and number of adverse events recorded.

The risk of bias for controlled studies was assessed separately by two individuals and agreement then reached if required by a third person. The scope for confounding, selection bias, missing data, as well as information and reporting bias was assessed[[16](#_ENREF_16)]. For pregnancy exposure registry studies, where there are no unvaccinated control groups, a more limited assessment only was possible namely, scope for selection bias and ability to exclude mother-child pairs that are not susceptible to vaccine virus infection because the mother had already been infected prior to vaccination (i.e. the foetus is protected against vaccine virus by natural maternal antibodies).

# Methods of analysis

In addition to a narrative synthesis of the study data, sufficient data from controlled studies were available to calculate the difference in the risk and 95% CIs of some outcomes in vaccinated compared to unvaccinated women. We did this based on the actual reported counts. The overall risk difference for each outcome was combined across studies using Mantel-Haenszel (M-H) fixed effects meta-analysis. Meta-analysis of the risk differences is appropriate when comparisons have zero counts in one arm of all studies or zeroes in both arms. Relative measures such as odds ratios cannot be estimated in these circumstances. Thus for controlled studies with zero outcome events e.g. CRS, we were able to calculate the maximum theoretical extra risk of CRS that could be excluded with an error of 5% by taking the upper bound of the 95% CI of the combined risk difference.

Risk of congenital rubella infection was estimated based on pregnancy exposure registry cohort studies where only data on those susceptible and vaccinated in pregnancy were available and CRI events had occurred. There were no comparison unvaccinated groups. We estimated the overall exact combined risks of CRI using fixed effects meta-analysis for proportions. Results are given overall and where only RA 77/3 vaccine was used. For CRS, as there were no events, we used simulation (using all studies irrespective of vaccine used) to obtain the risk that could be excluded based on the upper 95% CI. We simulated the count of the number of cases that would be seen in each of the studies using different fixed rates, and regarded the upper confidence limit as that rate which gave 95% of the simulations resulting in zero events. We also pooled all the studies since a crude pooling in these circumstances will lead to the same upper limit for a 95% confidence interval. The initial rate chosen was the upper 95% confidence interval derived from the pooled data using an exact binomial confidence interval. We then assessed how often we might find zero cases across all the studies, with the total number of women observed. To do so we carried out several thousands of simulations, varying the fixed rate around the rate derived from the upper limit for the pooled data, to obtain the proportion of the simulations that would result in zero cases across all studies. The final value of the upper 95% CI is taken as the fixed rate that gave 95% of the simulations having zero cases across all studies. All analyses were carried out in STATA 13[[17](#_ENREF_17)].

# Results

# A total of 6360 records after de-duplication were retrieved from database searches and two more from checking references from reviews and included studies (figure 1). After independent screening by two individuals, 406 were identified as potentially relevant for whichfull texts were obtained . After two separate assessments and agreement on eligibility of the full texts found, the following were included: 4 cohort studies with an unvaccinated comparison group, 17 vaccinated pregnancy exposure registries of vaccinated pregnancy cohorts with information on those susceptible to rubella when vaccinated, 9 vaccinated pregnancy cohorts with no information on prior susceptibility, 8 case series or case reports and 4 studies on volunteer women vaccinated before a therapeutic induced abortion where permission to test products of conception were obtained.

# Cohort studies with an unvaccinated comparison group

# Of the four vaccinated pregnancy cohorts with comparable unvaccinated pregnant women followed up, two were a result of the mass MR vaccination programme in Iran in 2003 offered to all males and females aged 5 to 25 years old (table 1)[[18](#_ENREF_18),[19](#_ENREF_19)]. These were from different major hospitals serving different regions, thus were assumed not to be duplicated reports on the same subjects. Subjects were passively recruited having been advised to attend if they became pregnant soon after vaccination[[20](#_ENREF_20)]. The comparison pregnancy cohorts were unvaccinated pregnant women or women vaccinated more than three months before conception [[18](#_ENREF_18)]. The vaccine used was the current RA27/3 vaccine In both Iranian studies and a third from Canada[[21](#_ENREF_21)]. Information was not available on prior natural or vaccine derived immunity and hence whether they were at risk of vaccine related CRI. An assumption was that the proportion with pre-existing immunity was the same in those pregnant soon after vaccination and the comparison group. However data were not available to check this assumption. The potential for a serious risk of bias from confounding was thus judged possible (table 5). All live born infants were clinically assessed after birth for CRS. No cases of CRS were identified. There were no tests for CRI carried out. Duration of follow-up of infants varied thus we judged there was also moderate scope for bias from missing data if CRS was initially undetected or if some malformations due to CRS might have become apparent in later life.

# The forth cohort study from the US[[22](#_ENREF_22)] was with the Cendehill or the HPV-77 vaccine. It is the only one of the four that had information on prior susceptibility to rubella in 9/60 of the vaccinated pregnant women included in the study. No such information was available on the unvaccinated women. Out of the nine women assessed as rubella susceptible before vaccination, one intra-uterine infection was documented. This was after undergoing a therapeutic abortion. The infection was attributed to vaccine virus based on characteristics of the virological isolate from culture of the products of conception (table 1).

# Combining results across all four studies, the risk difference for CRS in infants of vaccinated (n=634) compared to unvaccinated (n=664) women gave an upper 95% CI of 6 per 1000 (table 2); i.e. given the current evidence in just these four studies of no cases of CRS, it is unlikely, based on a 95% interval, that six or more additional cases of CRS per 1000 vaccinated women would be seen. Restricting the studies to three only using the currently available RA27/3 vaccines did not change the combined estimate (table 2). There was no evidence of an additional risk of other adverse outcomes combined across studies that collected information on: other congenital malformations; spontaneous abortions; still births; neonatal deaths or pre-term delivery (table 2).

Cohorts of vaccinated women who were susceptible for rubella

More information on risk of CRS as well as CRI was available from the 17 vaccinated pregnancy cohorts found. Pregnant women susceptible to rubella at the time of vaccination were identified, based either on negative tests for both rubella (Ig) M and IgG antibodies or positive tests after birth for IgM, which signalled a new infection (Table 3). No case of CRS due to the vaccine virus was noted in any of the studies, however all the studies had varying rates of follow up and losses to follow up with the attendant potential for underestimating risk of the outcome (appendix table 5). Most of the data are from a multicentre study summarized by Castillo-Solorzano[[23](#_ENREF_23)]. It included Brazil where over 80% of the total number of susceptible pregnant women come from (see table 3). One infant was diagnosed with CRS due to wild type rubella virus based on PCR tests[[24](#_ENREF_24)]. The combined risk of CRS across all these studies of susceptible vaccinated women, using simulation as described above, gave an estimated upper bound of the 95% confidence level of 1 in 1008 i.e. a maximum theoretical risk of CRS of 0.099% in susceptible women vaccinated with any rubella vaccine.

The risk of congenital rubella infection (CRI) was also examined in subgroups of some of the vaccinated susceptible pregnancy cohorts (table 3). The risk of CRI varied among studies and vaccine strains e.g. from 3/61 (4.1%) in susceptible women in the US from 1971-1979 inadvertently vaccinated with the Cendehill rubella vaccine[[25](#_ENREF_25)], 3.54 % in the individual pooling analysis of the cohort studies from Latin America and 1.95 % in the ACIP analysis in studies with the RA 27/3 strain (table 4). The studies by Lina[[26](#_ENREF_26)] and Reyna[[27](#_ENREF_27)] had markedly lower rates than any of the other studies and the reasons for this is not known. This led to a statistically significant heterogeneity. If these two studies were omitted then the heterogeneity was entirely removed (see supplementary Figure 1). The point estimate of CRI was also rather higher and the confidence interval was wider. Using fixed effects meta-analysis of proportions, the combined risk of CRI, irrespective of the rubella vaccine strain administered, was 1.74%, (95% CI 1.21 to 2.28)) (figure 2a) and was similar when limited to studies on the RA 27/3 vaccine only (appendix figure 2). Using a random effects model (which has been criticised by some meta-analysts[[28](#_ENREF_28)]) gives more weight to small studies and leads to a slightly higher estimate and upper confidence limit, 2.11% (95%CI 0.37 to 3.85) (figure 2b). There was a lack of comparable unvaccinated rubella susceptible women to compare risk from vaccination compared to risk from natural infection. As virological tests to exclude vaccine virus transmission to the infant were absent, the conservative assumption was that exposure to vaccine virus strain from maternal vaccination was likely to be associated with neonatal infection if any anti-rubella IgM was detected.

These studies focussed on risk of CRS and CRI. The comparison of risk of other adverse pregnancy outcomes was not possible given the lack of an unvaccinated control group.

