Post-exposure passive immunisation for preventing rubella and congenital rubella syndrome (Protocol)

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Post-exposure passive immunisation for preventing rubella and congenital rubella syndrome

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the effectiveness of intramuscular injection or intravenous infusion of polyclonal immunoglobulins of human sera or plasma origin for preventing rubella and congenital rubella syndrome when administered to exposed susceptible people before the onset of disease.

BACKGROUND

Global rubella control has progressed since the introduction of rubella vaccine (Usonis 2011; WHO 2011). However, country-specific control varies greatly, with some countries citing evidence of rubella elimination (Best 2007; Reef 2011), while the burden of disease is unknown and rubella vaccination is still unavailable in others (Goodson 2011). Many countries report large numbers of cases and outbreaks of rubella (Muscat 2012; Usonis 2011; WHO 2011). Though vaccination is available in these countries, rates are not sufficiently high to achieve adequate rubella control (Muscat 2012; Usonis 2011). In 2009, more than 120,000 cases of rubella and 165 cases of congenital rubella syndrome (CRS) (see Description of the condition) were reported to the World Health Organization (WHO) by member states (Strebel 2010). However, these figures are believed to be a gross underestimate of the global burden of disease, with modelling predicting 110,000 cases of CRS in low-income countries during the non-epidemic year of 1996 (Cutts 1999). Under-reporting of rubella and CRS is thought to be a particular problem in the WHO’s African, South-East Asia and Eastern Mediterranean Regions (Strebel 2010). Even in countries with low incidences of rubella, groups with low vaccination coverage persist and cases of CRS are still reported (Muscat 2012; Song 2012).

The proportion of women of child bearing age who are not immune to rubella also varies around the world. Some countries, such as Sweden, the Czech Republic and Australia, have recorded figures of less than 5% (between 1996 and 2004) (Nardone 2008), while others have much higher proportions; for example, Bangladesh (16% in 2004 to 2005) (Nessa 2008), Singapore (16% in 2004) (Ang 2010), Morocco (17% in 2000) (Caidi 2009), India (12% to 23% between 2000 to 2008) (Dewan 2012) and Turkey (45% in one city in 2005) (Sasmaz 2007).
The cost of treating a child with CRS has been estimated in several countries. In Panama in 1989, the annual treatment cost was estimated as USD 2291, while in Jamaica in 1997, it was estimated as USD 13,482 (Hinman 2002). The lifetime cost of treating a child with CRS was estimated to be USD 50,000 and USD 63,990 in Barbados and Guyana respectively in 1997, and USD 300,000 in the United States of America in the 1980s (Hinman 2002).

While vaccination is the cornerstone to preventing CRS at the population level, there is little in the way of prevention to offer susceptible pregnant woman exposed to the rubella virus. Before rubella vaccine became available, passive immunisation was investigated as a means of preventing rubella infection, with mixed results (Green 1965a; McDonald 1963). Countries with low incidences of rubella still recommend the use of passive immunisation for the individual exposed and susceptible pregnant woman in certain circumstances.

The national recommendations in the United States (US), the United Kingdom (UK), New Zealand (NZ) and Australia suggest offering passive immunisation (a single injection of human immunoglobulin (IG)) to exposed pregnant women for whom termination of pregnancy is not acceptable should rubella infection occur (ATAGI 2008; CDC 2001; CDC 1998; IDHPA 2009; NZMoH 2011; UKDoH 2010). The rationales for this recommendation differ. For example, the UK Immunoglobulin Handbook suggests IG “does not prevent infection in non-immune contacts but may reduce the likelihood of clinical symptoms, which may possibly reduce the risk to the foetus” (IDHPA 2009); the NZ Immunisation Handbook states “Although IG has been shown to reduce clinically apparent infection in the mother, there is no guarantee that foetal infection will be prevented” (NZMoH 2011 p241); and the Australian Immunisation Handbook states that IG may prolong the incubation period, which may reduce the risk to the foetus (ATAGI 2008). The recommended doses of IG also differ.

Despite the differences, these countries’ national recommendations suggest some degree of effectiveness of passive immunisation for preventing rubella. However, they do not indicate the magnitude of the effect, nor adequately explain why a woman’s thoughts about termination should influence the practice of passive immunisation in this situation.

Description of the condition

Rubella is a single-stranded ribonucleic acid (RNA) virus that is transmitted by respiratory droplets or direct contact with the respiratory secretions of an infectious person (Heymann 2008). Someone with rubella is infectious from up to seven days before and until 14 days after the onset of rash, though the time of greatest infectivity is at rash onset (Usonis 2011; WHO 2011). A susceptible person exposed to rubella will develop the disease between 12 and 23 days after exposure (WHO 2011). Rubella is typically a mild, self limiting disease in susceptible children and adults (WHO 2011). Up to 50% of rubella virus infections are asymptomatic (Heymann 2008; Pattison 1975). When present, symptoms include fever, headache, a generalised red blotchy rash, tender enlarged lymph nodes, joint pain and mild conjunctivitis (Usonis 2011). Occasionally (one in 6000 cases), rubella infection may be complicated by encephalitis (WHO 2011).

The diagnosis of rubella is typically confirmed by measuring the increase in a particular type of rubella-specific antibody (rubella-specific IgG) in blood or by growing the virus from, or detecting the virus in, respiratory secretions, urine or blood (PHLN 2010). The presence of another type of rubella-specific antibody (rubella-specific IgM) is also indicative of disease (CDC 2001).

Control of rubella is desired because infection during the early part of pregnancy can result in miscarriage, foetal death or congenital abnormality (Usonis 2011). An infant born with any of the common congenital defects resulting from foetal rubella infection is said to have CRS. This includes cataracts, congenital heart disease, hearing impairment and microcephaly (WHO 2011). Estimates of the risk of CRS after rubella infection during pregnancy vary considerably, but it is agreed that the risk decreases as the pregnancy progresses (Best 2007; De Santis 2006). De Santis et al have summarised a large number of studies, indicating that the risk of CRS when rubella infection occurs in the first trimester (12 weeks) of pregnancy is between 38% and 100%, when infection occurs in the second trimester is between 4% and 60%, and when infection occurs in the third trimester is between 0% and 18% (De Santis 2006). The types of defects likely to manifest also vary according to the stage of pregnancy when infection occurs (Banatvala 2004). Multiple defects are more likely to occur when infection is early in the pregnancy (Best 2007). Hearing impairment is typically the only defect resulting from infection after the 16th week of pregnancy (WHO 2011), while impairment of foetal growth may continue to occur as a result of infection in the third trimester (De Santis 2006).

The diagnosis of congenital rubella syndrome is confirmed in babies with suggestive congenital malformations by detecting rubella-specific IgM in their blood, measuring the increase in rubella-specific IgG in the first year of life, or by growing the virus from, or detecting the virus in, respiratory secretions or urine (PHLN 2010).

Description of the intervention

In the early days of passive immunisation, a number of formulations of immunoglobulins were used. These included the serum of someone who was convalescing from the disease; the serum of an animal that had been actively immunised against the disease; or concentrated gamma-globulins (one class of immunoglob-
Modern passive immunisation has changed little from this last technique. It involves administration of concentrated immunoglobulins, mostly gamma-globulins, derived from at least 1000 adult blood donations (WHO 1994). Different products are available for intramuscular and intravenous administration (Burnouf 2007). With respect to rubella, the product recommended is usually human polyclonal immunoglobulins for intramuscular injection (IG). The concentration of rubella-specific immunoglobulins (antibodies) in polyclonal immunoglobulin products may vary depending on manufacturing processes and the average level of rubella-specific antibodies in the donated blood (Simon 2003).