Vaccinated cohorts with unknown susceptibility

All available vaccinated pregnancy cohort studies without information on prior immunity are summarised in appendix table 1. These studies have to be interpreted with caution due to small sample sizes and multiple sources of bias (particularly information and misclassification bias) and the absence of unvaccinated comparison groups. Larson 1971[[29](#_ENREF_29)] followed up nine women with unknown susceptibility, eight of whom had a termination of pregnancy and one a normal birth. Rubella vaccine virus infection of products of conception (placenta and lining of the uterus) was suspected in two out of nine women. These two women were vaccinated with HPV-77. The experimental in-vitro marker tests used and available at that time suggested vaccine virus strain and not wild type virus. No virus was detected in foetal tissue[[29](#_ENREF_29)]. In another vaccine pregnancy follow up study of 19 women (17 with unknown susceptibility) by Fleet in 1974[[30](#_ENREF_30)], rubella virus was isolated from the eye of a aborted foetus of a 25 year-old woman with an equivocal anti-rubella antibody titre prior to vaccination. She had been immunized with HPV77 rubella vaccine strain approximately 7 weeks prior to conception (i.e. outside of the currently recognised window of potential risk of transmission to the foetus) and had an induced abortion at 13 weeks of gestation. Histopathological examination of the eye tissue was considered by the authors consistent with congenital rubella infection of the eye, and electron micrographs demonstrated the presence of virus-like particles. In-vitro cell culture characteristics of the eye specimens appeared similar to HPV77 vaccine virus strain characteristics. Thus, the authors suggested vaccine strain rubella was isolated from the eye of the foetus. Of the additional 9 infants followed up (for 3 to 11 months), all had normal development with no evidence of viral infection nor were there any infections identified in the products of conception of the other pregnancies that had induced abortions [[30](#_ENREF_30)].

Case reports

The published case reports are summarised in appendix table 2. Such reports by their nature are events not linked to any population group nor do they allow for comparisons to be made. Ascertainment is also biased to unusual events that are published. Phillips et al reported rubella infection in products of conception of a vaccinated susceptible woman identified based on in-vitro interferon assays and lymphocytic assays suggestive of vaccine virus[[31](#_ENREF_31)] . In another case report by Columbo et al of an infant with suspected CRS [[32](#_ENREF_32)] , virological tests had not been conducted and thus confirmation of vaccine virus infection was missing. In both case reports the vaccine type was not noted. The only PCR confirmed in-utero infection was reported by Hofmann et al[[33](#_ENREF_33)] in a rubella-susceptible woman who was vaccinated with the RA27/3 rubella vaccine at approximately 3 weeks of gestational age. She gave birth to a term infant without indication of CRS up to 14 months of follow-up. Persistence of foetal anti-rubella IgM and vaccine strain virus shedding based on PCR testing indicated long-term foetal infection as a consequence of maternal immunization with the RA27/3 vaccine strain. In this case the virus shedding ceased by five months of age[[33](#_ENREF_33)].

Volunteer studies

In some studies conducted in the late 1960s and early 1970s, rubella vaccination was given to volunteers scheduled for induced abortions (summarised in appendix table 3). Information on susceptibility to rubella infection was incomplete in these intervention studies and there were no control groups. In two of the four studies the occurrence of transmission of rubella virus to the foetus in rubella susceptible women was noted. In the study by Bolognese et al , CRI was assumed to be caused by a wild type rubella strain based on comparison of serological responses in rabbits injected with the isolated virus and the Freedman “wild” strain[[34](#_ENREF_34)] . In the study by Vaheri in which various specimens of placenta and foetus were tested, rubella virus was isolated and assumed by the authors to reflect vaccine virus strain, although no virological tests were carried out[[35](#_ENREF_35)] .

# Discussion

This systematic review found several studies that evaluated the incidence of congenital rubella syndrome (CRS) following inadvertent vaccination of pregnant women through rubella registries in the US as well as in several European countries and subsequently in the setting of large mass vaccination campaigns in Latin America and Iran. No case of confirmed CRS was identified. Based on the number of susceptible women exposed to rubella vaccination shortly prior or during early pregnancy we estimated a maximum theoretical risk of CRS, of 0.099%. With zero cases, i.e. no evidence of disease in the presence of non-zero background rates, our upper bounds are likely to be very conservative, we can be fairly reassured that if there is an increased risk it would be less than 0.099% based on these data only. In addition, a lack of spontaneous reports of CRS from passive surveillance of situations where inadvertent rubella vaccination has occurred in pregnancy provides supportive information on the safety of rubella vaccination shortly prior to or during early pregnancy. Vertical asymptomatic transmission of attenuated rubella vaccine virus infection, documented through nucleotide sequence analysis and serological testing (e.g. anti-rubella IgM antibody from cord blood/serum) of neonates, does however occur, which might be seen to support the theoretical rationale for the contraindication of this vaccine in pregnancy.

All types of studies were considered and the quality of these studies carefully assessed. For the four controlled studies, a comparison group of unvaccinated women were included allowing the ability to assess extra risk of an adverse pregnancy outcome on top of any baseline risk but numbers were small. It should be noted that the extra risk may vary depending on the baseline risk which might differ depending on the endemic situation. It was not possible to control for this. We pooled across studies where there were zero events, assuming the excess risk was similar across settings.

A more important source of bias was the missing information on the proportion of women already immune before vaccination. Uncontrolled confounding by differing levels of susceptibility prior to vaccination compared to the non-vaccinated group cannot be excluded with certainty. For the two studies in the US and Canada, the unvaccinated comparison groups were from the same health care services. Health care seeking behaviour could be considered comparable among both groups in contrast to both studies from Iran where no details on the mode of recruitment or the proportion vaccinated more than three months before conception in the comparison group were available. The preponderance of data from Brazil and the fact that data are not available from many countries limits the certainty with which the findings can be extrapolated to every country, but there is no known reason why these findings should differ systematically in different countries.

The pregnancy registers with information on prior susceptibility allow a better assessment of the absolute risk. However, follow-up of offspring may not have been long enough to pick up late manifestations of CRS, though those studies where CRI was detected did not reveal any case of CRS during the follow-up period in those infants.

We were also able from these studies to obtain an upper confidence interval of the absolute risk of CRS based on the proportion of simulations where a count of zero was obtained across all the pregnancy exposure cohort studies. This was by assuming the number of cases that might be seen in each of the studies was around the upper limit of the pooled data across all the studies. The value would be an underestimate if ascertainment in the large study (the Castillo-Solorzano multicentre study[[23](#_ENREF_23)]) was poorer than that in the other and smaller studies. This is unlikely given each country in the multicentre study used a standard protocol for testing and following up women who were inadvertently vaccinated in pregnancy during mass vaccination campaigns. These campaigns also included sensitisation of women offered the vaccine and support given to the obstetric services. Women were asked if they were pregnant, if so they were not vaccinated. If not pregnant and vaccinated they were instructed about avoiding pregnancy for one month (initially three months)[[36](#_ENREF_36)]. Thus they were more likely to attend obstetric services if they did become pregnant after rubella vaccination, resulting in higher ascertainment. We also included all studies irrespective of vaccines used in the simulation to maximise the sample size. If anything the earlier vaccines have a higher risk of transmission to the fetus and would act to increase the theoretical risk of CRS.

It was not possible to separate those who were vaccinated within one month or three months of pregnancy especially in the older studies, hence some subjects may not have been truly exposed to vaccine virus in pregnancy. Thus the pooled measures of excess or absolute risk given here should if anything be considered underestimates.

Other and much less robust data were available from case reports and case series e.g. where rubella virus has been isolated from the products of conception, obtained from women, who had been inadvertently vaccinated with rubella vaccine during pregnancy or, at that point in time, volunteered to have the vaccination when they were scheduled for an induced abortion. These latter studies were in women who would have been several weeks into their pregnancies and hence less at risk than those vaccinated peri-conceptually, thus these studies, if they contribute anything, would underestimate any risk. Published in the late 1960s and early 1970s, in these and other case reports or case series, a presumptive identification of vaccine strain, as opposed to wild-type rubella virus was often made by in-vitro tests including comparing the growth characteristics of the isolate to the reference strains in cell culture. The assays used thus had inherent limitations and were relatively non-specific. The latter would have acted to misclassify rubella virus detected in the foetus as either vaccine virus or wild-type virus. Definitive identification of the vaccine strain by nucleotide sequencing was not possible at that time.

No individual cases of definitive vaccine-virus confirmed CRS following inadvertent vaccination of pregnant women have been reported in the published literature. One case report investigation using PCR testing noted shedding of the vaccine virus for up to five months after birth but there were no signs of CRS. Another case report was considered by the authors to be consistent with congenital rubella infection of the eye of the foetus after an induced abortion at 13 weeks where the woman had been vaccinated with the HPV77 vaccine 7 weeks before conception[[30](#_ENREF_30),[31](#_ENREF_31)]. The report was initially one of the reasons for the previous advice not to become pregnant within 3 months after vaccination but the timing of vaccination is now considered not plausible to result in foetal infection. Studies from Enders et al and Katow showed no rubella wild virus transmission across the placenta when natural infection of the mother occurred prior to gestation[[37](#_ENREF_37)] [[38](#_ENREF_38)]. Based on these and other data the Who in 200, the US ACIP in 2001 and others also revised their previous statement and recommended a shortened window of susceptibility of 28 days before conception[[10](#_ENREF_10),[11](#_ENREF_11)].

Other pregnancy outcomes such as other congenital malformations, spontaneous abortions, still births, neonatal deaths or pre-term delivery have been investigated in the controlled cohort studies. There was no evidence of an extra risk although the sample sizes were small.

Although no limits were applied for language we found only one case report of the Japanese vaccine strain and none for the Chinese BRD2 strain. Further searches in literature databases that specifically cover studies in those settings were beyond the scope of this study but their inclusion in future reviews may be helpful.

In summary from the evidence noted here no change is indicated in the current advice both that rubella vaccination in pregnancy should be avoided as a precaution, and that termination of pregnancy is however not advised if inadvertent vaccination in pregnancy does occur[[4](#_ENREF_4),[10](#_ENREF_10)]. No cases of CRS were observed with rubella vaccination but asymptomatic vaccine virus infection of the infant can occur. Vaccine programmes targeting women at childbearing age especially with live vaccines should have pregnancy surveillance programmes in place that also allows comparison between vaccinated and unvaccinated pregnant women.

Funding

This work was part funded by a small grant from The World Health Organisation’s Global Advisory Committee on Vaccine Safety, Geneva. The research did not receive any other specific grants from funding agencies, the public, commercial or not –for-profit sectors.

**References**

1 Keller-Stanislawski, B., Englund, J.A., Kang, G., Mangtani, P., Neuzil, K., Nohynek, H. *et al.* Safety of immunization during pregnancy: a review of the evidence of selected inactivated and live attenuated vaccines. *Vaccine* 2014, **32**(52), 7057-7064.

2 Miller, E., Cradock-Watson, J.E. & Pollock, T.M. Consequences of confirmed maternal rubella at successive stages of pregnancy. *Lancet* 1982, **2**(8302), 781-784.

3 Andrade, J.Q., Bunduki, V., Curti, S.P., Figueiredo, C.A., de Oliveira, M.I. & Zugaib, M. Rubella in pregnancy: intrauterine transmission and perinatal outcome during a Brazilian epidemic. *J Clin Virol* 2006, **35**(3), 285-291.

4 Rubella vaccines: WHO position paper. *Wkly Epidemiol Rec* 2011, **86**(29), 301-316.

5 Centers for Disease, C. & Prevention. Progress toward control of rubella and prevention of congenital rubella syndrome --- worldwide, 2009. *MMWR - Morbidity & Mortality Weekly Report* 2010, **59**(40), 1307-1310.

6 Cutts, F.T., Robertson, S.E., Diaz-Ortega, J.L. & Samuel, R. Control of rubella and congenital rubella syndrome (CRS) in developing countries, Part 1: Burden of disease from CRS. *Bull WHO* 1997, **75**(1), 55-68.

7 Lambert, N., Strebel, P., Orenstein, W., Icenogle, J. & Poland, G.A. Rubella. *Lancet* 2015.

8 Dabbagh, A., Laws, R.L., Steulet, C., Dumolard, L., Mulders, M.N., Kretsinger, K. *et al.* Progress Toward Regional Measles Elimination - Worldwide, 2000-2017. *MMWR Morb Mortal Wkly Rep* 2018, **67**(47), 1323-1329.

9 Preblud, S.R., Stetler, H.C., Frank, J.A., Jr., Greaves, W.L., Hinman, A.R. & Herrmann, K.L. Fetal risk associated with rubella vaccine. *JAMA* 1981, **246**(13), 1413-1417.

10 Centers for Disease, C. & Prevention. Revised ACIP recommendation for avoiding pregnancy after receiving a rubella-containing vaccine. *MMWR - Morbidity & Mortality Weekly Report* 2001, **50**(49), 1117.

11 Rubella vaccines. WHO position paper. *Weekly Epidemiological Record* 2000, **75**(20), 161-172.

12 Tookey, P.A., Jones, G., Miller, B.H. & Peckham, C.S. Rubella vaccination in pregnancy. *CDR (London: England Review)* 1991, **1**(8), R86-88.

13 Congenital Rubella Syndrome in *Vaccine-preventable diseases. Surveillance standards* WHO, Geneva, 2018.

14 Mangtani P, S.J., Lange B, Drechsel-Baeuerle U, Keller-Stanislawski B. Safety profile of rubella vaccine administered to pregnant women: a systematic review of adverse events in the mother, infant or foetus. in [*http://www.crd.york.ac.uk/PROSPERO/display\_record.asp?ID=CRD42013006129*](http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42013006129)PROSPERO 2013 CRD42013006129 edn Prospero, University of York, 2013.

15 McLean H, R.S., Abernathy E,Icenogle J, Wallace,G. Chapter 15: Congenital Rubella Syndrome. in *Manual for the Surveillance of Vaccine-Preventable Diseases* 5th edn Centers for Disease Control Atlanta,Georgia,USA, 2012.

16 Sterne JAC, H.J., Reeves BC on behalf of the development group for ACROBATNRSI. A Cochrane Risk Of Bias Assessment Tool: for Non-Randomized Studies of Interventions (ACROBATNRSI), Version 1.0.0, 24 September 2014. Available from <http://www.bristol.ac.uk/population-health-sciences/centres/cresyda/barr/riskofbias/robins-i/acrobat-nrsi/>

[accessed {05/04/2019}] 24 September 2014 edn Vol. Version 1.0.0, <http://www.riskofbias.info>

17 2013., S. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP. 2013.

18 Namaei, M.H., Ziaee, M. & Naseh, N. Congenital rubella syndrome in infants of women vaccinated during or just before pregnancy with measles-rubella vaccine. *Indian Journal of Medical Research* 2008, **127**(6), 551-554.

19 Shahhosseini, Z., Khani, S. & Abedian kasgary, K. Complications of MR vaccination in pregnant women during mass campaign for measles/rubella vaccination on December 2003 in Iran. *International Journal of Gynecology and Obstetrics* 2009, **107**, S634.

20 Hamkar, R., Jalilvand, S., Abdolbaghi, M.H., Esteghamati, A.R., Hagh-Goo, A., Jelyani, K.N. *et al.* Inadvertent rubella vaccination of pregnant women: evaluation of possible transplacental infection with rubella vaccine. *Vaccine* 2006, **24**(17), 3558-3563.

21 Bar-Oz, B., Levichek, Z., Moretti, M.E., Mah, C., Andreou, S. & Koren, G. Pregnancy outcome following rubella vaccination: a prospective controlled study. *American Journal of Medical Genetics. Part A* 2004, **130A**(1), 52-54.

22 Ebbin, A.J., Wilson, M.G., Chandor, S.B. & Wehrle, P.F. Inadvertent rubella immunization in pregnancy. *American Journal of Obstetrics & Gynecology* 1973, **117**(4), 505-512.

23 Castillo-Solorzano, C., Reef, S.E., Morice, A., Vascones, N., Chevez, A.E., 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**, S713-717.

24 da Silva e Sa, G.R., Camacho, L.A., Stavola, M.S., Lemos, X.R., Basilio de Oliveira, C.A. & Siqueira, M.M. Pregnancy outcomes following rubella vaccination: a prospective study in the state of Rio de Janeiro, Brazil, 2001-2002. *Journal of Infectious Diseases* 2011, **204 Suppl 2**, S722-728.

25 Bart SW, S.H., Preblud SR, Williams NM, Orenstein WA, Bart KJ, Hinman AR, Herrmann KL. & et al. Fetal risk associated with rubella vaccine: an update. *Reviews of Infectious Diseases* 1985, **7**(1), 95-102.

26 Lina, M.D. & María Teresa, E. Seguimiento al estado serológico de mujeres embarazadas que recibieron inadvertidamente la vacuna antirrubeólica, Bogotá, Colombia, 2005-2006. *Investig. Andina* 2008, **10**(17), 77-84.

27 Reyna J, H.I., Gomez M, Vidal P, Cruz P, Puente A, Richardson V. Perinatal outcome of inadvertent immunization with the measles-rubella vaccine in pregnant Mexican women during the campaign for the eradication of congenital rubella in 2008. *World Journal of Vaccines* 2011, **1**, 1-4.

28 Thompson, S.G. & Pocock, S.J. Can meta-analyses be trusted? *Lancet* 1991, **338**(8775), 1127-1130.

29 Larson, H.E., Parkman, P.D., Davis, W.J., Hopps, H.E. & Meyer, H.M., Jr. Inadvertent rubella virus vaccination during pregnancy. *New England Journal of Medicine* 1971, **284**(15), 870-873.