**How the intervention might work**

Whether injected or infused, the administered immunoglobulins distribute throughout the recipient’s body into the spaces between cells (Birdsall 2009). The mechanism by which the recipient might be protected from disease involves interaction between the immunoglobulins (antibodies), the invading rubella virus particles and the cells and molecules of the recipient’s immune system (Reading 2007). The exact mechanisms by which viral infectivity is mitigated by antibodies within the body are not comprehensively understood but vary according to the structure and functionality of the particular antibodies as they encounter the particular virus particles (Reading 2007). For viruses in general, several mechanisms of action are thought to occur. Firstly, and most importantly, antibodies bind to the invading particles, directly preventing their entry into cells; a process called neutralisation (Birdsall 2009; Burton 2002). Secondly, antibodies may block cell surface receptors, preventing the virus from entering the cell (Reading 2007). Thirdly, antibodies can activate other parts of the immune system resulting directly in viral destruction (Birdsall 2009; Law 2008). Finally, antibodies bind to infected cells facilitating their destruction (Burton 2002; Law 2008).

**Why it is important to do this review**

No systematic review of the effectiveness of passive immunisation for the prevention of rubella currently exists and the evidence on which public health practice is based with regards to non-immune pregnant rubella contacts is limited and somewhat contradictory. UK guidelines do not reference the statement that “there is no evidence that it is effective” (referring to using IG for post-exposure prophylaxis for pregnant women) (IDHFA 2009 p359). The Australian Immunisation Handbook references the US guidelines for each of the statements about post-exposure passive immunisation for rubella (ATAGI 2008). These Australian guidelines state that post-exposure passive immunisation “does not prevent infection in non-immune contacts” (ATAGI 2008 p281). Whereas, the NZ guidelines state that “IG has been shown to reduce clinically apparent infection in the mother”, but do not reference this statement (NZMoH 2011 p241). The US guidelines provide two references at the end of the paragraph on post-exposure passive immunisation against rubella (CDC 1998). One is a primary controlled study on passive immunisation under experimental conditions that indicated efficacy of high-dose immunoglobulin within 24 hours of exposure but limited efficacy at lower doses (Schiff 1969). The other is a book chapter that does not include in-text citations (Waagner 1993). It states that: “Immunoglobulin may reduce clinical findings, but does not prevent viraemia”. There is no indication of the dose of IG, anti-rubella antibody concentration or timing of administration to which this statement is referring. The statement conflicts with the study by Schiff 1969 (the other reference used in the US guidelines) that concluded viraemia was prevented with high-dose IG. Waagner’s book chapter (Waagner 1993) goes on to indicate the author’s personal preference for only using immunoglobulin for pregnant women presenting within 72 hours of exposure for whom therapeutic abortion is not an option. In addition to the claim that IG given post-exposure will not prevent viraemia, the author reasons that asymptomatic infection may occur in the mother post-IG, anti-rubella antibody titres in IG vary, and there have been infants born with CRS despite post-exposure prophylaxis with IG. Again, each of these points is un-referenced. The author does not consider the possibility of detecting asymptomatic infection in the women post-IG administration using serial serological testing, despite the recommendation that exposed pregnant women undergo such testing immediately post-exposure and then at two to three and six weeks post-exposure.

No primary research evidence has been published in the last three decades on the use of IG or immunoglobulins generally for preventing rubella in non-immune exposed pregnant women. However, a number of controlled studies have been identified that examine the effectiveness or efficacy of passive immunisation against rubella post-exposure (Bass 1949; Doege 1967; Green 1965b; Macrae 1968; McCallin 1972; Neumann-Haefelin 1975; Petersen 1978; Schiff 1969), including one quasi-randomised controlled trial (Bass 1949). Each of these studies includes small numbers of participants and varying conclusions are drawn about the effectiveness of the intervention. No significant adverse events are noted.

A systematic review of the evidence will provide a firm foundation on which to review current policy and practice of passive immunisation for preventing rubella and congenital rubella syndrome.

**OBJECTIVES**

To assess the effectiveness of intramuscular injection or intravenous infusion of polyclonal immunoglobulins of human sera or
plasma origin for preventing rubella and congenital rubella syndrome when administered to exposed susceptible people before the onset of disease.

METHODOLOGY

Criteria for considering studies for this review

Types of studies
To assess the effectiveness of polyclonal immunoglobulins for preventing cases of rubella:
We will include randomised controlled trials (RCTs) and quasi-RCTs that examine this outcome, irrespective of blinding, publication status, language or unit of randomisation.