30 Fleet, W.F., Jr., Benz, E.W., Jr., Karzon, D.T., Lefkowitz, L.B. & Herrmann, K.L. Fetal consequences of maternal rubella immunization. *JAMA* 1974, **227**(6), 621-627.

31 Phillips, C.A., Maeck, J.V., Rogers, W.A. & Savel, H. Intrauterine rubella infection following immunization with rubella vaccine. *JAMA* 1970, **213**(4), 624-625.

32 Colombo, M.L. & Dogliani, P. A case of rubellar embryopathy due to vaccination with unusual features. [Italian] Embriopatia Rubeolica Da Vaccinazione. Un Caso Clinico Con Peculiari Caratteristiche. *Minerva Pediatrica* 1976, **28**(39), 2429-2436.

33 Hofmann, J., Kortung, M., Pustowoit, B., Faber, R., Piskazeck, U. & Liebert, U.G. Persistent fetal rubella vaccine virus infection following inadvertent vaccination during early pregnancy. *Journal of Medical Virology* 2000, **61**(1), 155-158.

34 Bolognese, R.J., Corson, S.L., Fuccillo, D.A., Sever, J.L. & Traub, R. Evaluation of possible transplacental infection with rubella vaccination during pregnancy. *American Journal of Obstetrics & Gynecology* 1973, **117**(7), 939-941.

35 Vaheri, A. Undesirable properties of rubella vaccines with special reference to their use in women of fertile age. *Scandinavian Journal of Infectious Diseases* 1972, **6**, Suppl 6:24-27.

36 Soares, R.C., Siqueira, M.M., Toscano, C.M., Maia, M.D.L.S., Flannery, B., Sato, H.K. *et al.* Follow-up study of unknowingly pregnant women vaccinated against rubella in Brazil, 2001-2002. *Journal of Infectious Diseases* 2011, **204**(SUPPL. 2), S729-S736.

37 Enders, G., Nickerl-Pacher, U., Miller, E. & Cradock-Watson, J.E. Outcome of confirmed periconceptional maternal rubella. *Lancet* 1988, **1**(8600), 1445-1447.

38 Katow, S. Rubella virus genome diagnosis during pregnancy and mechanism of congenital rubella. *Intervirology* 1998, **41**(4-5), 163-169.

39 Levichek, Z., Bar-Oz, B., Moretti, M., Mah, C., Andreou, S. & Koren, G. Pregnancy outcome following rubella vaccination: A prospective controlled study. *Clinical Pharmacology & Therapeutics* 2001, **69**(2), P83-P83.

40 Emadi, H., Hajabdolbaghi, M., Rasoolinejad, M., Jafari, S., Khairandish, P., Taheri, L. *et al.* Outcome of pregnancy in pregnant women vaccinated in the mass campaign against measles/rubella in Tehran, Iran. *International Journal of Antimicrobial Agents* 2007, **29**, S288-S289.

41 Anonymous. Leads from the MMWR. Rubella vaccination during pregnancy--United States, 1971-1982. *JAMA* 1983, **250**(11), 1383-1384.

42 Rubella vaccination during pregnancy--United States, 1971-1983. *Mmwr* 1984, **Morbidity and mortality weekly report. 33**(26), 365-368, 373.

43 Rubella vaccination during pregnancy--United States, 1971-1985. *Mmwr* 1986, **Morbidity and mortality weekly report. 35**(17), 275-276, 281-284.

44 Rubella Vaccination During Pregnancy. *Drug Intelligence and Clinical Pharmacy* 1986, **20**, 637-640.

45 Rubella vaccination during pregnancy--United States, 1971-1986. *Mmwr* 1987, **Morbidity and mortality weekly report. 36**(28), 457-461.

46 Rubella vaccination during pregnancy--United States, 1971-1988. *Mmwr* 1989, **Morbidity and mortality weekly report. 38**(17), 289-293.

47 Anonymous. Leads from the MMWR. Rubella vaccination during pregnancy--United States, 1971-1985. *JAMA* 1986, **255**(21), 2867, 2873, 2876.

48 Anonymous. Leads from the MMWR. Rubella vaccination during pregnancy--United States, 1971-1986. *JAMA* 1987, **258**(6), 753, 757.

49 The American College Of, O., Gynecologists, T. & Bulletin Number, a. Rubella and pregnancy. *International Journal of Gynecology and Obstetrics* 1993, **42**(1), 60-66.

50 Anonymous. Leads from the MMWR. Rubella vaccination during pregnancy--United States, 1971-1988. *JAMA* 1989, **261**(23), 3374-3375, 3383.

51 Tookey, P. Pregnancy is contraindication for rubella vaccination still. *BMJ* 2001, **322**(7300), 1489.

52 Sheppard, S., Smithells, R.W., Dickson, A. & Holzel, H. Rubella vaccination and pregnancy: preliminary report of a national survey. *British Medical Journal Clinical Research Ed.* 1986, **292**(6522), 727.

53 Enders, G. Rubella antibody titers in vaccinated and nonvaccinated women and results of vaccination during pregnancy. *Reviews of Infectious Diseases* 1985, **7 Suppl 1**, S103-107.

54 Enders, G. [Accidental rubella vaccination at the time of conception and in early pregnancy]. *Bundesgesundheitsblatt, Gesundheitsforschung, Gesundheitsschutz* 2005, **48**(6), 685-686.

55 Enders, G. [Accidental rubella vaccination in pregnancy]. *Deutsche Medizinische Wochenschrift* 1984, **109**(47), 1806-1809.

56 Badilla, X., Morice, A., Avila-Aguero, M.L., Saenz, E., Cerda, I., Reef, S. *et al.* Fetal risk associated with rubella vaccination during pregnancy. *Pediatric Infectious Disease Journal* 2007, **26**(9), 830-835.

57 Minussi, L., Mohrdieck, R., Bercini, M., Ranieri, T., Sanseverino, M.T., Momino, W. *et al.* Prospective evaluation of pregnant women vaccinated against rubella in southern Brazil. *Reproductive Toxicology* 2008, **25**(1), 120-123.

58 Mistchenko, A.S., Keller, G.A., Acevedo, M.E., Jacquez, O.A., Di Girolamo, G. & Diez, R.A. Inadvertent Rubella Vaccination of Pregnant Women during the Nationwide Rubella Vaccination Campaign in Buenos Aires, Argentina. *Drug Safety* 2008, **31**(10), 934-935.

59 da Silva e Sa, G.R., Camacho, L.A., Siqueira, M.M., Stavola, M.S. & Ferreira, D.A. Seroepidemiological profile of pregnant women after inadvertent rubella vaccination in the state of Rio de Janeiro, Brazil, 2001-2002. *Pan American Journal of Public Health* 2006, **19**(6), 371-378.

60 Pardon, F., Vilarino, M., Barbero, P., Garcia, G., Outon, E., Gil, C. *et al.* Rubella vaccination of unknowingly pregnant women during 2006 mass campaign in Argentina. *Journal of Infectious Diseases* 2011, **204 Suppl 2**, S745-747.

61 Sato, H.K., Sanajotta, A.T., Moraes, J.C., Andrade, J.Q., Duarte, G., Cervi, M.C. *et al.* Rubella vaccination of unknowingly pregnant women: the Sao Paulo experience, 2001. *Journal of Infectious Diseases* 2011, **204 Suppl 2**, S737-744.

62 Artimos de Oliveira, S., Bastos Camacho, L.A., Uzeda Barreto, M.C., Coca Velarde, L.G. & Siqueira, M.M. Serologic status of women in an urban population in Brazil before and after rubella immunization campaign using routine screening data. *Journal of Infectious Diseases* 2011, **204 Suppl 2**, S664-668.

63 Brown, L., D; Tony Cai,T; DasGupta,A Confidence intervals for a binomial proportion and asymptotic expansions *The Annals of Statistics* 2002, **30**, 160-201.

Captions to illustrations

**Figure 1: Flow of information from screening and inclusion process**

**Figure 2a:** Individual study risk of CRI (as a %) and overall meta-analysis (fixed-effects) of the risk of CRI in pregnancy cohorts of women susceptible to rubella and vaccinated against rubella peri-conceptually\*

**\***The pooled risk for CRI was 1.69% (1.15-2.24) limited to studies examining those vaccinated with the RA77/3 rubella vaccine only (ie excluding ACIP ‘71-’79, Enders et al and Tookey et al).