To assess the effectiveness of polyclonal immunoglobulins for preventing congenital rubella infection and congenital rubella syndrome:
We will include RCTs, quasi-RCTs and prospective controlled studies (cohort studies) that examine either or both of these outcomes, irrespective of blinding, publication status, language or unit of randomisation. We will include prospective controlled studies for these outcomes given that pregnant women would ethically not have been randomised to treatment and control groups, given that this intervention was felt to be beneficial from the time it was first used.

To be considered an eligible prospective controlled study, the intervention and control groups of relevance need to be recruited over the same (or similar and overlapping) timeframe and from the same population, and the study must specify that the intervention and control populations of relevance were exposed to rubella during pregnancy and were susceptible to rubella at the time of exposure. We will exclude the study if any of these points cannot be determined from the information available either in the publication or from the trial authors.

To assess adverse events:
We will include data on adverse events from any of the studies included in the review as above.

Types of participants
People of any age, sex or ethnic origin who were susceptible (no history of rubella and not vaccinated against rubella and/or rubella IgG negative) and exposed to rubella virus or exposed to someone diagnosed with rubella, and who did not already have rubella at the time of intervention or control administration. The primary study's definition of exposed will be accepted and any differences explored via subgroup analysis. For the congenital rubella infection and congenital rubella syndrome outcomes, participants must have been pregnant at the time of rubella exposure.

Types of interventions
To assess the effectiveness of polyclonal immunoglobulins for preventing cases of rubella:

Intervention:
1. intramuscular injection of polyclonal immunoglobulins;
2. intravenous infusion of polyclonal immunoglobulins.

Control:
1. no intervention or placebo;
2. live attenuated rubella virus vaccine;
3. different preparation and/or dosage of polyclonal immunoglobulins.

To assess the effectiveness of polyclonal immunoglobulins for preventing congenital rubella infection and congenital rubella syndrome:

Intervention:
1. intramuscular injection of polyclonal immunoglobulins;
2. intravenous infusion of polyclonal immunoglobulins.

Control:
1. no intervention or placebo;
2. different preparation and/or dosage of polyclonal immunoglobulins.

For all outcomes, polyclonal immunoglobulins must originate from human plasma or serum. We will exclude studies of immunoglobulins of animal origin and studies of immunoglobulins derived from placentas or given as human whole blood as these are not used in modern day practice.

Types of outcome measures

Primary outcomes
1. Cases of rubella. The diagnosis may be made by detection or isolation of rubella virus in urine, respiratory secretions or blood; by rubella-specific IgG seroconversion or a four-fold or greater rise in titre; by serological detection of IgM to rubella in the presence of a compatible clinical illness and no recent vaccination; or by symptoms consistent with rubella (fever, a generalised maculopapular rash and one or more of arthralgia/arthritis, lymphadenopathy, conjunctivitis) in the absence of other diagnoses as judged by a medical professional.

2. Cases of congenital rubella infection. The diagnosis may be made by detection or isolation of rubella virus in the infant's urine, respiratory secretions or blood or in the products of conception; by serological detection of rubella-specific IgM in the infant's serum; or by rising rubella-specific IgG in the infant's serum in the first year of life.

3. Cases of congenital rubella syndrome. A live or stillborn infant with any of the following compatible defects: cataracts, congenital glaucoma, congenital heart disease, hearing impairment, pigmentary retinopathy, microcephaly, mental retardation, purpura, hepatosplenomegaly, meningencephalitis,
radiolucent bone disease; and evidence of congenital rubella infection or maternal antepartum rubella infection.

Secondary outcomes

1. Occurrence of serious adverse events.
2. Occurrence of non-serious adverse events.
A serious adverse event is "any untoward medical occurrence that at any dose: results in death; is life-threatening; requires inpatient hospitalisation or prolongation of existing hospitalisation; results in persistent or significant disability/incapacity; or is a congenital anomaly/birth defect" (EMEA 1995; p4). All other events will be classified as non-serious.
We will specifically extract data on blood-borne virus infection; anaphylaxis (a rapidly evolving generalised multi-system allergic reaction characterised by one or more symptoms or signs of respiratory and/or cardiovascular involvement AND involvement of other systems such as skin or gastrointestinal tract (ATAGI 2008 p360); generalised hypersensitivity/generalised allergic reaction (non-anaphylactic generalised reaction characterised by one or more symptoms or signs of skin and/or gastrointestinal tract involvement without respiratory or cardiovascular involvement (ATAGI 2008 p360); and injection site reactions. Any other adverse event reported as such by study authors will also be included.