**Figure 2b:** Individual study risk of CRI (as a %) and overall meta-analysis (random-effects) of the risk of CRI in pregnancy cohorts of women susceptible to rubella and vaccinated against rubella peri-conceptually

**Figure 1: Flow of information from screening and inclusion process**

Identification

2 additional records identified from expert library

8623 records identified through database searching

Included

Eligibility

406 full texts assessed

for eligibility

406 records identified as potentially relevant to the study

Screening

6360 records screened (title and abstract)

8625 records

2265 duplicates removed

5954 records excluded

0 full texts not found

121 not primary studies

74 no rubella vaccination

133 vaccination not administered to pregnant women

12 did not assess for adverse events

24 were duplicates

42 studies included

8 case Series/ case report studies

4 cohort studies of induced abortions where women agreed to be vaccinated beforehand

9 pregnancy cohort studies no information on susceptibility

17 pregnancy cohorts with information on sucsceptility to rubella

4 cohort studies with vaccinated and unvaccinated groups

5 Case Series/ Case report studies

**Figure 2a:** Individual study risk of CRI (as a %) and overall meta-analysis (fixed-effects) of the risk of CRI in pregnancy cohorts of women susceptible to rubella and vaccinated against rubella peri-conceptually\*

\*The pooled risk for CRI was 1.69% (1.15-2.24) limited to studies examining those vaccinated with the RA77/3 rubella vaccine only (i.e. excluding ACIP ‘71-’79, Enders et al and Tookey et al).

**Figure 2b:** Individual study risk of CRI (as a %) and overall meta-analysis (random-effects) of the risk of CRI in pregnancy cohorts of women susceptible to rubella and vaccinated against rubella peri-conceptually

**Table 1. Baseline study characteristics of pregnancy cohort studies with a rubella vaccinated and unvaccinated group**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **First author, year** | **Location, Recruitment year(s), Publication type** | **Vaccine**  **R/MR/MMR and rubella strain**  **Type of programme,** | **N vaccinated/ N unvaccinated** | **N (%) vaccinated by timing pre-conception/**  **trimester** | **Length and type of follow up** | **N (%) Adverse event(s) assessed** | | **Comments** |
| **Vaccinated** | **Unvaccinated** |
| **Ebbin, A. J., 1973**[[22](#_ENREF_22)]**\*** | US, 1969-1972, Journal article | HPV 77 (41 women), Cendehill (16 women),  HPV-77 (1 woman),  (2 unknown)  Inadvertent vaccination during pregnancy | 60/47  (Controls matched for maternal age, race, parity, sex of infant and practice or type of hospital) | ***<3 months before LMP:*** 32 (53.3%)  5/9 susceptible women, thereof 1 < 30 days  ***<3 months after LMP:***  28 (46.7%)  *4/9 susceptible women* | Culture of throat swabs in infants or products of conception in abortions in the 9 susceptible women.  Infants had physical, developmental, and audio-logic evaluations at 3 to 6 month intervals until 2 years of age | ***41 live births, 0 CRS***  *Susceptible women:*  1/9 (11.1%) intrauterine infection after therapeutic abortion\*\*  2 spont. ab (1 negative virus culture results, 1 virus culture not done)  *Unknown susceptibility:*  1/51 (2.0%) spont. ab.  13/51 (25.5%) ther. ab.  1/41 (2.0%) preterm birth and neonatal death  1/41 (2.0%) neonatal deathiv  1 child with heart murmur | ***44 live births, 0 CRS***  3/47 (6.4%) spont. ab.  2/47 (4.3%) ther. ab.  (No information available on the immune statuses of these women) | Identification of vaccine strain in virological culture in the products of conception of a susceptible woman was by Parkman (based at the FDA in the USA).  An additional woman with unknown susceptibility was vaccinated and had a therapeutic abortion. Wild type virus was isolated from the products of conception. |
| **Bar-Oz, B., 2004**[[21](#_ENREF_21)] | Canada, NK,  Journal article | MMR vaccine, RA27/3  (4 unknown)  Inadvertent vaccination in pregnancy, | 94/ 94  (Controls unvaccinated attending the same counselling service matched for age, smoking, alcohol and drug use) | ***≤ 3 months pre-conception:***  56 (59.5%)  ***1st trimester:***  38 (40.4%) | Maternal reports and child’s primary care physician records collected at least 6 months after birth | ***81 live births, 0 CRS***  6/94 (6.4%) Spont. ab.  7/94 (9.4%) ther ab.  1/81 (1.2%) neonatal death (died of hyaline membrane disease)  7/81 (8.6%) preterm births  3/81 (3.7%) malformations | ***87 live births, 0 CRS***  8/95 (8.4%) Spont. ab.  0 ther. Ab.  0 neonatal death  8/87 (9.2%) preterm births  3/87(3.4%) malformations | This study is also reported in Levicheck,Z, et al. (2001)[[39](#_ENREF_39)] |
| **Namaei, M. H., 2008**[[18](#_ENREF_18)] | Iran, 2003-2004, Journal article | MR vaccine, RA27/3,  Nationwide campaign targeting 5-25year olds | 106 / 40  Unclear how vaccinated women were referred to services, how unvaccinated were recruited or % vaccinated 3 months prior to pregnancy. | ***≤ 3 months pre-conception:***  71 (67.0%)  ***1st trimester:***  35 (33.0%) | All pregnancies followed up until delivery. Blood samples collected at birth. During first 24 hours of life infants were examined by paediatrician for CRS. | ***107 live births, 0 CRS***  1/106 (0.9%) still birth  8/106 (7.6%) preterm birth  2/106 (1.9%) malformations – both mothers vaccinated in 1st trimester | ***42 live* births*, 0 CRS***  0 still birth  3/42 (7.1%) preterm birth  0 malformations | No IgM rubella ab in any maternal and infant cord blood.  Overlap of women cases with Shahhosseini, Z[[19](#_ENREF_19)]., Hamkar, R.[[20](#_ENREF_20)] and Emadi, H[[40](#_ENREF_40)]. unlikely as different province |
| **Shahhosseini, Z., 2009**[[19](#_ENREF_19)] | Iran, NK, Abstract | (see above Namaei, M. H., 2008) | 406 / 493 | NK | NK | ***0 CRS***  Malformations and pregnancy outcomes balanced across both groups. Figures not given. | | Overlap with women reported in Namaei, M. H.[[18](#_ENREF_18)] Hamkar, R.[[20](#_ENREF_20)] and Emadi, H.[[40](#_ENREF_40)] unlikely as different province |

Spont. ab. = spontaneous abortion Ther. ab. = therapeutic abortion Susc. = Susceptible women

. \*This was the only study in this table that assessed the immunity status (prior to vaccination) of participants. \*\* Attenuated rubella virus isolated from the products of conception from 1 case of therapeutic abortion (mother vaccinated 55 days after LMP) \*\*\* with signs of inflammation of the abortus material, 1 gave negative virus culture results, 1 virus culture not done. iv  died of hyaline membrane disease

**Table 2: Risk and effect estimates of congenital rubella syndrome and adverse pregnancy outcomes in cohort studies of inadvertent maternal rubella vaccination with unvaccinated control groups**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  | | **Crude Risk difference** | **Pooled risk difference** | | |
|  | **Author**  **Study year** | **Vaccine strain** | **N vaccinated/Nunvaccinated** | **outcome vaccinated (%)** | **outcome unvaccinated (%)** | **RD (%)**  **95% CI** | **RD% 95%CI** | **Test for heterogeneity (P-value)** |
| **CRS\*\*** | Ebbin. A.J. 1973[[22](#_ENREF_22)] | HPV-77 (n=29)  Cendehill (n=11)  1 unknown | 41/44 | 0 (0.0%) | 0 (0.0%) | 0.0  (-4.5, 4.5) | 0.0  (-0.6, 0.6) | 1.000 |
| Bar-Oz. B. 2004 [[21](#_ENREF_21)] | RA 27/3 | 81/87 | 0 (0.0%) | 0 (0.0%) | 0.0  (-2.3, 2.3) |
| Namaei. M.H. 2008[[18](#_ENREF_18)] | RA27/3 | 106/40 | 0 (0.0%) | 0 (0.0%) | 0.0  (-3.6, 3.6) |
| Shahhossei Z.2009[[19](#_ENREF_19)] | MR (not specified assumed RA27/3)\* | 406/493 | 0 (0.0%) | 0 (0.0%) | 0.0  (-0.4, 0.4) |
| **Malformations** | Bar-Oz. B. 2004[[21](#_ENREF_21)] | HPV-77  Cendehill | 81/87 | 3 (3.7%) | 3 (3.4%) | 0.3  (-5.4, 5.9) | 0.9  (-2.9, 4.7) | 0.626 |
| Namaei, M. H. 2008 [[18](#_ENREF_18)] | RA 27/3 | 106/40 | 2 (1.9%) | 0 (0.0%) | 1.9  (-2.5, 6.3) |
| **Induced abortion** | Ebbin, A. J. 1973 [[22](#_ENREF_22)] | HPV-77  Cendehill | 60/47 | 14 (23%) | 2 (4.3%) | 19.1  (6.9, 31.2) | 11.6  (5.9, 17.3) | 0.059 |
| Bar-Oz, B. 2004[[21](#_ENREF_21)] | RA 27/3 | 94/94 | 7 (7.4%) | 0 (0.0%) | 7.4  (1.8, 13.1) |
| **Spontaneous abortion** | Ebbin, A. J. 1973[[22](#_ENREF_22)] | HPV-77  Cendehill | 60/47 | 3 (5.0%) | 3 (6.4%) | -1.4  (-10.3, 7.5) | -1.8  (-7.6, 3.9) | 0.911 |
| Bar-Oz, B.2004[[21](#_ENREF_21)] | RA 27/3 | 94/95 | 6 (6.4%) | 8 (8.4%) | -2.0  (-9.5, 5.4) |
| **Neonatal death** | Ebbin, A. J. 1973[[22](#_ENREF_22)] | HPV-77  Cendehill | 41/44 | 2 (4.9%) | 0 (0.0%) | 4.9  (-2.9, 12.7) | 2.5  (-1.0, 5.9) | 0.343 |
| Bar-Oz, B.2004 [[21](#_ENREF_21)] | RA 27/3 | 81 | 1 (1.2%) | 0 (0.0%) | 1.2  (-2.1, 4.5) |
| **Still birth** | Namaei, M. H. 2008 [[18](#_ENREF_18)] | RA 27/3 | 106\*/40 | 1 (0.9%) | 0 (0.0%) | 0.9  (-3.1, 5.0) | 0.9  (-3.2, 5.1) | - |
| **Preterm delivery** | Ebbin, A. J. 1973 [[22](#_ENREF_22)] | HPV-77  Cendehill | 41/44 | 1 (2.4%) | 0 (0.0%) | 2.4  (-4.0, 8.8) | 0.3  (-4.8, 5.5) | 0.793 |
| Bar-Oz, B. 2004[[21](#_ENREF_21)] | RA 27/3 | 81/87 | 7 (8.6%) | 8 (9.2%) | -0.6  (-9.2, 8.1) |
| Namaei, M. H. 2004 [[18](#_ENREF_18)] | RA 27/3 | 106\*/40 | 8 (7.5%) | 3 (7.5%) | 0.0  (-9.5, 9.6) |

\*including two pregnancies with twins in both exposed and unexposed groups i.e. 107 live births in vaccinated group and 42 live births in the unvaccinated group.

\*\*If limited to studies on RA77/3 (excluding Ebbin et al) the results were unchanged

**Table 3. Baseline table of study characteristics of cohorts of rubella vaccinated susceptible pregnant women.**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **First author, year** | **Location, recruitment year(s), publication type** | **R/MR/MMR, Vaccine, rubella strain**  Type of programme, | **N(%) susceptible,**  **N(%) immune,**  **N(%) unknown** | **N (% ) vaccinated by timing of vaccination** | **N, length and type of follow up by outcome assessed** | **Type and N (%) outcomes by immunity status** | **Virological test for vaccine strain done?** | **Comments** |
| **Vaccine in Pregnancy register, ACIP, 1979**  **(JAMA 1983)[**[**41**](#_ENREF_41)**]** | US, 1971- 1979, Report | Cendehill and HPV-77 (538 women)  Unknown vaccine strain (3 women- 1 susc., 1 immune, 1 unknown)  Inadvertent vaccination during pregnancy, | 149 (27.7%) susc.  25 (4.6%) immune  364 (67.7%) unknown | Known for 86 susc.  Preconception: 63%  33 (38.4%) were vaccinated within the week before and the 4th week after the estimated date of conception | 290 live births. 143 (96.0%) susc. pregnancy outcomes measured,  94 (65.7%) susc. pregnancies carried to term.  196 infants from both immune mothers (n=22) and unknown immune status mothers (n=174) pregnancies. All children with CRI followed for at least 2 years | **0 CRS** /94 live births susc. pregnancies  **3 CRI** out of 61live born infants tested.  **17 Intrauterine infection** out of 85 (20%) products of conception from susc. tested, no details if vaccine virus or otherwise | Yes, but unclear type of test | other references refer to this [[42](#_ENREF_42)],[[43](#_ENREF_43)],[[44](#_ENREF_44)] ,[[45](#_ENREF_45)] , [[46](#_ENREF_46)],[[41](#_ENREF_41)],[[47](#_ENREF_47)] ,[[48](#_ENREF_48)] , [[49](#_ENREF_49)]  The 3 women with unknown vaccine all had live births with no adverse events |
| **Vaccine in Pregnancy register, ACIP, 1989[**[**50**](#_ENREF_50)**]** | US, 1979- 1988, Report | RA 27/3  Inadvertent vaccination during pregnancy | 272 (39.8%) susc.,  32 (4.7%) immune,  379 (55.4%) unknown | Known for susc. only: Median= 14 days before conception | 254 susc. pregnancies with complete follow up.  212 live infants by 210 mothers followed up with serologic evaluations performed on 154 of them | **0 CRS** in 212 live births  **3/154 (1.9%)** **CRI** susc.  **Spontaneous Abortions:**  13/254 (5.1%) in susc.  1/31 (3.2%) in immunes,  8/351 (2.3%) in unknown,  **Induced abortions:**  31/254 (12.2%) susc.  **Intrauterine infections**  (1/32 (3.1%) culture of products of conception of susc. with “replicating rubella virus”  24/351 (6.8%) unknown | Yes, but unclear type of test | other references refer to this [[9](#_ENREF_9),[25](#_ENREF_25),[42](#_ENREF_42)] [[43](#_ENREF_43)],[[44](#_ENREF_44)] , [[45](#_ENREF_45)], [[46](#_ENREF_46)], [[41](#_ENREF_41)], [[47](#_ENREF_47)],[[48](#_ENREF_48)],[[49](#_ENREF_49)]  For the one intrauterine infection with replicating rubella virus identified. “No attempt was made to differentiate vaccine from wild virus[[25](#_ENREF_25)]” |
| **Tookey, P. A., 2001[**[**51**](#_ENREF_51)**]** | UK, 1981- 2001, Journal letter | RA27/3 (61 women),  Cendehill (7 women)  unknown (24 women). | 92 pregnancies through 1991, Serology was performed on 46/56 live births to RA27/3 vaccinated mothers. 25 susc. through 2001 | Only stated for cases with adverse event observed | Earlier report 1991 notes 63 prospective reports, 29 retrospective reports from paediatricians: 1st blood sample at birth, 2nd blood sample and examination by paediatrician at 9 months of age. 22 children followed up until 3 years or older. | **0/25 CRS** susc.  4/25 CRI susc.  Earlier 1991 report 87 live births  3 still births (2 in susc., 1 in woman with unknown status)  2 spontaneous abortions both in susc.  1 pulmonary atresia\*\*\*  1ventricular septum defect\*\*\*.  1 rubella IgM at birth+ | No, presence of Rubella-specific IgM taken as evidence of intra-uterine- infection. | See also [[12](#_ENREF_12),[52](#_ENREF_52)] |
| **Enders, G., 1985[**[**53**](#_ENREF_53)**]** | Germany,1971- 1984, Journal article | Cendehill (340 women),  RA 27/3 (25 women)  1969-1971: individual basis  1974-1975: targeted campaigns school girls 10-14 yrs  1980 onwards:  Vaccination of boys and girls aged 15 months recommended) | 146(40.0%) susc.,  65 (17.8%) immune,  154 (42.2%) unknown | 9% 9-12 weeks before conception, 24% 4-8 weeks before conception, 59% within two weeks before and up to six weeks after conception , 8% 7-15 weeks after conception | 194 live infants born by the time of writing  119 neonates tested for rubella infection (those born to mothers with susceptible or unknown immune status) | **0 CRS** in 98 susc. assessed.  **CRI (**IgM antibody in cord blood**):**  2/95 (2.1%) susc.+++.  **1 Intrauterine infection** in 34 (2.9%)++ where examined obtained products of conception after therapeutic abortion):  1/23 (4.3%)susc.  **Other congenital defects:**  2/95 (2.1%) sucs.  0 immune  3/24 (12.5%) unknown  **Induced abortions**  23/146 (15.6%) susc.  0 immune  11/154 (7.1%) unknown | Unclear |  |
| **Enders, G., 2005[**[**54**](#_ENREF_54)**]** | Germany, 2001-2004,  Journal article | MMR vaccine,  RA 27/3,  1. MMR vaccination from the age of 12 months, 2. MMR vaccination before starting school | 57 women susc. | 33 within 1-2 weeks before to 6 weeks after conception | NK | **0/57 CRS susc**  **1/13 tested (7.7%) CRI** | NK | 1/13 CRI does not overlap with the 1985 study[[53](#_ENREF_53)]. However there are also 6/126 CRI 1971-2000 which overlaps with the previous Enders paper (1971-1983)[[55](#_ENREF_55)] and so are not given here |
| **Hamkar, R.,**  **2006[**[**20**](#_ENREF_20)**]** | Tehran, Iran, 2003, Journal article | MR vaccine, RA27/3  Nationwide campaign, 5-25year olds | 117 (14.5%) susc.,  693 (85.5%) immune | No information | Women were followed up until delivery. All neonates were examined by physicians for  probable CRS related symptoms. All CRI cases were  followed clinically by physicians for probable delayed CRS related symptoms for up to 1 year of age. | **0/117 CRS** susc.  **5 CRI (Cord blood serum)‡:**  2/35 (5.7%) susc.  0/16 (0%) immune  3/500 (0.6%) unknown | No- no virus isolation noted in methods | Possible overlap of cases with [[40](#_ENREF_40)] as one of the same hospitals reported from (Imam Khomeini Hospital). Unclear if any overlap with others in Iran but unlikely as different provinces covered in [[18](#_ENREF_18),[19](#_ENREF_19)] |
| **Emadi, H., 2007[**[**40**](#_ENREF_40)**]** | Iran, 2003, Conference proceedings  **From Imam Khomeini Hospital** | See above (Hamkar, R.,  2006) | 30 (12.8%) susc.,  205 (87.2%) immune | No information | No information | “no increase the rate of  still birth, congenital malformation and abortions in rubella susceptible  vaccinated mothers as compared to immune mothers”. “no significant difference in stillbirth, congenital malformation and abortions between non-vaccinated and vaccinated pregnant women” | No information | Graph in conference proceedings shows still birth, abortions and still birth  (likely overlap of cases with[[20](#_ENREF_20)]) |
| **Badilla, X., 2007[**[**56**](#_ENREF_56)**]** | Costa Rica, 2001, Journal article | MR  RA 27/3, nationwide measles-rubella vaccination campaign among men and women (15-39 years old) implemented in May 2001 | 104 (8.7%) susc.,  219 (18.4%) immune,  868 (72.9%) unknown | 119 (10.0% )1-3 months preconception  272 (22.8%) <1 month preconception  789 (66.2%) 1st trimester  11 (0.9%) >1st trimester | 3810 women vaccinated. 1191 with complete clinical and serological evaluation  Umbilical cord blood sample, paediatrician evaluation of all children at birth to detect clinical manifestations of CRS. | **0 confirmed CRS /93 tested** susc  **CRS like defects-not test positive:**  5/104 (4.8%) susc.  9/219 (4.1%) immune  31/868 (3.6%) unknown  **Miscarriage**:  10/104 (9.6%) susc.  36/219 (16.4%) immune  82/868 (9.4%) unknown  **Stillbirth**:  1/104 (1%) susc.  2/219 (0.9%) immune  11/868 (1.3%) unknown | Yes, molecular typing reverse transcription nested PCR | No positive tests i.e. no defects compatible with CRS due to vaccine strain  Included in pooling in [[23](#_ENREF_23)] |