Search methods for identification of studies

Electronic searches
We will search the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, current issue at the time), which contains the Cochrane Acute Respiratory Infections (ARI) Group's Specialised Register, MEDLINE (1946 to present), CINAHL (1981 to present), EMBASE (1980 to present), LILACS (1982 to present) and Web of Science (1900 to present). We will use the search strategy in Appendix 2 to search MEDLINE and CENTRAL. We will adapt the strategy for the other databases. We will combine the MEDLINE and EMBASE searches with the filter for study type in Appendix 2 only if the search results retrieved are too large to be manageable. We will adapt the filter as necessary for the other databases.

Searching other resources
We will search reference lists of retrieved relevant studies and reviews. To locate further published or unpublished studies, we will attempt to contact companies manufacturing IG products for countries with low rubella incidences and also attempt to contact the corresponding author of any included studies. We will search the reference lists of published national public health guidelines on rubella control. We will search www.clinicaltrials.gov and other appropriate trials databases to identify completed and ongoing trials and we will attempt to contact the investigators as necessary.

Data collection and analysis

Selection of studies
Two review authors (MY, GN) will independently inspect the title and abstract (as available) of each reference identified by the electronic searches and determine the potential relevance of each article. If identified by either review author as potentially relevant, we will retrieve the full article. One review author (MY) will search trials databases and the reference lists of relevant retrieved full-text articles for further studies and retrieve those where the title indicates the study may be relevant. Both review authors will inspect each retrieved full-text article (or details of unpublished study) independently, using an eligibility checklist based on the inclusion criteria, to determine inclusion in the review. We will resolve any disagreements through discussion, or by consulting a third review author (AC). We will exclude studies not meeting the eligibility criteria and we will state the reasons for exclusion. We will list duplicate publications with the main publication for included studies. We will attempt to write to corresponding authors if uncertainties about duplicate publications exist.

Data extraction and management
Two review authors (MY, AC) will independently extract data from the included studies using pre-designed data extraction forms into RevMan 5.2 (RevMan 2012). We will resolve disagreement by discussion, or by a third review author (GN) independently extracting the data, as necessary. We will attempt to contact study authors for clarification or further information as necessary. We will extract the following data.

1. The study
   i) First author, publication year/not published.
   ii) Setting of the study.
   iii) Date study undertaken.
   iv) Study design: randomised, quasi-randomised or non-randomised.

2. Participants
   i) Number in each group.
   ii) Age range in each group.
   iii) Gender distribution in each group.
   iv) Range of gestation in each group if relevant.
   v) Range of time since exposure in each group.
   vi) Average time since exposure in each group.
   vii) Any measure of baseline comparability and result of this, if calculated.

3. Intervention
i) Intervention group: product used, concentration of rubella antibody if known, volume given, route of administration.
ii) Control group: placebo/vaccine/product/other, concentration of rubella antibody if relevant and known, volume given, route of administration.

4. Outcomes
   i) Primary and secondary (as above).
   ii) Length of follow-up.
   iii) Loss to follow-up.

Assessment of risk of bias in included studies

Two review authors (MY, AC) will independently assess the risk of bias for included studies. We will resolve any disagreements by discussion or by including a third review author (GN) as needed.

For randomised and quasi-randomised studies:
We will assess randomisation sequence generation; allocation concealment; blinding of participants, personnel and outcome assessors; incomplete outcome data; drop-out/ selective reporting; and other potential sources of bias. We will report the risk of bias using The Cochrane Collaboration’s tool for assessing ‘Risk of bias’ (Higgins 2011).

For non-randomised prospective controlled studies:
We will assess group differences at baseline; blinding of participants, personnel and outcome assessors; incomplete outcome data; drop-out/ selective reporting; management of confounders and other potential sources of bias. We will report the risk of bias using a modified version of the risk of bias tool (Higgins 2011). We will conduct a subgroup analysis based on study type, and conduct sensitivity analyses based on the risk of bias of included studies. We will report these results descriptively.