| **Lina, M., 2008[**[**26**](#_ENREF_26)**]** | Bogota, Colombia 2005-2006 | RA 27/3, national wide vaccination days | 3489 pregnant women vaccinated  364 susc., 277 of these followed up, 262 live births | NA | Only one child serologically positive was followed up, the other 261 children were only followed up until birth | 262 babies born  1(1%) CRI, followed up for a year, without sign of CRS**.** | Not mentioned |  |
| **Minussi L., 2008[**[**57**](#_ENREF_57)**]** | Rio Grande do Sul (RS), Brazil. 2002, Journal article | MR vaccine,  RA 27/3  State vaccination campaign, targeted at women of reproductive age (12-39) | 4398 pregnant women vaccinated in total.  171 (out of 423) susc. included in study | Unknown pregnant or became pregnant within 30 days post vaccination | Until birth and 3 months of age for live infants. | **Data duplicated in Castillo-Solorzano**  **0 CRS** (at 3 months of age)  3/153 (2.0 %)) stillbirth  13/153 (8.7 %) birth weight < 2500 g  16/153 (10.7%) Gest Age< 37 weeks  19/171 (11.1%) spontaneous miscarriage  10/149 (6.7%) of live infants had anti-rubella IgM antibodies | Not mentioned | Comparison with total births in the population in Rio Grande in 2002  (RR (95% CI) Stillbirth: 2.82 (0.92-8.66), Birth weight < 2500 g: 0.94 (0.56-1.58), GA < 37 weeks. 1.36 (0.86-2.16)  (Data duplicated in[[23](#_ENREF_23)] ) |
| **Mistchenko, A. S, 2008[**[**58**](#_ENREF_58)**]** | Buenos Aires, Argentina, 2006, abstract | MR vaccine, RA27/3  Nation-wide vaccination campaign of women of child-bearing age (15-39 years), | 6 (2.59%) susc.  219 (94.4%) immune  7 (3.02%) unknown | Unknown pregnant or became pregnant within 30 days post vaccination | Children of mothers with susceptible or unknown immune status were followed up. 2 new-borns were studied due to clinical suspicion of CRS. 50 children born to vaccinated mothers were tested for rubella PCR in urine | **0/13 CRS**  0/6 susc.  1/6 (16.7 %) **CRI** susc.  **1 spontaneous abortion** (woman indeterminate status)  **1 preterm delivery** (unknown status)  2 infants presented cardiomyopathy, one of them with rubella virus detection by PCR in urine but negative IgM; the other presented serum IgM but no virus was detected by PCR | No | The RT-PCR positive result in urine of 1 newborn with IgM neg status is unclear  (Data duplicated in [[23](#_ENREF_23)]) |
| **da Silva e Sa, G. R., 2011[**[**24**](#_ENREF_24)**]** | Brazil, Rio de Janeiro, 2001- 2002, Journal article | MR vaccine  RA 27/3  mass vaccination 12-39 year old women in the state of Rio de Janeiro | 217 (12.6%) susc. with known outcomes;  316 (13.8%) immune,  1576 (68.8%) indeterminate,  8 (0.3%) ineligible, and 104 (4.5%) lost to follow-up tested >30 days after vaccination | Gestational age at vaccination available for 1070 women, 65.1% 1st trimester  among susc., 64.5% vaccinated <5 weeks gestational age, rest >5 weeks. In 15.5% of the women vaccination was prior to pregnancy. | 1636 (71.4%) pregnancy outcomes known.  9 Infants with CRI followed up for 1 year  IgM negative  infants were only observed if they had a malformation consistent with CRS and/or prematurity and/or low birth  weight, with a second blood sample collected to assess IgG titres | **Data duplicated in Castillo-Solorzano**  **0 CRS**  **9 (0.6%) CRI**  5/196 (2.6%) susc.  0/51 (0%) immune  2/742 (0.3%)Indeterminate  2/531 (0.4%) Unknown  **7 (0.4%) Stillbirth:**  2/217 (0.9%) susc.  0/59 (0%) immune  4/794 (0.5%) indeterminate  1/566 (0.2%) unknown  **52 (3.2%) Miscarriage:**  10/217 (4.6%) susc.  5/59 (8.5%) immune  18/794 (2.3%) indeterminate  19/566 (3.4%)unknown | Yes, identified through genotypical characterization. | Other references refer to this [[59](#_ENREF_59)] same data,  1 CRS case detected among the 288 susceptible pregnant women due to wild type virus infection (Data duplicated in [[23](#_ENREF_23)]) |
| **Pardon, F., 2011[**[**60**](#_ENREF_60)**]** | Argentina, 2006, Journal article | MR vaccine, RA27/3  nation-wide vaccination campaign of women 15-39 years, | 7 (12.5%) susc.,  48 (85.7%) immune,  1 ( 1.8%) indeterminate | NK | 5 newborns of susc. women and 28 pregnancies in Buenos Aires were clinically evaluated to identify CRS- compatible symptoms | 0/5 **CRS susc.**  0/5 **CRI susc.**  1 molar pregnancy and 5 abortions all in immune group | NA (as no CRI) | 1 immune patient presented with rash and a fever  (Data duplicated in[[23](#_ENREF_23)]) |
| **Reyna, J, 2011[**[**27**](#_ENREF_27)**]** | Mexico, 2008, Journal article | MR vaccine, RA27/3  nation-wide vaccination campaign of men and women 19-29 | 1,924 pregnant women  175 (9.1%) susc.  174 liveborn | Gestational age of susc. women <11 weeks (86.9%), >11 weeks 13.1% | 174 live-born | Preterm birth 9/174 (5.1%)  CRI 0/174  CRS 0/174 |  |  |
| **Sato, H. K., 2011[**[**61**](#_ENREF_61)**]** | Sao Paulo, Brazil, 2001, Journal article | MR vaccine RA27/3  Mass vaccination campaign of women of childbearing age | 811/5580 (14.5%)  Susc.,  2135 (38.3%) immune,  27 (0.5%) undetectable  2607 (46.7%) indeterminate (due to serum sample collection >70 days after vaccination) | ***Pre-conception:***  Susc.: 170 (26.6%)  Immune: 244 (17.3%)  **0–4 weeks post-conception:**  Susc.: 347 (54.4%)  Immune: 780 (55.4%)  **5–12 weeks post-conception**:  Susc.: 99 (15.5%)  Immune: 311 (22.1%)  **>12 weeks post-conception**  Susc.: 22 (3.4%)  Immune: 73 (5.2%) | Household interviews to determine birth outcomes were conducted for 644 (79.4%) susc. and 1433 (70.5%) previously immune women. 580 serum samples from new-borns of susc. 541 live-born infants with a second household visit with clinical examination and referral to paediatric specialist if neonate tested positive for rubella IgM antibodies at birth. | **Data duplicated in Castillo-Solorzano**  **0/580 CRS** susc.  **27/580 (4.7%) CRI** Susc.  6/10 IgM + infants tested and found positive for rubella vaccine virus (RA27/3)  **Spontaneous abortion**  Susc.: 34/644 (5.3%)  Immune: 103/1433 (7.2%)  **Still birth**  Susc.: 2/644 (0.3%)  Immune: 10/1433 (0.7%)  **LBW**  Susc.: 38/608 (6.2%)  Immune:116/1320 (8.8%) | Some viral tests by PCR available (see p 740) | CRI defined as positive antirubella IgM ELISA in a neonate born to a susceptible mother without evidence of exposure to wild-type virus(.See p. S739)  None of the 27 neonates presented clinical manifestations compatible with CRS. (Data duplicated in [[23](#_ENREF_23)]) |
| **Soares, R. C.,**  **2011[**[**36**](#_ENREF_36)**]** | Brazil, 2001- 2002, Journal article | MR vaccine, RA27/3  Mass vaccination campaign of women of childbearing age | 2332 (11.4%) susc.,  7484 (40.3%) immune,  8694 (46.8%) indeterminate, | Known for 3098 women:  ***Pre-conception(<28 days):***  437 (14.1%)  ***1st trimester:***  2015(65.0%) <4 weeks  646(20.9%) ≥4 weeks | 1860 (78.8%) susc. pregnancies actively followed up until birth.  1647 (94.5%) infant serological testing results available.  Infected infants were followed through 12 months of age. | **Data duplicated in Castillo-Solorzano**  0 **CRS**  **Susc. mothers:**  67/1647 (4.1%) CRI  103 (5.3%) miscarriage  14 still birth (0.8 %) based on 677 states | Yes | 1 CRS, Wild virus  (Data duplicated in[[23](#_ENREF_23)] as well as [[57](#_ENREF_57)] which presented data collected from Rio Grande do Sul, Brazil during same time period) |
| **Castillo-Solorzano, C., 2011[**[**23**](#_ENREF_23)**]** | Argentina, Brazil, Costa Rica, Ecuador,  El Salvador, Paraguay,  2001- 2008,  Journal article | RA 27/3  mass vaccination campaigns | 2,894 (10%) susc. | 30 days preconception to 3 months post conception, no further details | 1980 susc. mothers had live births, length of follow up not available | Data for 1980 susc. women:  **0 CRS due to vaccine**  **70 (3.5%) CRI**: in live births  **158 (5%)** **Foetal death or miscarriage**:  IgM antibody positive infants with clinical features of CRS: 2 (1 found to be due to wild rubella virus (noted in Da Silva) and 1 due to CMV)  Examination of infants by paediatricians/specialists  No mention of those immune | Yes, 1 case of CRS due to wild rubella virus as determined by molecular genotyping | Maximum theoretical risk of CRS 0.2%. Pooling of results of cohort studies in 6 SA countries, (PAHO protocol): Costa Rica[[56](#_ENREF_56)], Brazil Rio De Janeiro[[24](#_ENREF_24)], Argentina[[60](#_ENREF_60)], Brazil Sao Paulo[[61](#_ENREF_61)], Brazil Rio Grande do Sol[[57](#_ENREF_57)]., Argentina, Buenos Aires[[58](#_ENREF_58)], and Brazil (nationally)[[36](#_ENREF_36)]. |