Measures of treatment effect
Outcomes, as identified above, are dichotomous. We will express these outcomes as risk ratios (RR) and calculate 95% confidence intervals (CIs) for each.

Unit of analysis issues
Should cluster-randomised trials be included in the review, we will attempt to extract RRs and 95% CIs resulting from analyses that have accounted for the clustering directly from the paper/s. If this is possible, we will proceed to meta-analyse the data using the inverse variance method. If this is not possible, we will extract the number of clusters, the average size of each cluster, the outcome data at the level of the individuals and an estimate of the intra cluster correlation coefficient and proceed to reduce the trial/s to their ‘effective sample size’ for meta-analysis following the recommendations in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011).

Should studies with multiple intervention groups, for example, different doses of immunoglobulins compared to control, be included in the review, we will split the shared group/s and initially include the relevant pair-wise comparisons in the meta-analysis (Higgins 2011). If there is no significant heterogeneity between the different interventions/controls from the same study, we will combine the groups and include the single intervention and single control group in the final meta-analysis. If significant heterogeneity exists, we will explore the differences in subgroup analyses.

Dealing with missing data
We will attempt to contact the trial authors for any missing data.
For remaining missing data we will analyse using the intention-to-treat (ITT) principle with all missing data considered treatment failures. In the event of an ITT analysis, we will undertake a sensitivity analysis assuming worst-case (all missing data are treatment failures) and best-case scenarios (missing data assigned as successful as in reported data or last observation carried forward or all missing data considered successful).

Assessment of heterogeneity
We will consider heterogeneity firstly by considering the populations, settings, methods and outcomes of the different studies. If clinically important heterogeneity is present we will not pool the studies in meta-analysis but describe them separately. Secondly, we will inspect the forest plot for each primary outcome. If heterogeneity is clear visually, we will proceed to subgroup and sensitivity analyses and re-examine the heterogeneity of these results separately. If heterogeneity is not obvious in the initial forest plots, we will perform the Cochrane Chi² test and I² statistic for each outcome. We will consider an I² statistic estimate of 60% or more, alongside a Chi² test P value of 0.1 or less to indicate important heterogeneity and again proceed to subgroup and sensitivity analyses.

Assessment of reporting biases
In the event of multiple publications of the same study, we will list the subsequent papers with the main paper and only enter data once. If uncertainty exists in this respect, we will attempt to contact the study authors. We will assess publication bias by examining funnel plots if we have sufficient studies (at least 10). In the event of funnel plot asymmetry, we will assess possible reasons for this and report these descriptively.

Data synthesis
We will calculate the RRs and 95% CI for each outcome measured in each study. We will initially include all studies relevant to each outcome, subdivided by intervention, control or both, and examine the forest plots to assess heterogeneity. We will explore possible
reasons for apparent heterogeneity via subgroup and sensitivity analyses. If these do not explain the apparent heterogeneity, we will report the results descriptively. In the absence of significant heterogeneity we will pool the results using a fixed-effect model. We will report the results of the secondary outcome descriptively.

Subgroup analysis and investigation of heterogeneity
We will consider the following subgroup analyses where relevant and possible:
- study type;
- age of participants (children; adults; mixed);
- stage of gestation (trimester of pregnancy);
- dose of immunoglobulins;
- dose of rubella-specific immunoglobulins;
- route of administration of immunoglobulins;
- timing of administration of intervention in relation to exposure;
- differences in primary study definitions of ‘exposed’;
- differences in primary study measurement of outcomes (laboratory confirmed versus clinical only);
- funder (those with potential conflict of interest versus no known conflict of interest); and
- per protocol versus ITT analysis (to account for missing data).

Sensitivity analysis
We will perform sensitivity analyses to assess the impact of heterogeneity, risk of bias and missing data on the pooled estimate/s of meta-analyses. For heterogeneity, we will gradually remove single trials that seem to contribute to heterogeneity upon inspection of the forest plot. For risk of bias, we will pool the studies with low risk of bias and then gradually add the studies assessed as having a high risk of bias. For missing data, we will undertake separate analyses using ITT, worst and best-case scenarios.