Susc. = Susceptible women

\*\*\* Both infants were born to mothers who had received Cendehill vaccine (unstated susceptibility status), but had no serological evidence of CRS and both were healthy at 3 years of age

+  Mother susceptible and received RA27/3 5 weeks after LMP.

++ This woman was vaccinated with Cendehill vaccine at the fourth week of pregnancy

+++ vaccinated between 3rd and 7th week of pregnancy with Cendehill - both infants healthy at birth.

**‡** After 1 year of follow-up, all 5 children effected by CRI, were clinically normal, and none of the CRS related developmental symptoms were seen upon their examination

**Table 4: Risks of CRS and CRI in rubella vaccinated women known to be susceptible to rubella before rubella vaccination pre or early conception**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Author** | **Year** | **Vaccine strain** | **N Susceptible at risk** | **N outcome susceptible** | **CRI Crude risk (%) (95% CI)** | **CRS upper bound of the 95% CI for crude risk\*\*\*** | **Pooled risk (%) (95% CI)** |
| **CRI** | ACIP ’71-‘79[[41](#_ENREF_41)]  Enders[[53](#_ENREF_53)]  ACIP ’79-‘88[[50](#_ENREF_50)]  Tookey[[51](#_ENREF_51)]  Enders [[54](#_ENREF_54)]  Hamkar[[20](#_ENREF_20)]  Lina[[26](#_ENREF_26)]  Castillo- Solorzano[[23](#_ENREF_23)]\*  Reyna[[27](#_ENREF_27)]  Total  Total RA27/3 | 1983  1985  1989  2001  2005  2006  2008  2011  2011 | Cendehill or HPV-77  Cendehill, RA 27/3  RA27/3  Cendehill, RA 27/3\*\*  RA27/3  RA 27/3  RA 27/3  RA 27/3  RA 27/3 | 61  95  154  25  13  35  262  1980  174  2799  2618 | 3  2  3  4  1  2  1  70  0  87  78 | 4.9% (1.0 to 13.7)  2.1% (0.3 to 7.4)  1.9% (0.4 to 5.6)  16.0% (4.5 to 36.1)  7.7% (0.2 to 36.0)  5.7% (0.7 to 23.1)  0.38% (0.01 to 2.1)  3.5% (2.8 to 4.4)  0.0% (0 to 2.1)  3.1% (2.5 to 3.8)  3.0% (2.4 to 3.7) |  | 1.74%, (95% CI 1.21 to 2.28))\*\*\*\*  1.69% (1.15-2.24) limited to RA77/3 rubella vaccine only studies  Above using fixed effects meta-analysis  (2.11% (95%CI 0.37 to 3.85) using random effects) |
| **CRS** | ACIP ’71-‘79[[41](#_ENREF_41)]  ACIP ’79-‘88[[50](#_ENREF_50)]  Hamkar[[20](#_ENREF_20)]  Enders[[53](#_ENREF_53)]  Tookey, P[[51](#_ENREF_51)]  Enders[[54](#_ENREF_54)]  Lina[[62](#_ENREF_62)]  Castillo- Solorzano[[23](#_ENREF_23)]\*  Reyna[[27](#_ENREF_27)]  Total  **Total RA 27/3** | 1983  1989  2006  1985  2001  2005  2008  2011  2011 | Cendehill or HPV-77  RA27/3 e  RA27/3  Cendehill, RA 27/3  Cendehill, RA 27/3\*\*  RA 27/3  RA 27/3  RA 27/3  RA 27/3 | 94  212  117  98  25  57  262  1980  174  3019  2802 | 0  0  0  0  0  0  0  0  0  0  0 |  | 2.6%  1.18%  2.12%  2.52%  9.47%  4.29%  0.95%  0.13%  1.4%  0.083%  0.090% | Upper 95% CI 0.099% ie a maximum theoretical risk of 0.99 per 1000 susceptible women based on all studies  (using simulation) |

\*Includes data from 6 countries (Costa Rica, Brazil, El Salvador, Ecuador, Paraguay, and Argentina).\*\* assumed based on other publications (Tookey 1991[[12](#_ENREF_12)] and Castillo-Solorzano 2011[[23](#_ENREF_23)]) \*\*\* Based on the “Jeffreys” method[[63](#_ENREF_63)] \*\*\*\* test for heterogeneity p<0.001

**Table 5. Risk of bias for controlled cohort studies**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Author** | **Risk of confounding bias** | **Risk of selection bias** | **Risk of bias due to departure from interventions** | **Risk of bias due to missing data** | **Risk of information bias** | **Risk of reporting bias** |
| Ebbin, A. J[[22](#_ENREF_22)] | Serious | Moderate | Moderate | Moderate | Moderate | moderate |
| Bar-Oz, B[[21](#_ENREF_21)]. | Serious | Moderate | Moderate | Moderate | Moderate | moderate |
| Namaei, M. H.[[18](#_ENREF_18)] | Serious | Moderate | moderate | Moderate | Moderate | moderate |
| Shahhosseini, Z[[19](#_ENREF_19)] | Serious | Moderate | moderate | No information | Moderate | No information |