ACKNOWLEDGEMENTS
We would like to thank Liz Dooley and Clare Dooley for their support and guidance on the development of this protocol.

REFERENCES

Additional references

Ang 2010

ATAGI 2008

Banatvala 2004

Bass 1949

Best 2007

Birdsall 2009

Burnouf 2007

Burton 2002

Caidi 2009

CDC 1998

CDC 2001
Cutts 1999

De Santis 2006

Dewan 2012

Doege 1967

EMEA 1995

Goodson 2011

Green 1965a

Green 1965b

Heymann 2008

Higgins 2011

Hinman 2002

IDHPA 2009

Law 2008

Macrae 1968

McCallin 1972

McDonagh 1966

McDonald 1963

Muscat 2012

Nardone 2008

Nessa 2008

Neumann-Haefelin 1975

NZMoH 2011

Pattison 2013

Petersen 1978
Petersen EE, Neumann-Haefelin D, Heusler M. Rubella in pregnancy: experimental studies on the value of gamma-
globulin after wild virus infection [Rotehninfektion in der schwangerschaft: experimentelle studie zum wert einer gammaglobulingabe nach rotehwnwildvirusinfektion].


PHLN 2010

Reading 2007

Reef 2011

RevMan 2012

Sasmaz 2007

Schiff 1969

Simon 2003

Song 2012

Strebel 2010

UKDoH 2010

Usonis 2011

Wagner 1993

WHO 1994

WHO 2011

* Indicates the major publication for the study
APPENDICES

Appendix 1. MEDLINE and CENTRAL search strategy

1 exp Rubella/
2 exp Rubella virus/
3 rubella or rubeole.tw.
4 german adj measles.tw.
5 or/1-4
6 exp Immunoglobulins/
7 (immunoglobulin* or immuno-globulin* or immun* globulin*).tw nm.
8 (gamma globulin* or gamma-globulin* or gamma globulin*).tw nm.
9 exp Immunization, Passive/
10 (passiv* adj2 (immuni* or antibody transfer* or prophyla*)).tw.
11 Post-Exposure Prophylaxis/
12 ((post exposur* or post-exposur* or postexposur*) adj2 (prophyla* or prevent* or immuni*)).tw.
13 or/6-12
14 5 and 13

Appendix 2. MEDLINE and EMBASE filter for study type

We will combine the following filter for non-randomised prospective intervention studies (not before and after and not time-series studies) with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials (Higgins 2011).

1. exp Cohort Studies/
2. Epidemiologic Studies/
3. Intervention Studies/
4. Evaluation Studies/
5. Program Evaluation/
6. Random Allocation/
7. Clinical Trial/
8. Single-Blind Method/
9. Double-Blind Method/
10. Control Groups/
11. Pilot Projects/
12. controlled clinical trial.pt.
13. clinical trial.pt.
15. multicenter study.pt.
16. evaluation studies.pt.
17. Comparative Study/
18. Multicenter Study/
19. Follow-Up Studies/
20. Prospective Studies/
21. (cohort adj (study or studies)).tw.
22. cohort analy*.tw.
23. cohort*.tw.
24. ("follow up" or follow-up) adj (study or studies or assessment)).tw.
25. (observational adj (study or studies)).tw.
26. longitudinal.tw.
27. prospective.tw.
28. ((single or double* or triple* or treb*) and (blind* or mask*)).tw.
29. trial*.tw.
30. placebo.tw.
31. groups.tw.
32. ("pre test" or pretest or pre-intervention or preintervention or "pre intervention" or "post test" or posttest or post-intervention or postintervention or "post intervention").tw.
33. (pre adj5 post).tw.
34. ((evaluat* or intervention or interventional or treatment) and (control or controlled or study or studies or program* or comparison or comparative or "usual care")).tw.
35. ((intervention or interventional or process or program) adj8 (evaluat* or effect* or outcome*)).tw.
36. (program or programme or secondary analyse*).tw.
37. (quasi-experiment* or Quasiexperiment* or "quasi random*" or quasirandom* or "quasi control*" or quasi control* or ((quasi* or experimental) adj3 (method* or study or studies or trial or design*)).tw.
38. random*.tw.
39. (study adj3 aim*).ab.
40. "our study".ab.
41. multivariate.ab.
42. compared.ab.
43. intervention*.ti.
44. pilot.ti.
45. (multicentre or multicenter or multi-centre or multi-center).ti.
46. controlled.ti.
47. (rat or rats or cow or cows or chicken* or horse or horses or mice or mouse or bovine or animal*).ti.
48. exp animals/ not humans.sh.
49. (or/1-46) not (47 or 48)

Appendix 3. Glossary
antibody - any of a large number of proteins that are produced by specialised cells of the immune system. Also called immunoglobulin.
congenital - existing at or dating from birth; acquired during development in the uterus.
encephalitis - inflammation of the brain.
epidemic - an outbreak; suddenly and greatly increased numbers of cases of disease.
foetal - pertaining to a developing human, usually from two months after conception to birth.
gamma-globulins - IgG; a subclass of immunoglobulins.
gestation - pregnancy; the period of development from the time of conception until birth.
glaucoma - eye disease characterised by an increase in pressure inside the eye resulting in defects in the field of vision.
hepatosplenomegaly - abnormal enlargement of the liver and the spleen.
IG - human immune globulin; a blood product; a protein fraction of blood rich in antibodies.
IgG - gamma-globulins; a subclass of immunoglobulins.
IgM - a subclass of immunoglobulins usually produced first in an immune response prior to IgG.
immunoglobulin - any of a large number of proteins produced by specialised cells of the immune system. Also called antibodies.
incidence - the rate of occurrence of new cases of a particular disease within a population.
intramuscular - into or within a muscle.
meningoencephalitis - inflammation of the brain and tissue covering the brain and spinal cord.
microcephaly - abnormal smallness of the head resulting from failure of brain growth.
passive immunisation - the transfer of antibodies from donor to recipient.
pigmentary retinopathy - a disease where excessive pigment is produced by cells at the back of the eye leading to blindness.
plasma - the fluid remaining after the cells are removed from blood.
polyclonal - produced by different cells (as opposed to monoclonal - produced by the same cell).
purpura - purplish discolouration resulting from bleeding into the skin.
radiolucent bone disease - bones that appear abnormal on x-ray as they allow the x-rays to pass through them.
seroconversion - the change of a serological test from negative to positive indicating the development of antibodies.
serological testing - a blood test that detects the presence of antibodies to a particular protein molecule (e.g. a virus particle).
serum - the fluid remaining after clotting factors (certain proteins and other molecules) have been removed from plasma by clot formation.
susceptible - capable of being infected.
titre - a measure of the concentration of a specific antibody in a sample of serum.
viraemia - the presence of viruses in the blood.

CONTRIBUTIONS OF AUTHORS
Dr Megan Young drafted the protocol.
Prof Allan Cripps, Prof Graeme Nimmo and Prof Mieke van Driel reviewed and edited the draft for intellectual content.
Planned contributions to the review:
Dr Megan Young (MY) and Prof Graeme Nimmo (GN) will obtain copies of the studies and select studies for inclusion in the review.
MY and Prof Allan Cripps (AC) will extract the data and assess the risk of bias in the studies.
MY and Prof Mieke van Driel (MVD) will enter the data.
MVD and MY will analyse the data and interpret the analysis.
All authors will complete the final review.

DECLARATIONS OF INTEREST
Dr Megan Young is a public health physician in Queensland, Australia who is involved in the public health management of rubella. She is undertaking a PhD examining the effectiveness and efficiency of passive immunisation with IG for the public health management of communicable diseases and is collaborating with staff of CSL Biotherapies, Australia on a study related to the review topic. She receives no financial benefits from CSL or any other pharmaceutical company.
Professor Allan Cripps is Dr Megan Young’s PhD supervisor.
Prof Graeme Nimmo is Dr Megan Young’s PhD supervisor.
Prof Mieke van Driel has no known conflicts of interest.

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